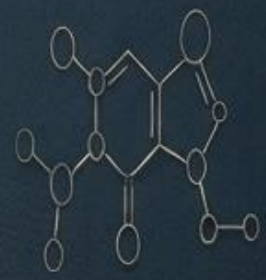

IMMUNOTOXICOLOGY

HANDOUT

Degree: Master 1 - Pharmacotoxicology

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Module: Immunotoxicology

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Intitulé de l'UE : Fondamentale

Intitulé de la matière 2 : Immuno-Toxicologie

Crédits : 6

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Objectif de l'enseignement

Cette unité d'enseignement a pour objectifs de présenter la relation entre certaine pathologie inflammatoire et le système immunitaire, le disfonctionnement de ce système et l'utilisation des éléments immunitaires en thérapeutique et d'autre et de fournir aux étudiants une formation théorique sur les interactions/relations existant entre les antigènes et le système immunitaire dans son ensemble.

Connaissances préalables recommandées

Immunologie cellulaire et moléculaire et bases en microbiologie.

Contenu de la matière

1 - Les diverses manifestations d'immunotoxicité.

2- Immunotoxicité des pesticides.

3- Immunotoxicité des métaux lourds.

4- Nutrition et immunité.

5- Les hypersensibilités.

6- Cibles immunologiques et mécanismes d'action des glucocorticoïdes.

7- L'autoimmunité liée aux substances toxiques.

8- Cibles et mécanismes d'action des autres immunosuppresseurs.

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AD: Atopic dermatitis

ADs: Autoimmune diseases

AERD: Aspirin-exacerbated respiratory disease

Ag-Ab reaction: Antigen-antibody reaction

AIHA: Autoimmune hemolytic anemia

Anti-CD20 mAb: Monoclonal antibodies targeting CD20 (e.g. rituximab, ocrelizumab, ofatumumab, veltuzumab)

Anti-CD22 mAb: Monoclonal antibody targeting CD22 (epratuzumab)

Anti-CD25 / Anti-IL-2 R: Monoclonal antibodies targeting IL-2 receptor alpha chain (CD25)

Anti-CD52: Monoclonal antibody targeting CD52 (alemtuzumab)

Anti-TNF: Anti-tumour necrosis factor agents (e.g. infliximab)

APC: Antigen-presenting cell

APRIL: A proliferation-inducing ligand

AR: Allergic rhinitis

ARC: Allergic rhinoconjunctivitis

ATG: Antithymocyte globulin (used with OKT3 for CD3 targeting)

B: B lymphocyte (B cell)

BAFF: B-cell activating factor

BAS: Basophil

C5aR: Complement component 5a receptor

CNS: Central nervous system

COX-1 / COX-2: Cyclooxygenase-1 / cyclooxygenase-2

CRS: Chronic rhinosinusitis (often “CRS with nasal polyps”)

CRTH2: Chemoattractant receptor-homologous molecule expressed on Th2 cells

CTLA-4-Ig: Cytotoxic T-lymphocyte–associated protein-4 immunoglobulin fusion protein

DC: Dendritic cell

EoE: Eosinophilic oesophagitis

EOS / EoE: Eosinophil / eosinophilic oesophagitis (context-dependent)

GM-CSF: Granulocyte-macrophage colony-stimulating factor

GN: Glomerulonephritis

IgE: Immunoglobulin E

IgG: Immunoglobulin G

IgGM: Immunoglobulin class GM (notation used in type II HS figure)

IgM: Immunoglobulin M

IL: Interleukin (general)

ILC1: Type 1 innate lymphoid cell

ILC2: Type 2 innate lymphoid cell

ILC3: Type 3 innate lymphoid cell

iNKT / NK-T: Invariant natural killer T cell / natural killer T cell

JAK: Janus kinase (in context of JAK inhibitors)

LT: Leukotrienes

LTC4, LTD4, LTE4: Leukotriene C4, D4, E4

MAC (again): Membrane-attack complex (listed above)

MAC: Membrane-attack complex (C5b-9)

MC: Mast cell

MMF: Mycophenolate mofetil

MO / M / Mf: Monocyte / macrophage (notation varies in figures)

mPGES-1: Microsomal prostaglandin E2 synthase-1

MS: Multiple sclerosis

mTOR: Mammalian target of rapamycin

NERD: NSAIDs-exacerbated respiratory disease

NET: Neutrophil extracellular trap

NEU: Neutrophil

NFAT: Nuclear factor of activated T-cells

NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB)

NK: Natural killer cell

NO: Nitrogen dioxide

NSAIDs: Nonsteroidal anti-inflammatory drugs

OKT3: Anti-CD3 monoclonal antibody (muromonab-CD3)

PGD2: Prostaglandin D2

PM: Particulate matter

RA: Rheumatoid arthritis

ROS: Reactive oxygen species

S phase: DNA synthesis phase of the cell cycle

sIgE / s IgE: Allergen-specific immunoglobulin E

SLE: Systemic lupus erythematosus

SO: Sulfur dioxide

ST2: Suppression of tumorigenicity 2 (IL-33 receptor)

TACI-Ig: Transmembrane activator and CAML interactor–immunoglobulin fusion protein

Tc: Cytotoxic T lymphocyte (T cytotoxic cell)

Tc17: Cytotoxic T cell producing IL-17 (Tc17 cell)

Tfh: T follicular helper cell

TGF-: Tumour necrosis factor-beta (here used for TGF-β context)

Th mem: T helper memory cells

Th: T helper lymphocyte (T cell)

Th1: Type 1 T helper lymphocyte (implied in Th1 memory cells)

Th17: T helper 17 lymphocyte

Th2: Type 2 T helper lymphocyte / type 2 immune response (context-dependent)

Th9: T helper 9 lymphocyte

TNF-: Tumour necrosis factor-alpha

TSLP: Thymic stromal lymphopoietin

Glossary

Xenobiotic: Any chemical substance foreign to an organism's normal biochemistry, including drugs, pollutants, pesticides or industrial chemicals.

Immune toxicity / Immunotoxicity: Harmful alteration of immune system structure or function caused by chemicals, drugs or environmental agents, leading to immunosuppression, immunostimulation or autoimmunity.

Immunosuppression: Decrease in immune responsiveness, resulting in higher susceptibility to infections, reduced vaccine efficacy and sometimes cancer.

Immunostimulation: Excessive or inappropriate activation of the immune system, often leading to chronic inflammation, hypersensitivity or autoimmune disease.

Autoimmune disorder: Disease in which the immune system attacks self-tissues due to loss of tolerance or molecular mimicry induced by genetic or environmental factors.

Innate immunity: Rapid, non-specific first line of defense involving physical barriers, phagocytes, NK cells and complement.

Adaptive immunity: Antigen-specific arm of immunity mediated by B and T lymphocytes with immunological memory.

Antigen-presenting cell (APC): Cell (e.g. dendritic cell, macrophage, B cell) that processes antigens and presents peptide–MHC complexes to T lymphocytes.

T helper (Th) cell: $CD4^+$ lymphocyte that orchestrates immune responses by secreting cytokines (Th1, Th2, Th17, etc.).

Cytotoxic T cell (Tc): $CD8^+$ T lymphocyte that kills virus-infected or tumor cells via perforin and granzymes.

Regulatory T cell (Treg): T cell subset that dampens immune responses and maintains self-tolerance through suppressive cytokines and cell–cell contact mechanisms.

Natural killer (NK) cell: Innate lymphoid cell that lyses infected or transformed cells without prior sensitization.

Innate lymphoid cells (ILC1/2/3): Non-T, non-B lymphoid cells that mirror Th1/Th2/Th17 functions and rapidly produce cytokines in barrier tissues.

Phagocytosis: Process by which cells such as macrophages and neutrophils engulf and degrade microbes, particles and apoptotic cells.

Antigen: Any molecule capable of being recognized by the immune system and inducing an immune response.

Hapten: Small molecule that becomes immunogenic only when covalently bound to a carrier protein.

Autoantibody: Antibody directed against self-antigens, often associated with autoimmune pathology.

Cytokine: Small secreted protein (e.g. interleukins, interferons, TNF) that modulates growth, differentiation and activation of immune cells.

Chemokine: Chemotactic cytokine that guides migration of leukocytes to sites of inflammation or lymphoid tissues.

Reactive oxygen species (ROS): Highly reactive oxygen-containing molecules (e.g. superoxide, hydrogen peroxide) that participate in microbial killing but also mediate oxidative damage.

Oxidative stress: Imbalance favoring ROS production over antioxidant defenses, leading to lipid, protein and DNA damage.

Complement system: Cascade of serum proteins that opsonize pathogens, recruit inflammatory cells and form the membrane-attack complex.

Membrane-attack complex (MAC): Terminal complement complex that perforates cell membranes and causes lysis.

Epigenetic modification: Heritable changes in gene expression (e.g. DNA methylation, histone modification, microRNA regulation) without altering DNA sequence.

Mitochondrial dysfunction: Impairment of mitochondrial electron transport and ATP generation, often accompanied by excess ROS.

Cell signaling pathway: Ordered series of molecular interactions (receptors, kinases, transcription factors) that transmit extracellular signals to nuclear responses.

Genotoxicity: Ability of a substance to damage DNA, causing mutations, chromosomal aberrations or carcinogenesis.

Comet assay: Single-cell gel electrophoresis method that visualizes DNA strand breaks as “comet tails” at the level of individual cells.

Epigenetic analysis: Experimental assessment of DNA methylation, histone marks or non-coding RNAs to study regulation of gene expression.

***In vitro* assay**: Test performed on isolated cells or tissues outside the organism (e.g. lymphocyte proliferation, cytokine release).

***In vivo* study**: Experiment performed in living organisms (e.g. rodents) to evaluate systemic immunotoxic effects of xenobiotics.

Delayed-type hypersensitivity (DTH) test: In vivo assay of cell-mediated immunity based on local skin reaction to antigen re-exposure after 24–72 h.

Local lymph node assay (LLNA): In vivo method for predicting skin sensitization by measuring lymphocyte proliferation in draining lymph nodes after topical exposure.

Human cell line activation test (h-CLAT): In vitro assay using human immune cell lines to detect up-regulation of surface markers indicative of sensitization potential.

Immunophenotyping: Characterization of immune cell subsets by flow cytometry using panels of surface and intracellular markers.

In silico prediction: Use of computational models and bioinformatics to predict immunotoxicity without wet-lab experiments.

Molecular docking: Computational simulation of the binding of a xenobiotic to a target protein to estimate affinity and potential functional impact.

Quantitative structure–activity relationship (QSAR): Statistical or machine-learning model linking chemical structure descriptors to biological activity, including immunotoxicity.

Systems biology / network analysis: Integration of omics data to model immune pathways and identify key nodes perturbed by xenobiotic exposure.

Machine learning / AI in toxicology: Use of algorithms (e.g. random forests, SVMs, deep neural networks) to classify compounds as immunotoxic or not based on large datasets.

Toxicogenomics / transcriptomics: Study of gene expression changes induced by toxicants in immune cells to identify pathways and biomarkers of immune dysfunction.

Pharmacokinetic–pharmacodynamic (PK–PD) modeling: Mathematical description of xenobiotic disposition in the body and its time-dependent effects on immune endpoints.

Hypersensitivity reaction: Exaggerated or inappropriate immune response causing tissue damage (Types I–IV, plus extended endotypes V–VII in your handout).)

Serum sickness: Systemic type III hypersensitivity due to immune complexes formed against foreign serum proteins.

Hypersensitivity pneumonitis / extrinsic allergic alveolitis: Immune-mediated granulomatous lung disease caused by repeated inhalation of organic antigens.

Silicosis: Fibrotic lung disease caused by inhalation of crystalline silica, often accompanied by chronic inflammation and autoimmunity.

Xenobiotics

1. Introduction

A xenobiotic is a chemical substance foreign to an organism's normal biological system, originating externally rather than being naturally produced or expected within the organism. The term stems from the Greek words xenos (foreign) and bios (life), reflecting its nature as an exogenous agent introduced through ingestion, inhalation, or absorption. Xenobiotics encompass a wide range of substances, including synthetic compounds like pharmaceuticals, pesticides, and plastics; environmental pollutants such as industrial toxins or heavy metals; and even naturally occurring compounds, like plant alkaloids, when encountered by organisms that do not typically interact with them. Upon entering a biological system, xenobiotics are often metabolized by detoxification pathways, primarily involving liver enzymes like cytochrome P450, to transform them into less harmful forms for excretion. Their effects vary widely: some are beneficial (e.g., lifesaving drugs), others neutral, and many harmful, acting as toxins, carcinogens, or endocrine disruptors.

Xenobiotics interact with the immune system in complex ways, often influencing immune responses or being targeted by immune defenses. These foreign substances—such as drugs, environmental pollutants, or synthetic chemicals—can modulate immunity through direct or indirect mechanisms, sometimes triggering protective reactions, unintended hypersensitivity, or immune suppression. The immune system is designed to recognize and respond to "non-self" molecules, including xenobiotics. Some xenobiotics are small molecules and may not directly trigger an immune response unless they bind to proteins or other biomolecules, forming haptens. These haptens can then be recognized by the immune system as foreign antigens. Certain xenobiotics, such as medications (e.g., penicillin) or chemicals in cosmetics, can trigger allergic reactions. This occurs when the immune system mistakenly identifies a harmless xenobiotic as harmful and mounts an exaggerated response, leading to symptoms like itching, swelling, or even anaphylaxis. Some xenobiotics can cause autoimmune diseases by altering self-proteins or mimicking self-antigens, tricking the immune system into attacking the body's own tissues. For example, certain drugs or environmental toxins have been linked to conditions like lupus or rheumatoid arthritis. Some xenobiotics suppress the immune system, making the body more susceptible to infections or cancer. Examples include immunosuppressive drugs used in organ transplantation and certain environmental pollutants like dioxins. Prolonged exposure to certain xenobiotics can damage immune cells or disrupt immune function, leading to immunodeficiency or increased susceptibility to disease.

2. Immune toxicity

Immune toxicity refers to the harmful effects that certain substances, chemicals, or drugs can have on the immune system. It involves any disruption or impairment of the normal functioning of the immune system, leading to increased susceptibility to infections, autoimmune diseases, or other adverse health outcomes. Immune toxicity can occur due to exposure to xenobiotics (foreign substances), environmental pollutants, medications, or other factors.

2.1. Types of Immune Toxicity

2.1.1. Immunosuppression

A reduction in the ability of the immune system to respond to pathogens or foreign antigens.

It can lead to an increased susceptibility to infections, reduced vaccine efficacy, and higher risk of cancer. For examples: Chemotherapeutic drugs used in cancer treatment often suppress the immune system as a side effect. Environmental pollutants like pesticides (e.g., organophosphates) can impair immune function.

2.1.2. Immunostimulation

An overactive immune response triggered by toxicants, leading to excessive inflammation or tissue damage. One of the consequences is allergic reactions, hypersensitivity, or autoimmune diseases. Drugs like sulfonamides can cause drug-induced hypersensitivity syndromes. Silica particles can induce chronic inflammation and fibrosis in the lungs.

2.1.3. Autoimmune Disorders

The immune system mistakenly attacks the body's own tissues, often due to altered self-recognition caused by toxicants. Some conditions like rheumatoid arthritis, lupus, or multiple sclerosis can be occurred by the toxicity of the immune system. Trichloroethylene (TCE), an industrial solvent, has been associated with autoimmune hepatitis. Ultraviolet (UV) radiation can modify DNA and proteins, potentially triggering autoimmunity.

2.2. Mechanisms of Immune Toxicity

Immune toxicity can occur through several mechanisms, depending on the nature of the toxicant and the dose of exposure:

2.2.1. Direct Damage to Immune Cells

Certain toxicants can directly damage or kill immune cells such as lymphocytes (T cells, B cells), macrophages, or neutrophils. Heavy metals like cadmium or mercury can disrupt immune cell function by binding to critical proteins or enzymes.

2.2.2. Alteration of Immune Cell Function

Toxicants may interfere with the signaling pathways, activation, or proliferation of immune cells. Polychlorinated biphenyls (PCBs) can suppress antibody production by B cells.

2.2.3. Induction of Autoimmunity

Some toxicants can cause the immune system to attack the body's own tissues by altering self-proteins or mimicking self-antigens. Example: Silica dust exposure has been linked to systemic lupus erythematosus (SLE).

2.2.4. Immunosuppression

Certain substances suppress the immune response, making the body more vulnerable to infections and cancer. Dioxins (e.g., TCDD) are potent immunosuppressants that inhibit T-cell activation and reduce antibody production.

2.2.5. Inflammation and Chronic Activation

Prolonged exposure to toxicants can lead to chronic inflammation, which can exhaust the immune system and increase the risk of diseases like cancer or cardiovascular disorders. Persistent organic pollutants (POPs) can activate inflammatory pathways via nuclear receptors like the aryl hydrocarbon receptor (AhR).

2.3. Factors influencing immune toxicity

The factors influencing immune toxicity are complex and multifaceted, involving interactions between the toxicant, individual biology, and environmental conditions.

2.3.1. Dose

The amount of a toxicant that enters the body plays a critical role in immune toxicity. Higher doses generally increase the likelihood and severity of immune toxicity because they overwhelm the body's detoxification and repair mechanisms. Conversely, low doses may not cause noticeable effects or could even stimulate the immune system, a phenomenon known as hormesis. For example, lead at high doses suppresses immune function by reducing white blood cell counts and impairing antibody production, while low-level exposure can still harm children's developing immune

systems. Similarly, chronic exposure to low levels of cadmium can gradually weaken the immune response over time.

2.3.2. Duration of Exposure

The length of time an individual is exposed to a toxicant significantly impacts immune toxicity. Short-term, high-dose exposure (acute exposure) can cause immediate but reversible immune suppression or stimulation. On the other hand, long-term, low-dose exposure (chronic exposure) can lead to cumulative damage, chronic inflammation, or irreversible changes in immune function. For instance, short-term exposure to silica dust may cause irritation, while long-term occupational exposure leads to silicosis, a condition associated with autoimmune diseases like systemic lupus erythematosus (SLE). Repeated exposure to pesticides like organophosphates can gradually suppress immune function, increasing susceptibility to infections.

2.3.3. Route of Exposure

The pathway through which a toxicant enters the body—such as inhalation, ingestion, dermal contact, or injection—can result in varying levels of absorption, distribution, and interaction with immune cells. Inhalation often causes localized effects in the respiratory system, while ingestion may affect the gut-associated lymphoid tissue (GALT). For example, asbestos fibers inhaled into the lungs cause inflammation and fibrosis, leading to conditions like mesothelioma and impaired pulmonary immunity. In contrast, ingestion of methylmercury (e.g., from contaminated fish) affects the central nervous system and immune system, while inhalation of mercury vapor directly impacts respiratory tissues.

2.3.4. Chemical Properties of the Toxicant

The physical and chemical characteristics of a toxicant, such as solubility, reactivity, and molecular structure, influence its impact on immune toxicity. Water-soluble substances are more likely to be absorbed and distributed throughout the body, potentially affecting systemic immunity. Reactive chemicals can bind to proteins or DNA, altering their structure and triggering immune responses. Persistent organic pollutants (POPs), like dioxins, accumulate in fatty tissues and have long-lasting effects on immune function. For example, polychlorinated biphenyls (PCBs) are lipophilic compounds that accumulate in adipose tissue and suppress immune function over time. Trichloroethylene (TCE), a volatile organic compound, induces autoimmune hepatitis by altering self-proteins.

2.3.5. Individual Susceptibility

Variations in genetic makeup, age, health status, and lifestyle influence how a person responds to toxicants. Genetic polymorphisms in genes involved in detoxification (e.g., cytochrome P450 enzymes) or immune regulation (e.g., HLA genes) can make some individuals more susceptible to immune toxicity. Infants and the elderly are more vulnerable due to immature or declining immune systems. Individuals with pre-existing immune disorders, malnutrition, or chronic diseases may experience more severe effects. Lifestyle factors such as smoking, alcohol consumption, and stress can exacerbate immune toxicity by weakening the immune system further. For example, children are more sensitive to lead exposure due to their developing immune systems, while smokers face increased risks of immune suppression from air pollutants like ozone or particulate matter.

2.3.6. Interaction with Other Substances

Co-exposure to multiple substances can amplify immune toxicity due to additive or synergistic effects. Some substances may enhance the absorption or metabolism of others, altering their immune impact. For example, combined exposure to heavy metals like lead and pesticides like organophosphates can exacerbate neurotoxicity and immunotoxicity. Similarly, alcohol can potentiate the immunosuppressive effects of certain drugs, such as corticosteroids.

2.3.7. Environmental Factors

External conditions that influence the uptake, distribution, and effects of toxicants also play a role in immune toxicity. Extreme temperatures can alter metabolic rates and immune responses, while high humidity can increase the absorption of certain airborne pollutants. Deficiencies in essential nutrients, such as vitamin D or zinc, can worsen immune toxicity by impairing immune function. For example, UV radiation increases skin cancer risk and suppresses local immunity, making individuals more susceptible to infections. Malnutrition reduces the body's ability to detoxify harmful substances and compromises immune defenses.

2.3.8. Immune System Status

The baseline state of the immune system before exposure to a toxicant influences its vulnerability to immune toxicity. Individuals with compromised immune systems, such as those with HIV/AIDS, undergoing chemotherapy, or experiencing aging, are more vulnerable to immune toxicity. A healthy immune system may better tolerate or recover from toxicant exposure compared to a weakened one. For example, HIV-positive individuals are more susceptible to the immunosuppressive effects of environmental pollutants like dioxins, while older adults with declining immune function are more prone to adverse effects from xenobiotics.

2.3.9. Gender Differences

Gender significantly influences susceptibility and response to immunotoxicity caused by xenobiotics due to physiological, hormonal, genetic, and environmental differences. Hormonally, estrogen in females enhances immune function, potentially increasing vulnerability to autoimmune responses but offering protection against infections, while testosterone in males tends to suppress immune activity, possibly reducing inflammation but increasing susceptibility to infections. Pharmacokinetic and pharmacodynamic variations, such as differences in metabolism, body composition, and receptor sensitivity, can alter how xenobiotics are processed and affect males and females differently. Genetic factors, including those linked to sex chromosomes, and epigenetic modifications also play a role in shaping immune system structure and function. Additionally, gender-specific behaviors, occupational exposures, and lifestyle choices contribute to varying levels of exposure to xenobiotics. Overall, these multifaceted differences mean that males and females may experience distinct risks and outcomes when exposed to immunotoxic substances.

Factor	**Description**	**Example**
Dose	Amount of toxicant entering the body	Lead at high doses suppresses immune function; low doses harm children
Duration of Exposure	Length of time exposed	Silica dust causes silicosis with chronic exposure
Route of Exposure	Pathway of entry (inhalation, ingestion, etc.)	Asbestos via inhalation causes lung inflammation
Chemical Properties	Solubility, reactivity, persistence	PCBs accumulate in fat and suppress immunity
Individual Susceptibility	Genetics, age, health status	Children are more sensitive to lead
Interaction with Other Substances	Combined effects of multiple toxicants	Lead + organophosphates exacerbate neurotoxicity and immunotoxicity
Environmental Factors	Temperature, humidity, nutrition	Malnutrition worsens immune toxicity
Immune System Status	Baseline immune function	Immunocompromised individuals are more vulnerable
Gender Differences	Biological and hormonal variations	Women are more prone to autoimmune reactions

3. Methods used in assessing immunotoxicity

Many methods are designed to evaluate how these substances affect the immune system, including their potential to cause immunosuppression, hypersensitivity, autoimmunity, or other adverse effects.

3.1. In Vitro Assays: Laboratory Testing on Cells

In vitro assays involve testing xenobiotics on isolated cells or tissues outside the body, typically in a controlled laboratory environment. These tests provide valuable insights into the direct effects of xenobiotics on immune cells.

3.1.1. Lymphocyte Proliferation Assays

Lymphocytes, including T cells and B cells, play critical roles in adaptive immunity. This assay measures the ability of lymphocytes to divide and multiply in response to stimuli like mitogens (substances that promote cell division). If a xenobiotic inhibits this process, it may suppress the immune system, making the organism more susceptible to infections.

3.1.2. Cytokine Release Assays :

Cytokines are small proteins that act as messengers between immune cells, regulating inflammation and immune responses. By measuring the levels of cytokines released by immune cells exposed to a xenobiotic, researchers can determine whether the substance causes excessive inflammation (cytokine storm) or suppresses immune signaling.

3.1.3. Phagocytosis Assays :

Phagocytes, such as macrophages and neutrophils, engulf and destroy pathogens. This test evaluates the efficiency of phagocytic activity after exposure to a xenobiotic. Reduced phagocytic capacity may indicate immunotoxicity, leading to impaired defense against infections.

3.2. In Vivo Studies: Testing in Living Organisms

In vivo studies involve administering xenobiotics to live animals (commonly mice or rats) to observe their effects on the entire immune system within a biological context.

3.2.1. Animal Models :

Animals are exposed to the xenobiotic, and researchers monitor changes in immune parameters such as white blood cell counts, antibody production, and overall immune function. These studies help bridge the gap between in vitro findings and real-world scenarios.

3.2.2. Delayed-Type Hypersensitivity (DTH) Tests :

The DTH test assesses cell-mediated immunity by injecting a small amount of antigen into the skin and measuring the inflammatory response after a few days. A diminished response suggests immunosuppression, while an exaggerated response may indicate hypersensitivity or allergic reactions.

3.3. Genotoxicity and Epigenetic Tests: Assessing DNA Damage and Gene Regulation

Some xenobiotics can damage DNA or alter gene expression, which may have long-term consequences for immune health.

3.3.1. Comet Assay :

Also known as single-cell gel electrophoresis, this test detects DNA strand breaks caused by xenobiotics. DNA damage in immune cells can impair their function and lead to chronic immune dysfunction.

3.3.2. Epigenetic Analysis :

Xenobiotics may modify gene expression through epigenetic mechanisms, such as DNA methylation or histone modification, without altering the DNA sequence. Changes in the expression of immune-related genes can be assessed using techniques like bisulfite sequencing or chromatin immunoprecipitation (ChIP).

4. Allergic Reaction Tests: Evaluating Sensitization Potential

Allergic reactions occur when the immune system overreacts to harmless substances. Testing for allergenicity is crucial, especially for drugs, cosmetics, and industrial chemicals.

4.1. Local Lymph Node Assay (LLNA) :

The LLNA is a widely used method to predict the sensitization potential of a substance. It involves applying the xenobiotic to the skin near the lymph nodes and measuring lymphocyte proliferation in the draining lymph nodes. Increased proliferation indicates a higher risk of causing allergic contact dermatitis.

4.2. Human Cell Line Activation Test (h-CLAT) :

This in vitro test uses human immune cell lines to evaluate the activation of surface markers associated with sensitization. It helps predict whether a substance might cause skin sensitization in humans.

5. Autoimmunity Assessment: Detecting Self-Reactivity

Autoimmune diseases occur when the immune system mistakenly attacks the body's own tissues. Some xenobiotics may trigger autoimmune responses.

5.1. Autoantibody Detection :

Autoantibodies are antibodies produced against the body’s own proteins. Blood samples from exposed individuals or animals are tested for the presence of autoantibodies using techniques like enzyme-linked immunosorbent assay (ELISA) or Western blotting.

5.2. Histopathological Examination :

Tissue samples from exposed animals are examined under a microscope for signs of inflammation, tissue damage, or abnormal immune cell infiltration. These findings can indicate autoimmune-like reactions.

6. Immunophenotyping: Characterizing Immune Cell Populations

Immunophenotyping involves identifying and quantifying different types of immune cells using flow cytometry or other techniques.

Flow cytometry allows researchers to analyze the expression of specific markers on immune cells, such as CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells. Changes in the proportions or activation states of these cells can reveal how the xenobiotic affects immune balance.

7. Challenge Tests: Evaluating Vaccine Response

Challenge tests simulate real-world conditions by exposing animals to pathogens after they have been vaccinated in the presence of the xenobiotic.

7.1. Vaccination Challenge :

Animals are vaccinated with a standard vaccine and then challenged with the corresponding pathogen. The immune response to the challenge is measured, providing insight into whether the xenobiotic impairs vaccine efficacy or compromises overall immune health.

8- In Silico Prediction and Study of Immune Toxicity

The assessment of immune toxicity, which involves evaluating the potential adverse effects of xenobiotics (foreign substances such as chemicals, drugs, or environmental pollutants) on the immune system, has traditionally relied on in vitro and in vivo methods. However, the advent of computational biology and advances in bioinformatics have introduced a powerful alternative: in silico approaches. These methods leverage computer simulations, algorithms, and databases to predict and study immune toxicity, offering significant advantages in terms of cost-effectiveness, speed, and ethical considerations. By integrating molecular modeling, machine learning, systems biology, and toxicogenomics, in silico techniques provide valuable insights into how xenobiotics interact with immune-related pathways and proteins, ultimately contributing to safer drug development and chemical risk assessment.

One of the foundational in silico tools for studying immune toxicity is molecular docking , which predicts the interaction between a xenobiotic and specific immune-related proteins, such as receptors, enzymes, or signaling molecules. This technique relies on computational algorithms to model the three-dimensional structure of both the target protein and the xenobiotic, calculating their binding affinity and predicting whether the interaction could disrupt normal immune processes. For instance, molecular docking can simulate how a compound might bind to toll-like receptors (TLRs), which play a critical role in innate immunity, or cytokine receptors that regulate inflammatory responses. By identifying potential interactions at the molecular level, researchers can gain early insights into the immunomodulatory properties of a substance, including its ability to activate or suppress immune functions.

Another widely used approach is Quantitative Structure-Activity Relationship (QSAR) modeling , which correlates the chemical structure of a xenobiotic with its biological activity, including immune toxicity. QSAR models extract chemical descriptors—such as molecular weight, polarity, and functional groups—from the xenobiotic's structure and use statistical or machine learning techniques to predict its likelihood of causing adverse immune effects. These models are trained using datasets containing information on known immunotoxicants and non-immunotoxicants, enabling them to classify new compounds based on their structural similarity to existing data. QSAR models are particularly useful for predicting allergenic potential, immunosuppression, or autoimmune reactions, making them an essential tool in the preclinical evaluation of drugs and chemicals.

To further unravel the complexity of immune responses, systems biology and network analysis employ computational models to integrate large datasets, such as gene expression profiles,

proteomics, and metabolomics, into comprehensive representations of biological networks. These models help researchers understand how xenobiotics affect intricate immune pathways by mapping immune-related genes, proteins, and signaling cascades into interconnected networks. Computational simulations can then predict how exposure to a xenobiotic might perturb these networks, leading to altered immune function. For example, systems biology approaches can identify key nodes in the immune network that are most vulnerable to disruption, providing mechanistic insights into the onset of immune dysfunction or disease.

Machine learning and artificial intelligence (AI) have revolutionized in silico studies of immune toxicity by enabling the processing of vast amounts of high-throughput screening data. Machine learning algorithms, such as random forests, support vector machines (SVMs), and deep neural networks, can be trained on extensive datasets containing information on known immunotoxicants and non-immunotoxicants. Once trained, these models classify new compounds based on their likelihood of causing immune toxicity, offering rapid and accurate predictions. Applications of machine learning in this context include predicting hypersensitivity reactions, classifying substances as immunosuppressants or immunostimulants, and identifying potential biomarkers of immune dysfunction. The integration of AI-driven approaches not only enhances predictive accuracy but also accelerates the discovery of novel immunomodulatory compounds.

Virtual screening libraries represent another powerful in silico tool for identifying potential immune-modulatory effects of xenobiotics. This approach involves computationally evaluating large libraries of chemical structures to prioritize candidates for further experimental testing. By screening these libraries against known immune targets, such as cytokine receptors, TLRs, or histocompatibility molecules, researchers can flag compounds predicted to interact strongly with these targets. Virtual screening is especially valuable in drug discovery, where it helps identify promising immunomodulatory agents from a pool of candidate compounds, as well as in environmental toxicology, where it screens pollutants for potential immune toxicity.

Toxicogenomics and transcriptomics analysis provide additional layers of insight into immune toxicity by examining how xenobiotics affect gene expression in immune cells. In silico tools analyze transcriptomic data to identify changes in gene expression patterns associated with immune dysfunction, comparing exposed cells or tissues to baseline conditions. Pathway analysis further elucidates which immune-related pathways are upregulated or downregulated due to xenobiotic exposure, offering clues about the underlying mechanisms of immune modulation. These approaches are instrumental in detecting early biomarkers of immune toxicity and understanding the long-term consequences of chronic exposure to low doses of xenobiotics.

Pharmacokinetic/pharmacodynamic (PK/PD) modeling complements in silico studies by simulating how a xenobiotic is absorbed, distributed, metabolized, and excreted in the body, as well as its effects on immune function over time. Mathematical models incorporate data on the xenobiotic's interaction with immune targets to predict its overall impact on immune health. PK/PD modeling enables researchers to estimate dose-dependent effects and evaluate the risk of chronic immune toxicity from repeated or prolonged exposure, bridging the gap between molecular-level predictions and real-world scenarios.

The utility of in silico approaches is further enhanced by the availability of extensive databases and knowledge repositories, such as TOXNET, ChEMBL, and ImmPort. These resources provide curated information on toxicology, hazardous chemicals, environmental health, bioactive molecules, and immunology-related data. Researchers can query these databases to mine existing information on immune toxicity, compare new compounds to known immunotoxicants, and identify trends or patterns that inform predictive models. The integration of database mining with advanced analytics amplifies the power of in silico methods, facilitating more comprehensive and accurate assessments of immune toxicity.

Despite their many advantages, in silico approaches are not without limitations. Predictive accuracy depends heavily on the quality and quantity of input data, and computational models may struggle to fully capture the complexity of real-world biological systems. Additionally, while in silico predictions offer valuable insights, they must always be validated through experimental studies to ensure reliability. Nevertheless, when combined with traditional in vitro and in vivo methods, in silico approaches provide a robust framework for assessing immune toxicity, accelerating the discovery of safer drugs and chemicals while minimizing the need for animal testing.

Immunotoxicity of Pesticides

1. Introduction

Pesticides are chemical or biological substances used to control pests such as insects, weeds, fungi, and rodents. They are classified into various types based on the target organism they are designed to eliminate or control.

2. Types of Pesticides

Insecticides are used to manage insects like mosquitoes, aphids, and beetles. These chemicals work by targeting the nervous system of insects, causing paralysis or death. For example, organophosphates inhibit an enzyme called acetylcholinesterase, leading to nerve overstimulation and eventual death. Neonicotinoids bind to nicotinic acetylcholine receptors in the insect's nervous system, disrupting neural transmission. Common examples include malathion, permethrin, imidacloprid, and carbaryl.

Herbicides are employed to control weeds or unwanted plants. These substances disrupt essential metabolic processes in plants, such as photosynthesis or hormone regulation. Glyphosate, for instance, inhibits an enzyme involved in amino acid synthesis, starving the plant of vital nutrients. Atrazine interferes with photosynthesis, while paraquat damages cell membranes, causing rapid plant death. Examples of herbicides include Roundup, atrazine, 2,4-D, and paraquat.

Fungicides are used to prevent or control fungal infections, including mold, mildew, and rust. These chemicals interfere with fungal cell walls, membranes, or metabolic pathways. Chlorothalonil disrupts fungal respiration, while copper sulfate forms complexes that damage fungal cells. Azoxystrobin inhibits mitochondrial function in fungi, stopping their growth. Common fungicides include chlorothalonil, copper sulfate, mancozeb, and azoxystrobin.

Rodenticides are designed to kill rodents such as rats and mice. These substances affect the internal systems of rodents, often causing internal bleeding or poisoning. Anticoagulant rodenticides like warfarin and brodifacoum interfere with blood clotting mechanisms, leading to internal bleeding. Zinc phosphide reacts with stomach acids to produce toxic phosphine gas, which poisons the rodent.

Nematicides are used to control nematodes, which are parasitic roundworms that attack plant roots or stems. These chemicals interfere with the nervous system of nematodes, paralyzing them or disrupting their reproductive cycles. Aldicarb acts as a neurotoxin, blocking nerve impulses in nematodes. Other examples of nematicides include fenamiphos and oxamyl.

Molluscicides are used to manage gastropod pests like snails and slugs, which feed on crops and garden plants. Metaldehyde causes excessive mucus production and muscle contractions in

mollusks, leading to dehydration and death. Methiocarb affects the nervous system, paralyzing the mollusk. These substances help protect plants from damage caused by these pests.

Acaricides are specifically formulated to control mites and ticks. Abamectin targets the nervous system of mites, causing paralysis and death. Bifenthrin disrupts sodium channels in nerve cells, leading to hyperexcitation and mortality. Pyridaben inhibits mitochondrial function in mites, preventing energy production. These chemicals are essential for managing infestations on plants or animals.

Larvicides are used to control insect populations at the larval stage before they mature into adults. Bacillus thuringiensis (Bt) produces toxins specific to insect larvae, damaging their gut lining. Temephos disrupts larval nervous systems, while methoprene interferes with larval development, preventing them from reaching adulthood. These substances are effective in reducing pest populations.

Fumigants are gaseous pesticides that penetrate soil, structures, or stored products to eliminate pests. Methyl bromide attacks the central nervous system of pests, while chloropicrin irritates respiratory systems and disrupts cellular metabolism. Sulfuryl fluoride inhibits enzyme activity in pests. These chemicals are used for broad-spectrum pest control.

Biological pesticides use living microorganisms or natural compounds to control pests without harming the environment. Bacillus thuringiensis produces proteins toxic to specific insects, while Beauveria bassiana is a fungus that infects and kills insects. Neem oil disrupts insect feeding, reproduction, and growth. These substances provide an eco-friendly alternative to chemical pesticides.

Defoliants cause leaves to drop off plants, often used in crop harvesting or weed control. Diquat disrupts plant cell membranes, leading to leaf desiccation and abscission. Pelargonic acid breaks down plant cell walls, causing leaves to dry out and fall. These chemicals are useful in agricultural practices.

Desiccants dry out plant tissues, killing weeds or preparing crops for harvest. Sodium chlorate inhibits photosynthesis and dehydrates plant cells, while pelargonic acid disrupts cell membranes, causing rapid water loss and plant death. These substances are effective in controlling unwanted vegetation.

Plant growth regulators alter plant growth patterns to improve yield, reduce flowering, or enhance resistance to pests. Gibberellins stimulate stem elongation and seed germination, while auxins regulate root formation and fruit development. Cytokinins promote cell division and delay aging in plants. These chemicals play a crucial role in optimizing plant growth and productivity.

3. Pesticides and Immunotoxicity

Pesticides can induce immunotoxicity by disrupting various components of the immune system, leading to altered immune function, increased susceptibility to infections, autoimmune diseases, or cancer. The mechanisms through which pesticides cause immunotoxicity are diverse and depend on their chemical structure and mode of action.

4. Mechanism of action of inducing immunotoxicity

4.1. Direct Toxicity to Immune Cells

Some pesticides directly damage immune cells such as lymphocytes, macrophages, or neutrophils, impairing their ability to function properly. For example: **Chlorpyrifos (an organophosphate insecticide)**: Chlorpyrifos inhibits acetylcholinesterase activity but also induces oxidative stress in immune cells, causing DNA damage and apoptosis (cell death). This reduces the number of functional immune cells, weakening the immune response. Studies show that chlorpyrifos exposure decreases the production of cytokines like interleukin-2 (IL-2) and interferon-gamma (IFN-γ), which are critical for T-cell activation and antiviral defense.

4.2. Disruption of Hormonal Regulation

Many pesticides act as endocrine disruptors, interfering with hormonal pathways that regulate immune function. For example: **Atrazine (a herbicide)**: Atrazine mimics estrogen and binds to estrogen receptors on immune cells, altering their function. This suppresses the activity of natural killer (NK) cells and decreases antibody production, making the body more susceptible to infections. Chronic exposure to atrazine has been linked to an increased risk of autoimmune disorders due to its interference with immune regulation.

4.3. Induction of Oxidative Stress

Pesticides generate reactive oxygen species (ROS) that overwhelm the body's antioxidant defenses, causing oxidative stress. This damages cellular components, including DNA, proteins, and lipids, and impairs immune cell function. For example: **Mancozeb (a fungicide)**: Mancozeb generates ROS, leading to lipid peroxidation and mitochondrial dysfunction in immune cells. This oxidative damage impairs the ability of macrophages to phagocytose pathogens and produce pro-inflammatory cytokines. Long-term exposure to mancozeb has been associated with suppressed immune responses and increased susceptibility to infections.

4.4. Alteration of Cytokine Production

Pesticides can interfere with cytokine signaling pathways, disrupting communication between immune cells and altering the balance between pro-inflammatory and anti-inflammatory responses. For example: **Glyphosate (a herbicide)**: Glyphosate alters the production of cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-6, which play key roles in inflammation and immune regulation. Imbalances in these cytokines can lead to chronic inflammation or immunosuppression. Research suggests that glyphosate exposure may contribute to autoimmune conditions by promoting Th17 cell differentiation, which is involved in inflammatory responses.

4.5. Epigenetic Modifications

Pesticides can modify gene expression through epigenetic mechanisms such as DNA methylation, histone modification, or microRNA regulation. These changes affect immune cell development and function. For example: **Dichlorodiphenyltrichloroethane (DDT) (an organochlorine insecticide)**: DDT exposure has been shown to alter DNA methylation patterns in genes involved in immune regulation, such as those encoding cytokines and transcription factors. This can result in long-lasting changes to immune function, even after pesticide exposure has ceased. DDT exposure during early life stages may increase the risk of developing allergies or autoimmune diseases later in life due to these epigenetic modifications.

4.6. Mitochondrial Dysfunction

Pesticides can damage mitochondria, the energy-producing organelles in cells, leading to reduced ATP production and impaired immune cell function. For example: **Rotenone (a botanical insecticide)**: Rotenone inhibits mitochondrial complex I, disrupting the electron transport chain and causing excessive ROS production. This mitochondrial dysfunction impairs the ability of immune cells, particularly lymphocytes and macrophages, to respond effectively to pathogens. Chronic rotenone exposure has been linked to immunosuppression and an increased risk of neurodegenerative diseases, likely due to its effects on mitochondrial health.

4.7. Interference with Cell Signaling Pathways

Pesticides can interfere with intracellular signaling pathways that regulate immune cell activation, proliferation, and differentiation. For example: **2,4-Dichlorophenoxyacetic acid (2,4-D) (a herbicide)**: 2,4-D disrupts nuclear factor-kappa B (NF-κB) signaling, a critical pathway for regulating immune responses. By inhibiting NF-κB activation, 2,4-D suppresses the production of pro-inflammatory cytokines and reduces the ability of immune cells to combat infections. Exposure

to 2,4-D has been associated with increased susceptibility to viral infections and delayed wound healing.

4.8. Autoimmune Triggering

Some pesticides can trigger autoimmune reactions by inducing molecular mimicry or breaking immune tolerance, leading to the production of autoantibodies against self-tissues. For example: **Paraquat (a herbicide)**: Paraquat exposure has been linked to the development of autoimmune diseases such as systemic lupus erythematosus (SLE). It induces oxidative stress and DNA damage, which may lead to the presentation of self-antigens to the immune system, triggering an autoimmune response. Paraquat also promotes the activation of autoreactive T-cells, further exacerbating autoimmune processes.

4.9. Inhibition of Phagocytic Activity

Some pesticides interfere with the cellular machinery required for phagocytosis, such as cytoskeletal rearrangement or receptor-mediated signaling. This inhibition reduces the ability of immune cells to recognize, engulf, and digest foreign particles or microbes. For example: **Organophosphates (e.g., chlorpyrifos)** have been shown to suppress phagocytic activity in macrophages by disrupting acetylcholinesterase activity and inducing oxidative stress, which impairs cellular function.

4.10. Impairment of Cellular Motility

Pesticides can affect the mobility of phagocytes, reducing their capacity to migrate toward sites of infection or inflammation. This impairment delays the clearance of pathogens and prolongs the inflammatory response. For example: **Pyrethroids (e.g., permethrin)** may disrupt calcium ion signaling, a key regulator of cell movement, thereby limiting the ability of phagocytes to reach target areas effectively.

4.11. Pesticides and Gut Microbiota

Exposure to Pesticides: Humans can be exposed to pesticides through contaminated food, water, air, or occupational exposure. These chemicals can enter the body and interact with the gut microbiota. Pesticides such as organophosphates, pyrethroids, and glyphosate have been shown to alter the composition and diversity of the gut microbiome in both animal models and humans.

They may promote dysbiosis (imbalance in microbial communities), reducing beneficial bacteria like Lactobacillus and Bifidobacterium while increasing harmful species like Escherichia coli or Clostridioides difficile. Some studies suggest that pesticide exposure can lead to decreased

microbial diversity, which is associated with various health issues. For example, glyphosate has been linked to impaired tryptophan metabolism, which affects serotonin production and contributes to inflammatory processes. Certain pesticides may also interfere with mitochondrial function in gut cells, further exacerbating oxidative stress and inflammation. Dysbiosis also leads to a reduced production of short-chain fatty acids (SCFAs) like butyrate, which are anti-inflammatory and essential for gut health.

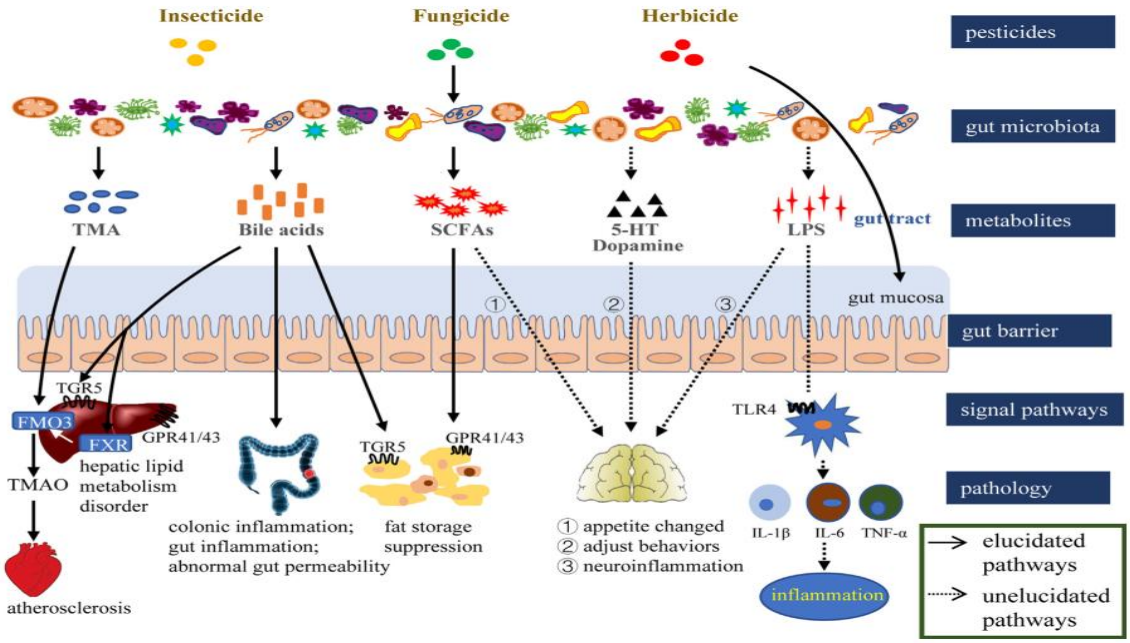

Figure 1 . Activation of immune cells, resulting in chronic low-grade inflammation.

5. Example of Immunotoxic Mechanisms of Permethrin

Permethrin is a synthetic pyrethroid insecticide widely used in agriculture, public health, and household applications to control pests such as mosquitoes, ticks, fleas, and lice. It acts primarily by targeting the nervous system of insects, causing hyperexcitation, paralysis, and death. However, permethrin can also have toxic effects on non-target organisms, including humans, particularly through its impact on the immune system. These effects may be due to the molecule or its common metabolites 3-phenoxybenzoic acid, 3-(4'-hydroxyphenoxy) benzoic acid and 3-phenoxybenzaldehyde.

5.1. Oxidative Stress and Inflammation

Permethrin exposure generates reactive oxygen species (ROS) and induces oxidative stress in cells. ROS can damage cellular components, including lipids, proteins, and DNA, leading to

inflammation and cell death. Immune cells, such as macrophages and lymphocytes, are particularly vulnerable to oxidative stress, which impairs their ability to function properly.

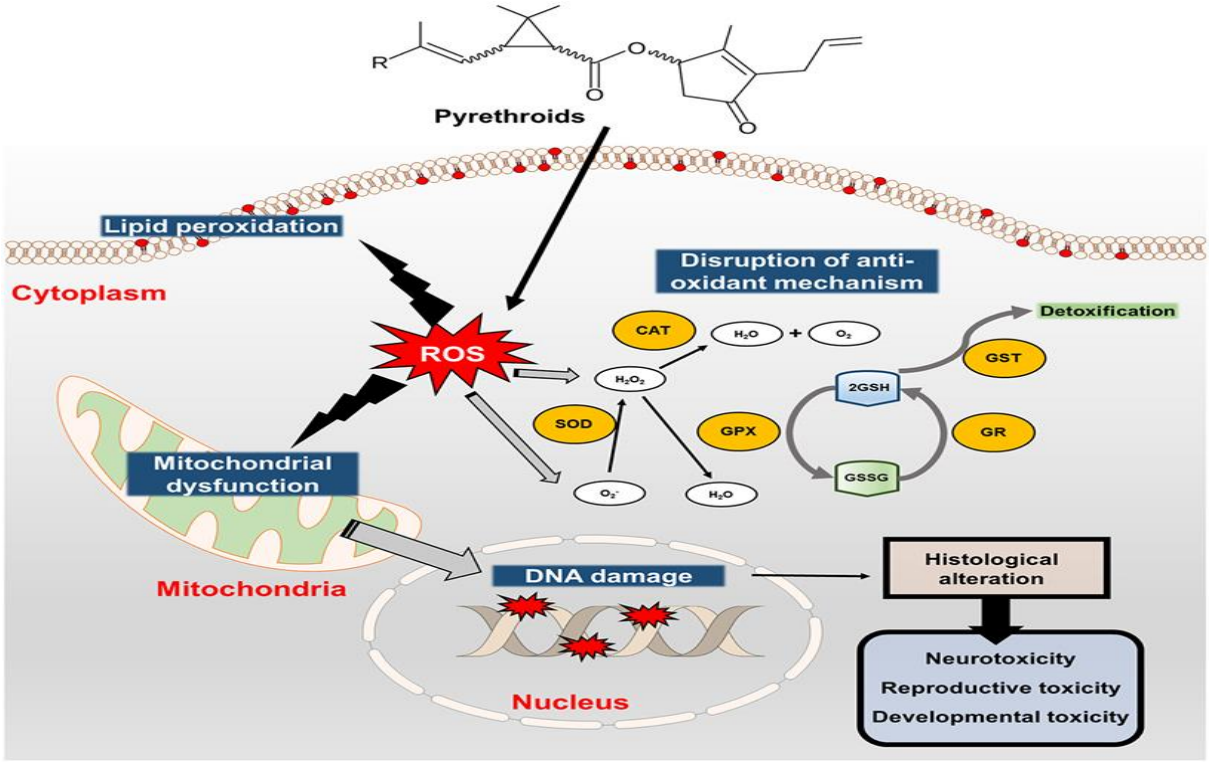

Figure 2. Reactive oxygen species-mediated cytotoxicity induced by pyrethroids

5.2. Suppression of Immune Cell Function

Permethrin has been shown to suppress the activity of key immune cells:

Macrophages : These phagocytic cells are less effective at engulfing and destroying pathogens after permethrin exposure.

Lymphocytes : Both B-cells (antibody producers) and T-cells (cell-mediated immunity) show reduced proliferation and activation when exposed to permethrin. Suppression of these cells compromises both humoral (antibody-based) and cell-mediated immunity, leaving the body more susceptible to infections.

5.3. Alteration of Cytokine Profiles

Permethrin exposure alters the production and balance of cytokines:

Pro-inflammatory cytokines : Increased levels of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β may lead to chronic inflammation.

Anti-inflammatory cytokines : Reduced levels of anti-inflammatory cytokines like IL-10 can impair the resolution of inflammation.

Imbalanced cytokine profiles can result in dysregulated immune responses, making the body more prone to autoimmune diseases or infections.

5.4. Epigenetic Modifications

Permethrin exposure can induce epigenetic changes, such as DNA methylation and histone modification, which alter gene expression in immune cells. These changes can persist long after exposure, potentially leading to lasting immunosuppression or heightened susceptibility to disease.

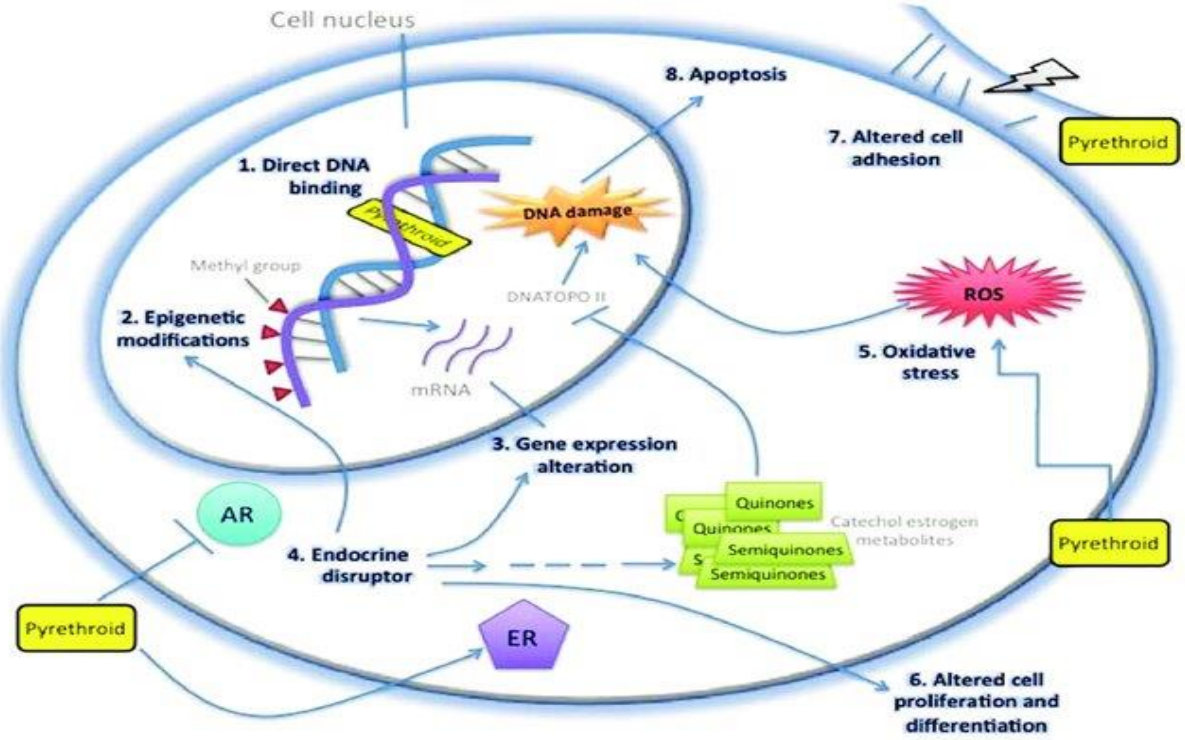

Figure 3 . Epigenic modification induced by pyrethroids.

5.5. Impact on Gut Microbiota

Emerging evidence suggests that permethrin exposure can disrupt the composition of gut microbiota, which plays a crucial role in regulating the immune system. Dysbiosis (imbalance in gut bacteria) can lead to impaired immune function, increased inflammation, and a higher risk of infections.

5.6. Apoptosis of Immune Cells

Permethrin exposure has been shown to induce apoptosis (programmed cell death) in immune cells, such as lymphocytes and macrophages. This reduction in immune cell numbers further weakens the immune response, making the body more vulnerable to pathogens.

5.7.Clinical Implications of Permethrin-Induced Immunotoxicity

Increased Susceptibility to Infections: Due to suppressed immune cell function and altered cytokine profiles, individuals exposed to permethrin may experience more frequent or severe infections.

5.7.1. Autoimmune Disorders

Chronic exposure to permethrin may contribute to the development of autoimmune diseases by disrupting immune tolerance and promoting abnormal immune responses against self-tissues.

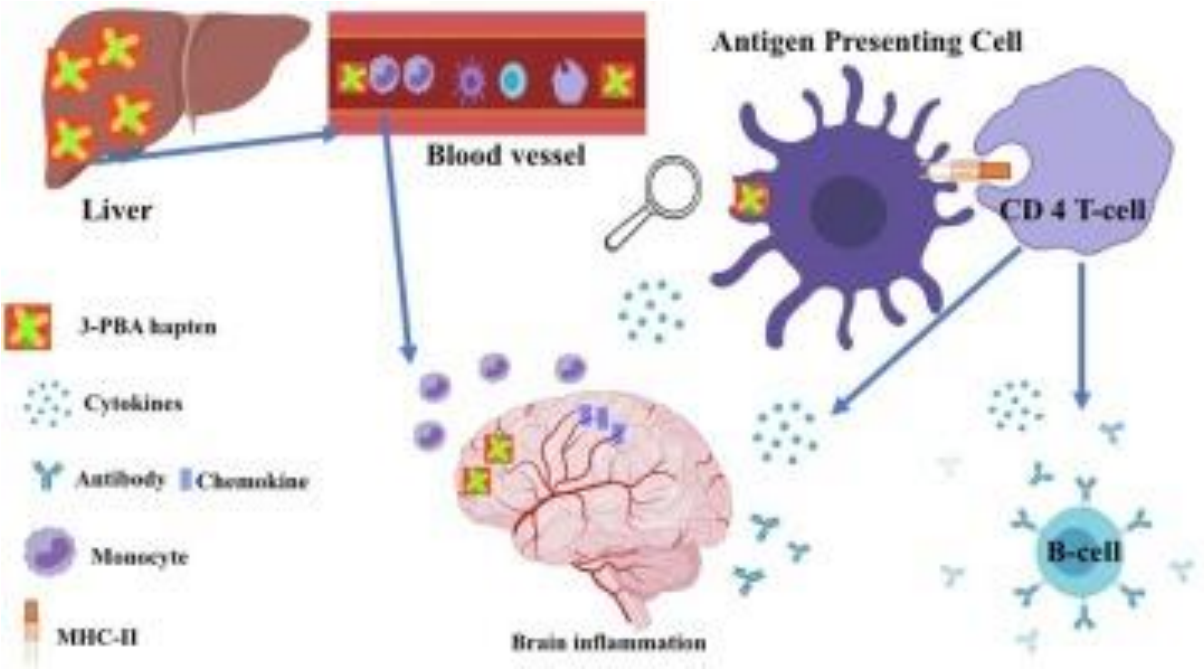

Figure 4 . Autoimmune disorders induced by pesticides.

5.7.2. Cancer Risk

Long-term immunosuppression caused by permethrin exposure could increase the risk of cancer, as the immune system plays a vital role in recognizing and eliminating cancerous cells.

6. Pyraclostrobin: Overview and Immunotoxic Mechanisms

Pyraclostrobin is a highly effective, broad-spectrum strobilurin fungicide, an agricultural pesticide used to kill fungi.

Pyraclostrobin, a widely used strobilurin fungicide, has been shown to exert significant immunotoxic effects through mechanisms involving oxidative stress, mitochondrial dysfunction, and inflammatory responses.

Exposure to pyraclostrobin disrupts intestinal integrity and increases permeability in carp, leading to compromised gut health and dysbiosis, which are critical precursors to immune system overactivation. Furthermore, studies indicate that this fungicide induces oxidative stress and

apoptosis in various organisms, which causes liver degeneration and steatosis, thereby impairing detoxification processes crucial to immune regulation. In mammals, pyraclostrobin-mediated inhibition of mitochondrial respiration not only impairs energy metabolism but also exacerbates immune dysfunction by triggering inflammatory pathways. These cumulative effects highlight the potential for pyraclostrobin to compromise the immune system or induce autoimmune disorders, as excessive cytokine release and immune overactivation can occur with prolonged exposure.

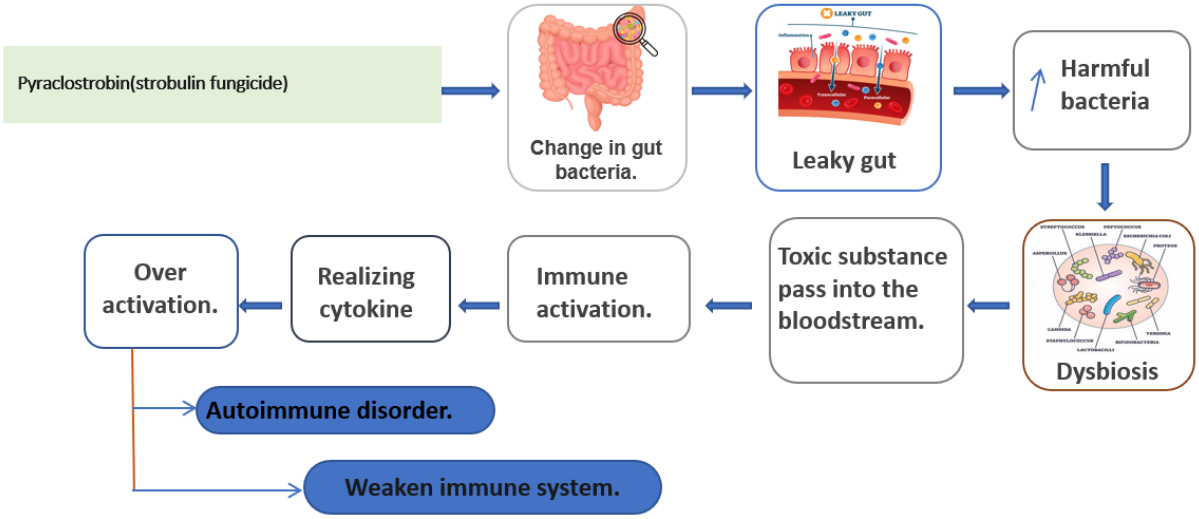

Figure 5 . Immune toxicity induced by pyraclostrobin pesticide.

Immunotoxicity of heavy metals

1. Introduction

Immunotoxicology of heavy metals is a complex field that explores how these toxic elements disrupt the immune system. Heavy metals induce immunotoxicity through several intricate mechanisms, each with its own set of biological processes and consequences. Below, we delve deeply into these mechanisms, providing detailed explanations and examples to illustrate their effects on human health.

Heavy metals are potent inducers of oxidative stress, which arises from an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense systems. ROS include superoxide radicals, hydrogen peroxide, and hydroxyl radicals, which can damage cellular components such as lipids, proteins, and DNA. Heavy metals contribute to oxidative stress in two primary ways: by directly generating ROS and by depleting antioxidants.

For example, lead (Pb) increases lipid peroxidation in immune cells, impairing membrane integrity and disrupting normal cell function. Studies conducted on rats exposed to lead have shown elevated levels of malondialdehyde (MDA), a marker of oxidative damage. Similarly, cadmium (Cd) induces mitochondrial dysfunction, leading to excessive ROS production. This oxidative stress not only damages mitochondria but also triggers apoptosis (programmed cell death) in immune cells, further weakening the immune response.

Another example is mercury (Hg), particularly methylmercury, which accumulates in neurons and immune cells. Mercury exposure has been shown to increase the production of hydrogen peroxide and decrease glutathione levels, a critical intracellular antioxidant. The resulting oxidative stress contributes to neuroinflammation and impaired immune signaling pathways.

In addition to direct ROS generation, heavy metals interfere with the activity of enzymes involved in detoxification processes. For instance, arsenic (As) inhibits the enzyme glutathione reductase, reducing the availability of reduced glutathione, which is essential for neutralizing free radicals. This enzymatic inhibition exacerbates oxidative stress and leads to widespread cellular damage.

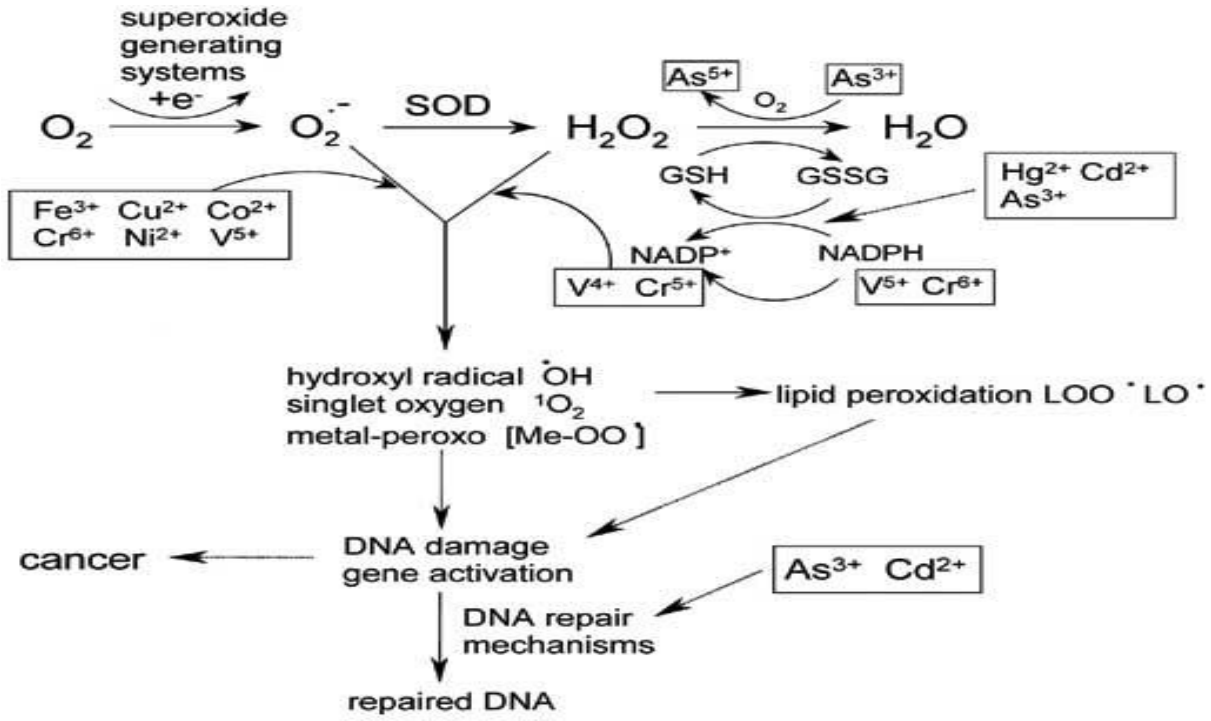

Figure 6 . Reactive oxygen species generation by heavy metals.

Heavy metals exert profound effects on immune cell function by interfering with the development, activation, and effector functions of various immune cell types. These disruptions can lead to both immunosuppression and dysregulated immune responses.

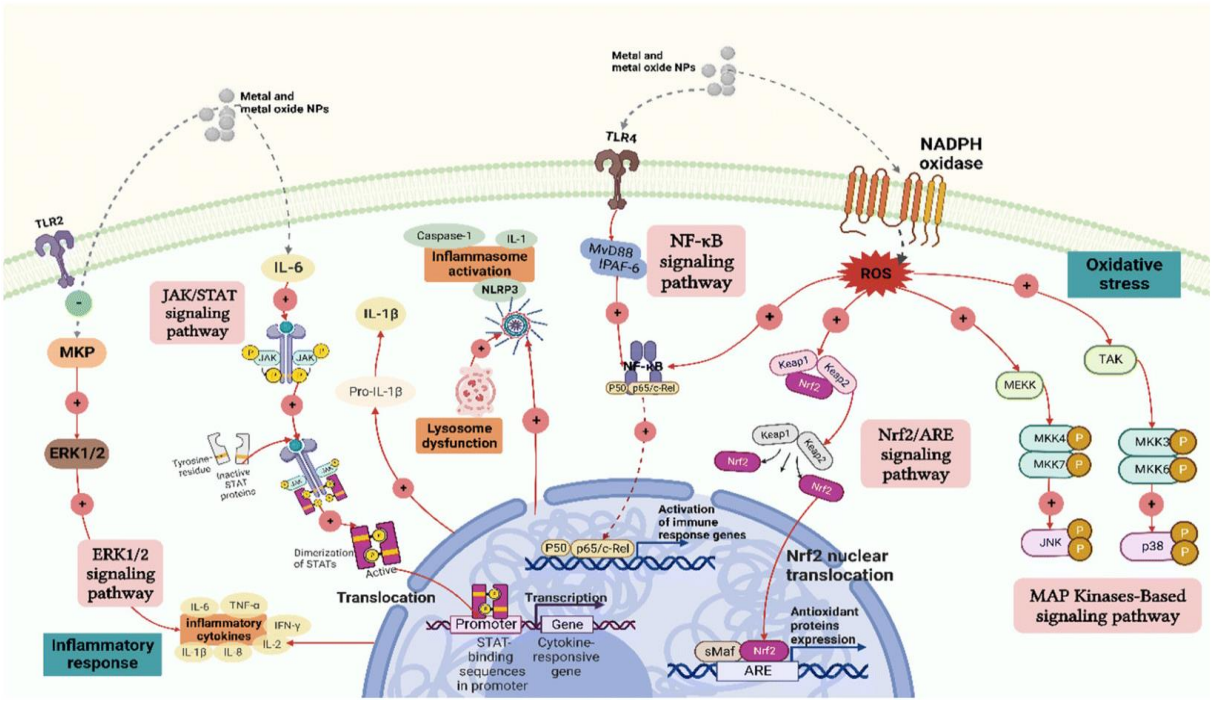

Figure 7 . Immune function disruption by heavy metals.

2. Effects of heavy metals on the immune system

2.1. Effects on immune cells

T cells, a critical component of adaptive immunity, are particularly vulnerable to heavy metal toxicity. Exposure to mercury (Hg) reduces the number of CD4+ T helper cells, which play a key role in coordinating immune responses against pathogens. Mercury also impairs the ability of T cells to produce cytokines like interferon-gamma (IFN-γ), which is necessary for controlling viral infections and activating macrophages. In experimental models, mice exposed to mercury exhibit significantly reduced T-cell proliferation and impaired delayed-type hypersensitivity reactions, indicating compromised cellular immunity.

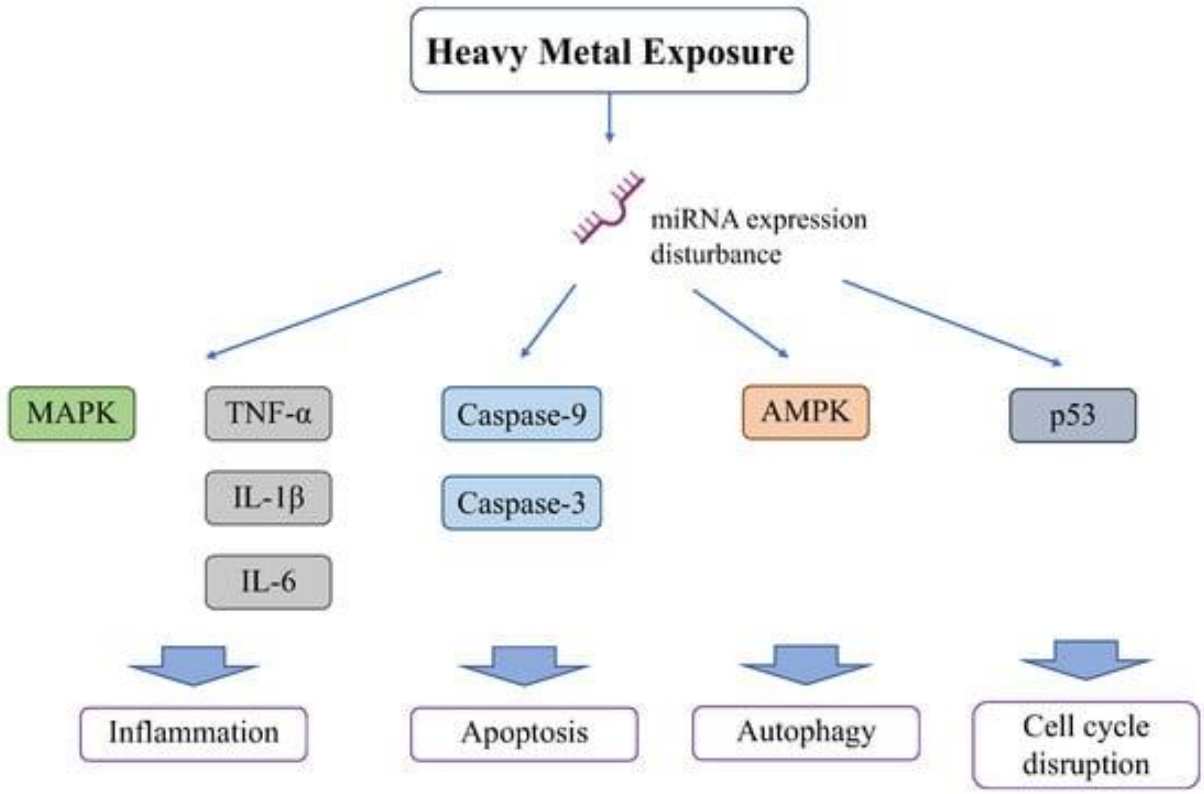

Figure 8 . **Mechanisms of action of induced immune toxicity by heavy metal exposure.**

B cells, responsible for producing antibodies during humoral immune responses, are similarly affected. Lead (Pb) exposure increases the levels of immunoglobulins IgG and IgM in serum. Lead achieves this by enhancing B-cell maturation and antibody secretion, leaving the host more susceptible to auto immune disorders.

Macrophages, key players in innate immunity, are also targeted by heavy metals. Cadmium (Cd) exposure impairs phagocytic activity, reducing the ability of macrophages to engulf and destroy bacteria. Cadmium does so by disrupting lysosomal function and inhibiting the production of reactive nitrogen intermediates, such as nitric oxide, which are crucial for microbial killing.

Furthermore, cadmium-exposed macrophages show decreased expression of major histocompatibility complex class II (MHC-II) molecules, impairing their capacity to present antigens to T cells.

Natural killer (NK) cells, part of the innate immune system, are responsible for recognizing and eliminating infected or transformed cells. Heavy metals like arsenic (As) reduce NK cell cytotoxicity, diminishing their ability to lyse target cells. This suppression leaves the host vulnerable to viral infections and cancer progression. Arsenic exposure has been linked to reduced perforin and granzyme B expression in NK cells, which are essential mediators of target cell lysis.

2.2. Effects on cytokines liberation

Cytokines are small signaling proteins that regulate immune responses by promoting communication between immune cells. Heavy metals alter cytokine profiles, leading to either pro-inflammatory or immunosuppressive states, depending on the specific metal and dose.

Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), are often upregulated following heavy metal exposure. For instance, lead (Pb) increases the production of TNF-α and IL-6, contributing to chronic inflammation. Chronic inflammation is associated with numerous diseases, including cardiovascular disorders, diabetes, and autoimmune conditions. In children, lead-induced inflammation has been linked to developmental delays and behavioral problems.

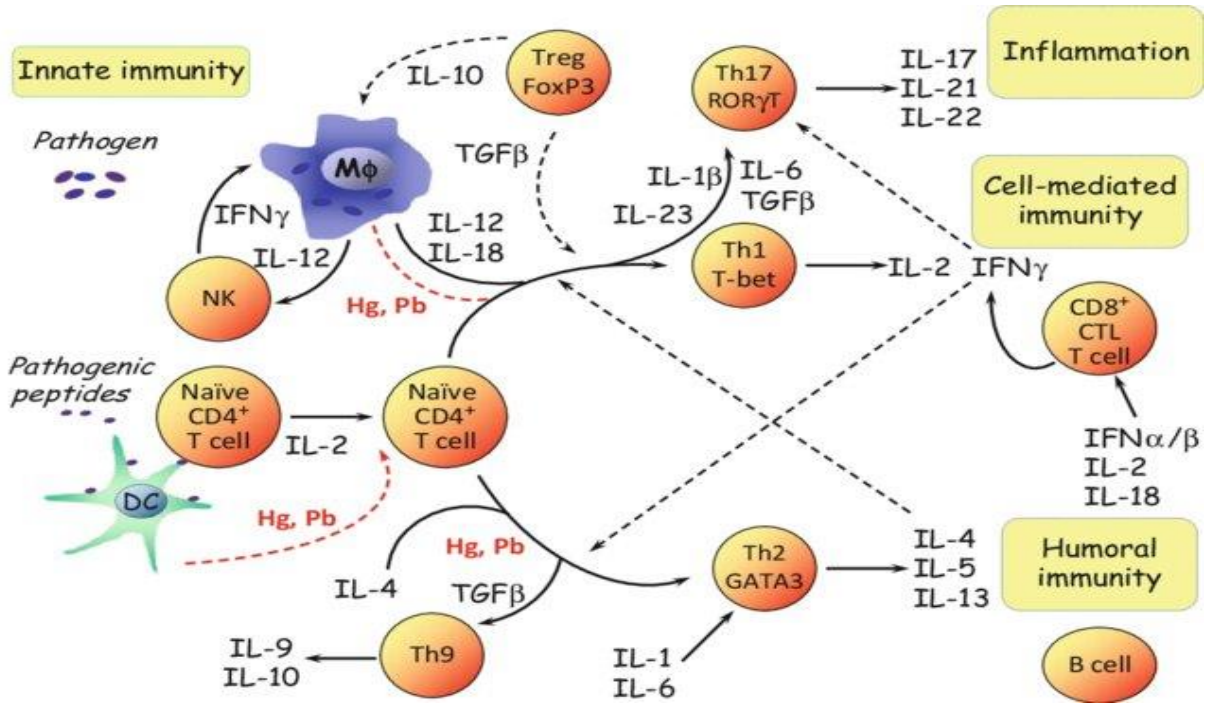

Figure 9 . Effects of heavy metals on innate and adaptive immune cells.

On the other hand, some heavy metals suppress anti-inflammatory cytokines, disrupting the delicate balance required for proper immune regulation. Cadmium (Cd) exposure reduces the production of interleukin-10 (IL-10), an important anti-inflammatory cytokine. This reduction promotes a state of persistent inflammation, which can lead to tissue damage and increased susceptibility to autoimmune diseases.

Moreover, heavy metals modulate cytokine networks in ways that affect immune cell differentiation and function. For example, chromium (Cr VI) exposure alters the balance between Th1 and Th2 cytokines, favoring a Th2-biased response. A Th2-dominant profile is associated with allergic reactions and parasitic infections, while suppressing effective responses against intracellular pathogens.

2.3. Genetic and epigenetic modification

Epigenetic modifications refer to changes in gene expression that do not involve alterations to the underlying DNA sequence. Heavy metals induce epigenetic changes through mechanisms such as DNA methylation, histone modification, and microRNA regulation. These changes can have long-lasting effects on immune function and disease susceptibility.

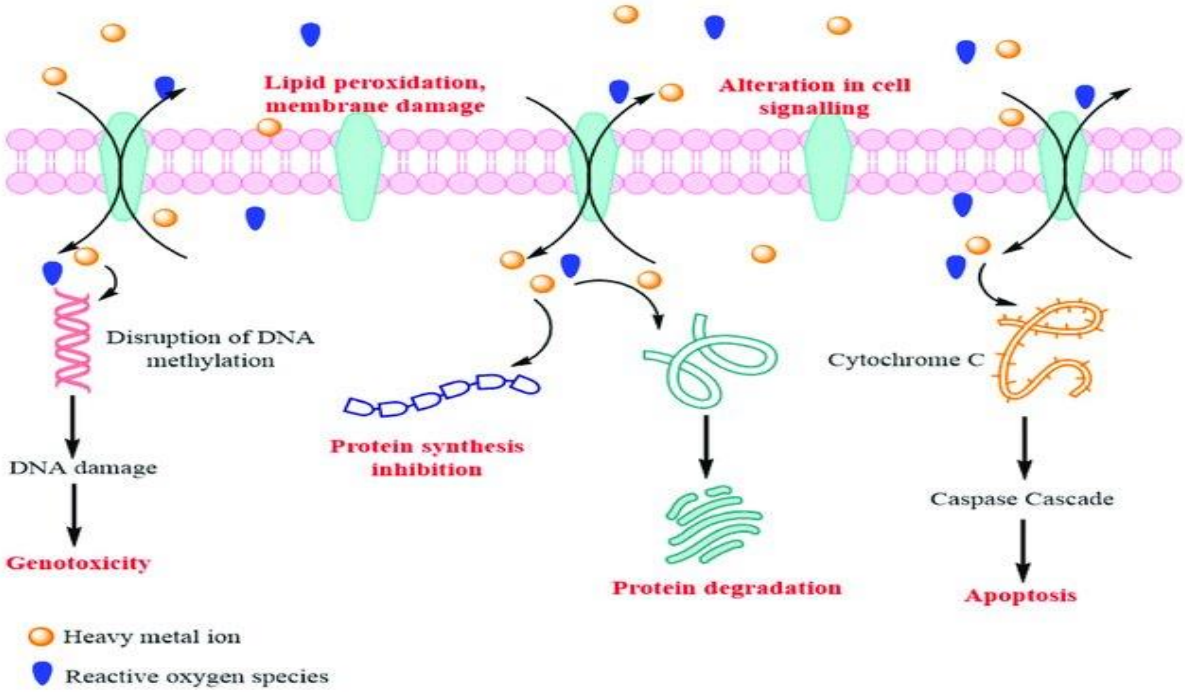

Figure 10 . Effects of heavy metals on protein synthesis in immune cells.

DNA methylation is one of the most well-studied epigenetic modifications influenced by heavy metals. Methylation involves the addition of a methyl group to cytosine residues in DNA, typically silencing gene expression. Arsenic (As) exposure increases DNA methylation of tumor suppressor

genes, such as p53 and RASSF1A, rendering them nonfunctional. This epigenetic silencing contributes to carcinogenesis by allowing uncontrolled cell growth and division.

Histone modifications, another form of epigenetic regulation, involve chemical alterations to histone proteins around which DNA is wrapped. These modifications influence chromatin structure and accessibility, thereby regulating gene transcription. Chromium (Cr VI) exposure alters histone acetylation patterns, affecting the expression of immune-related genes. For example, chromium exposure decreases histone H3 acetylation at promoters of genes involved in inflammatory responses, leading to altered cytokine production.

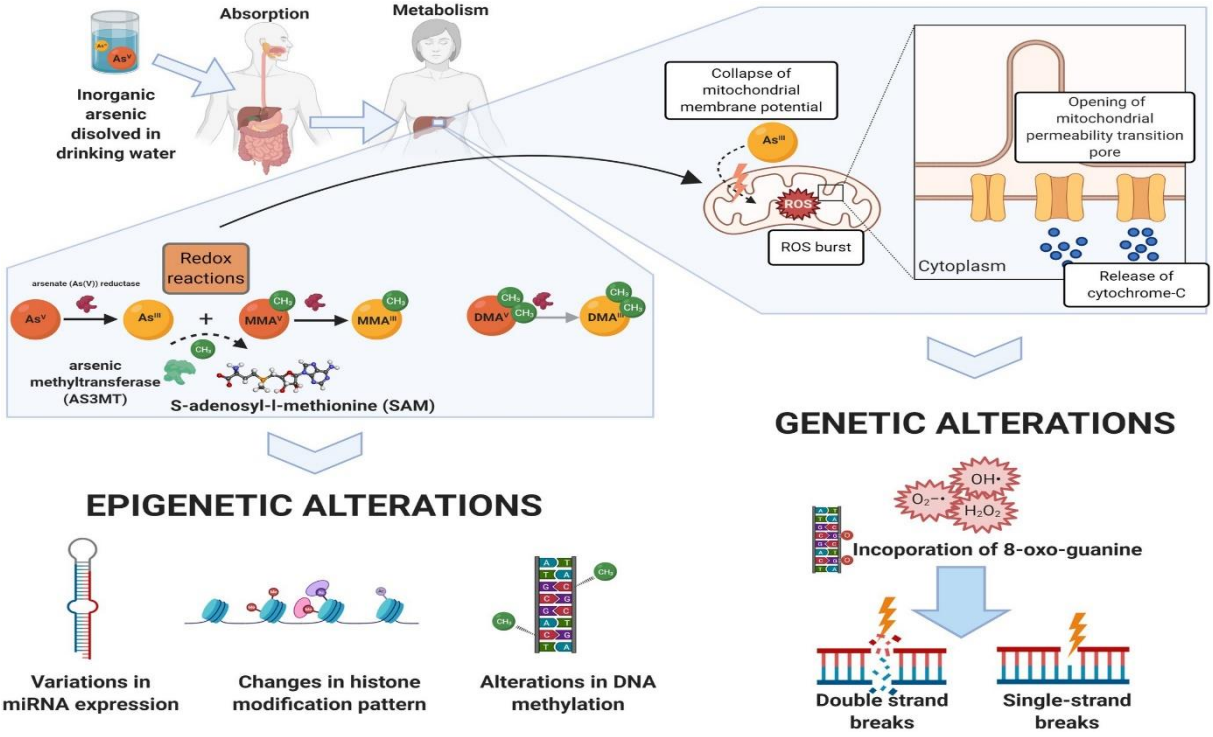

Figure 11 . Genetic and epigenetic modifications induced by heavy metals.

MicroRNAs (miRNAs) are short non-coding RNAs that regulate gene expression post-transcriptionally by binding to messenger RNA (mRNA) targets. Heavy metals regulate miRNA expression, influencing immune responses. Lead (Pb) exposure upregulates miR-155, a microRNA known to play a central role in immune regulation. Elevated miR-155 levels are associated with inflammation and autoimmune diseases, highlighting the potential of heavy metals to drive pathological immune responses via miRNA-mediated mechanisms.

Autoimmunity occurs when the immune system mistakenly attacks self-tissues, leading to chronic inflammation and tissue damage. Heavy metals can induce autoimmunity by breaking immune tolerance or through molecular mimicry, where foreign antigens resemble self-antigens, triggering an immune response against the body's own tissues.

2.4. Effect on antigen presentation

One mechanism by which heavy metals induce autoimmunity is through the alteration of self-antigens. For example, mercury (Hg) binds to proteins, modifying their structure and making them recognizable as foreign by the immune system. This process has been implicated in the development of systemic lupus erythematosus (SLE), a prototypical autoimmune disease characterized by the presence of autoantibodies against nuclear antigens. Experimental studies have demonstrated that mercury exposure induces autoantibody production in genetically susceptible animal models.

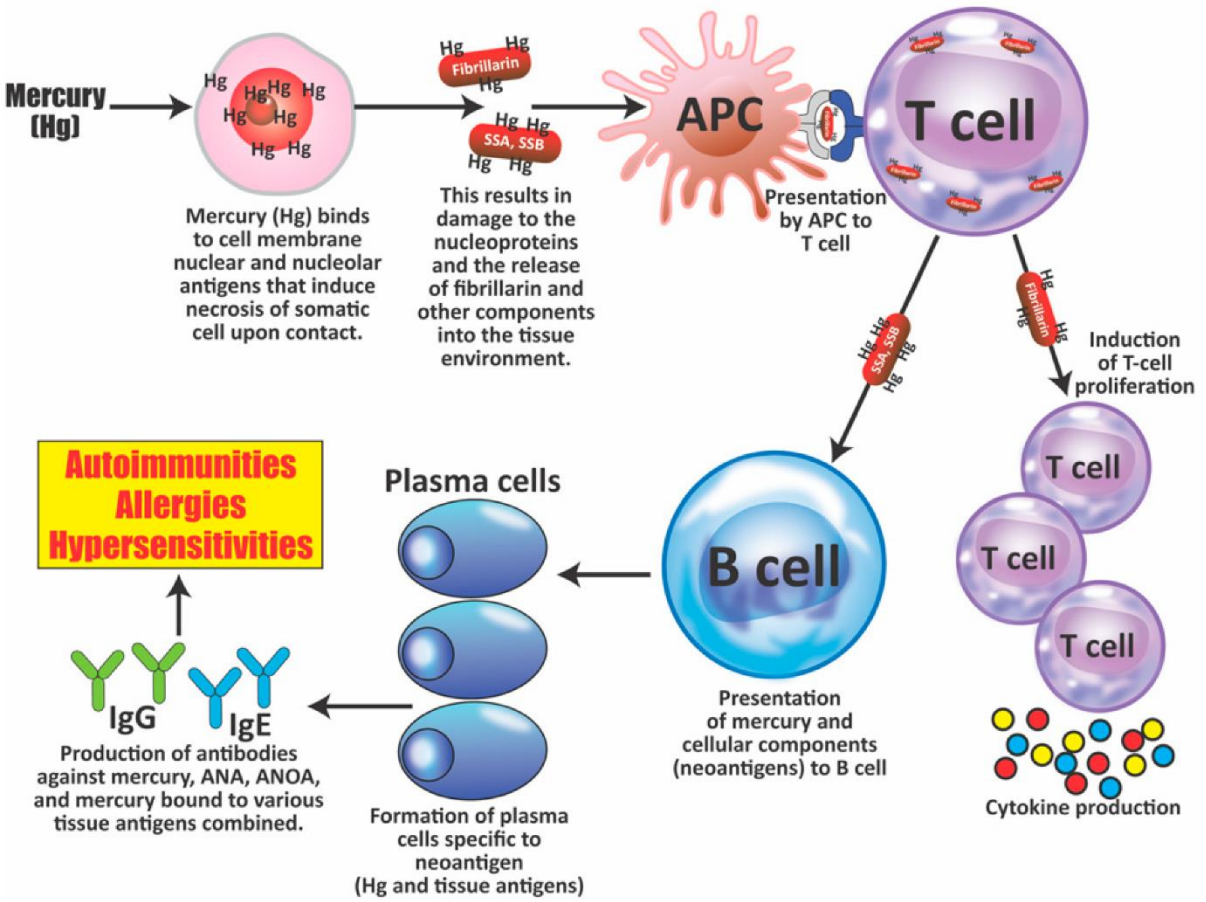

Figure 12 . Alteration of antigen presenting by heavy metals.

Molecular mimicry is another mechanism by which heavy metals trigger autoimmunity. Silica particles, although not a classic heavy metal, serve as an illustrative example. Silica exposure induces autoantibodies against double-stranded DNA, similar to those seen in SLE patients. This phenomenon suggests that environmental exposures, including heavy metals, may contribute to the pathogenesis of autoimmune diseases by mimicking self-antigens.

Heavy metals also promote autoimmunity by altering regulatory T cell (Treg) function. Tregs are specialized immune cells that maintain immune tolerance and prevent autoimmunity. Exposure to cadmium (Cd) reduces Treg numbers and impairs their suppressive function, tipping the balance

toward autoimmunity. This effect has been observed in both animal models and human populations exposed to high levels of cadmium.

3. Examples of induced immunotoxicity by heavy metals

3.1. Lead heavy metal immunotoxicity

likely lead (Pb), which enters cells via calcium channels and subsequently disrupts immune function through multiple pathways. Upon entry, the substance binds to cell surfaces and inhibits δ-aminolaevulinic acid dehydratase, leading to increased reactive oxygen species (ROS) production and oxidative stress in immune cells. This oxidative stress damages mitochondrial membranes, elevates mitochondrial ROS (mtROS), and triggers apoptosis. The innate immune system is affected through the activation of the NF-κB pathway, resulting in the upregulation of pro-inflammatory cytokines such as IL-4, IL-1β, TNF-α, and IL-6, while simultaneously suppressing phagocytic activity and reducing levels of IL-2 and IFN-γ. In the adaptive immune system, the substance impairs the CD4+/CD8+ ratio, suppresses MHC II expression, and weakens TH1 and TH2 responses, ultimately inhibiting humoral immunity, including IgA and IgG production. These disruptions culminate in adverse health outcomes, including immunodeficiency, autoimmune disorders, and an increased risk of cancer, underscoring the potential for chronic exposure to induce systemic immune dysfunction.

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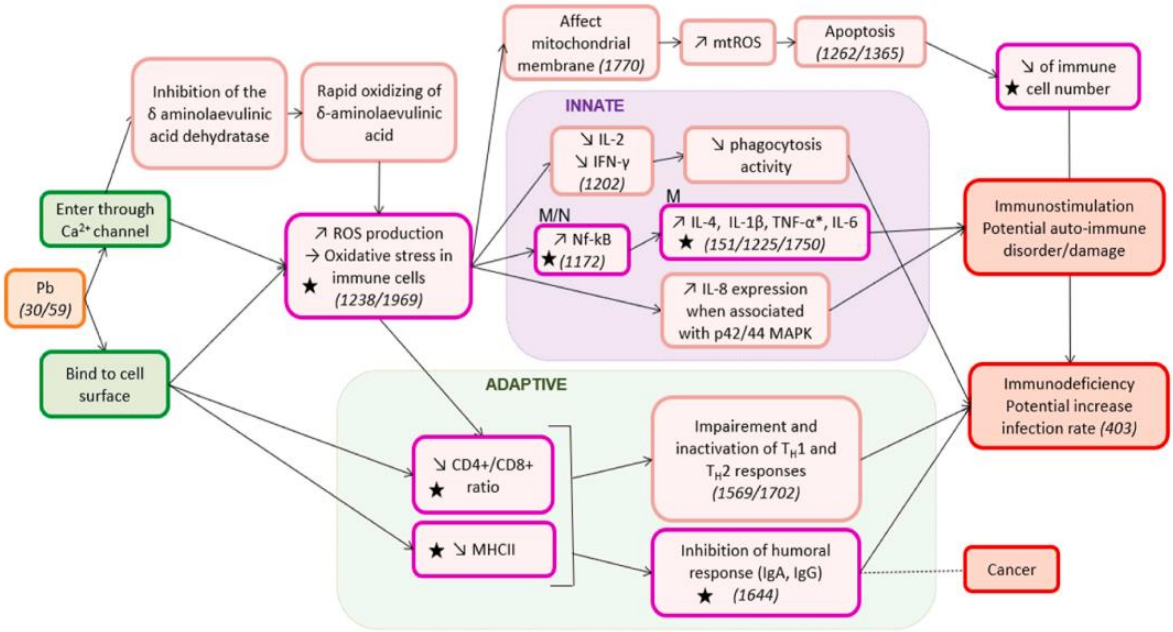


Figure 13 . Mechanism of action of lead on the immune system.

3.2. Cadmium heavy metal immunotoxicity

Cadmium (Cd) , a toxic heavy metal, on both the innate and adaptive immune systems. Upon exposure, Cd enters immune cells and induces oxidative stress by increasing reactive oxygen species (ROS) production, which disrupts mitochondrial function and leads to mitochondrial membrane damage. This oxidative stress further amplifies immune dysfunction by triggering apoptosis and impairing critical cellular processes. In the innate immune system, Cd suppresses phagocytic activity and reduces the production of key cytokines such as IL-2 and IFN-γ, while simultaneously activating the NF-κB pathway, resulting in excessive pro-inflammatory cytokine release, including IL-1β, TNF-α, and IL-6. In the adaptive immune system, Cd disrupts the balance of CD4+/CD8+ T cells, inhibits MHC II expression, and impairs TH1 and TH2 responses, leading to reduced humoral immunity, as evidenced by decreased IgA and IgG production. These cumulative effects contribute to adverse health outcomes, including immunodeficiency, autoimmune disorders, and an increased risk of cancer, highlighting the broad-ranging impact of Cd-induced immunotoxicity

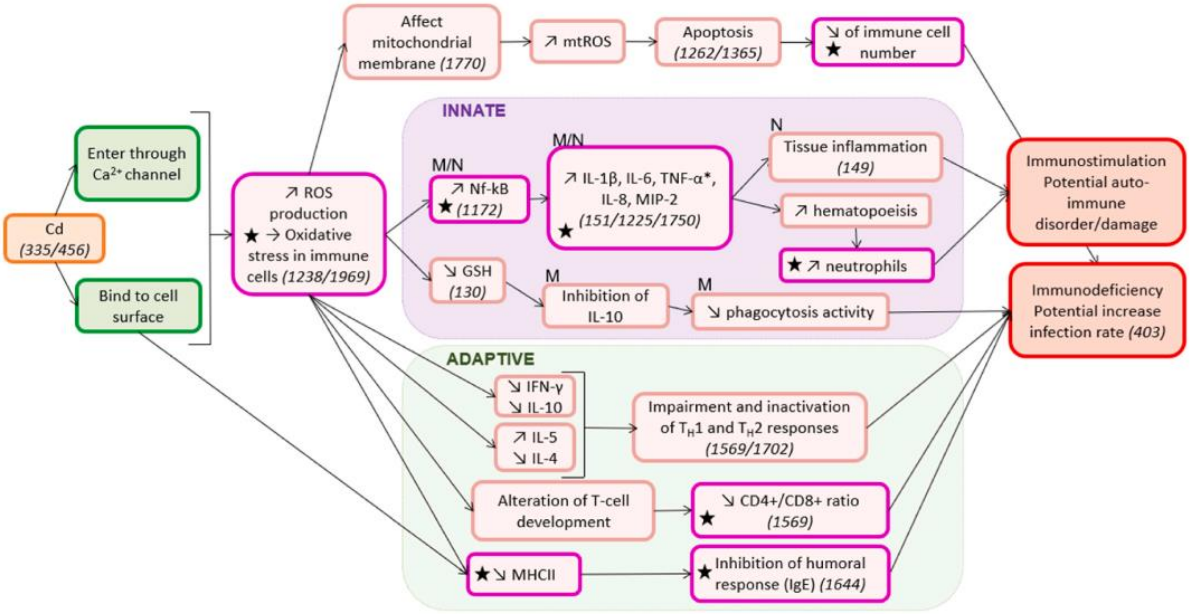


Figure 14 . Mechanism of action of cadmium on the immune system.

3.3. Combined immunotoxicity of Pb and Cd

combined immunotoxic effects of cadmium (Cd) and lead (Pb) on both innate and adaptive immune systems, emphasizing their synergistic mechanisms of action. Upon simultaneous exposure, Cd and Pb enter cells via calcium channels, where they induce oxidative stress by increasing reactive oxygen species (ROS) production. This oxidative stress damages mitochondrial

membranes, leading to elevated mitochondrial ROS (mtROS) levels, which subsequently trigger apoptosis and reduce immune cell viability. In the innate immune system, these metals activate the NF-κB pathway, upregulating pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and MIP-2, thereby promoting tissue inflammation and hematopoiesis. Simultaneously, they suppress phagocytic activity by inhibiting anti-inflammatory cytokines like IL-10, impairing pathogen clearance. In the adaptive immune system, Cd and Pb disrupt the balance of TH1 and TH2 responses, reduce CD4+/CD8+ T-cell ratios, and inhibit MHC II expression, compromising antigen presentation and T-cell activation. Furthermore, humoral immunity is weakened through the inhibition of IgE production, critical for allergic reactions and parasite defense. The cumulative effects of these disruptions result in immunodeficiency, characterized by increased susceptibility to infections, autoimmune disorders due to excessive immune stimulation, and an elevated risk of cancer linked to chronic inflammation and immune dysfunction. These findings underscore the importance of addressing co-exposure to Cd and Pb as a significant public health concern.

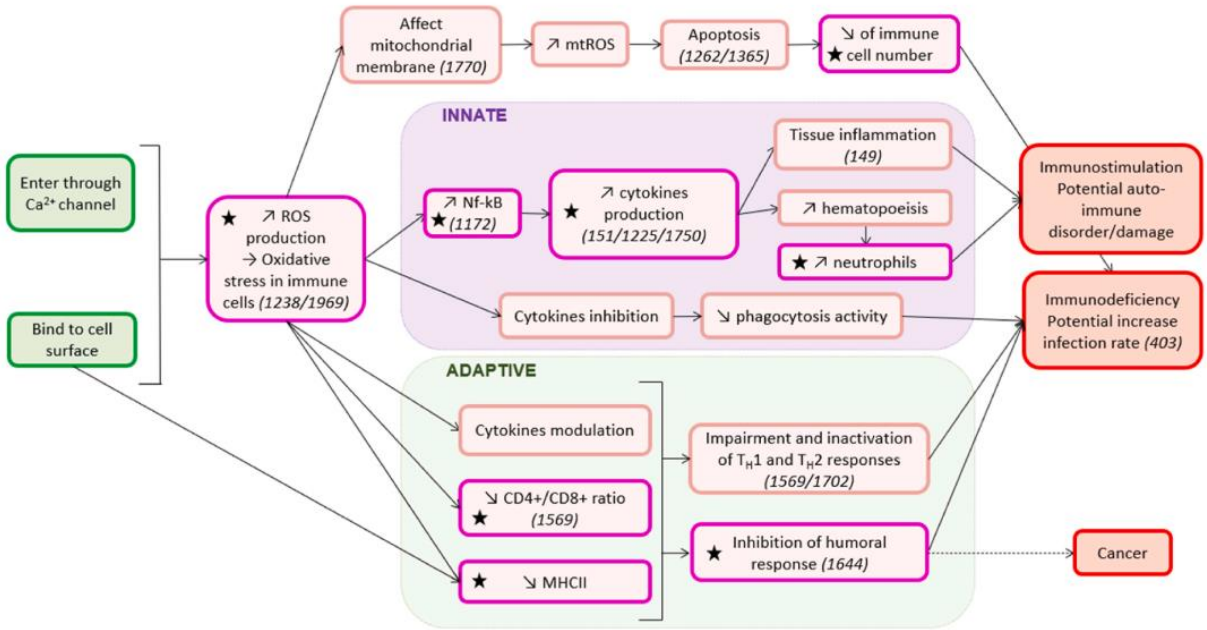


Figure 15 . Mechanism of action of combination of cadmium and lead on the immune system.

Nutrition and Immunity

1. Introduction

The intestinal immune system comprises a wide variety of cell types. It can be broadly divided into an innate component (epithelial cells and antigen-presenting cells) and an adaptive component (lymphocytes). The adaptive component is further split into inductive sites (e.g., Peyer's patches and isolated lymphoid follicles) and effector sites (immune cells throughout the mucosa).

1.1. Innate Immunity

Intestinal Epithelium:

The intestinal epithelium balances nutrient absorption with defense against environmental threats. It acts as a physical and chemical barrier.

Physical barrier: Tight junctions (sealing gaps between epithelial cells) and mucus (produced by goblet cells).

Chemical barrier: Antimicrobial peptides (e.g., defensins), synthesized constitutively or in response to microbial signals. Paneth cells, located in crypts, specialize in producing these peptides.

Innate Immunity Receptors:

Pathogen-associated molecular patterns (PAMPs), such as LPS, double-stranded RNA, and flagellin, are recognized by pattern recognition receptors (PRRs) like Toll-like receptors (TLRs). Activation of PRRs triggers intracellular signaling, leading to antimicrobial peptide production, pro-inflammatory cytokine secretion, and immune cell recruitment.

Antigen-Presenting Cells (APCs):

Dendritic cells and macrophages in the lamina propria sample luminal antigens (via dendrites) and bridge innate and adaptive immunity.

Luminal antigens are captured via Peyer's patches, dendritic cells extending into the lumen, or directly by epithelial cells.

Other Immune Cells:

Intraepithelial lymphocytes (IELs): CD8+ T cells with cytotoxic activity and IFN-γ production, located among epithelial cells.

Innate lymphoid cells (ILCs): Antigen-non-specific cells resembling T effector cells, contributing to infection defense and gut homeostasis through cytokine secretion.

1.2. Immune Tolerance to Food Antigens:

The human immune system faces the dual challenge of recognizing foreign antigens while maintaining tolerance to harmless dietary components. This delicate balance is achieved through a network of cellular and molecular mechanisms that prevent inappropriate immune responses to food, a process termed oral tolerance. Disruption of these mechanisms can lead to food allergies, autoimmune reactions, or chronic inflammation. Below, we review the key pathways and factors governing food antigen tolerance.

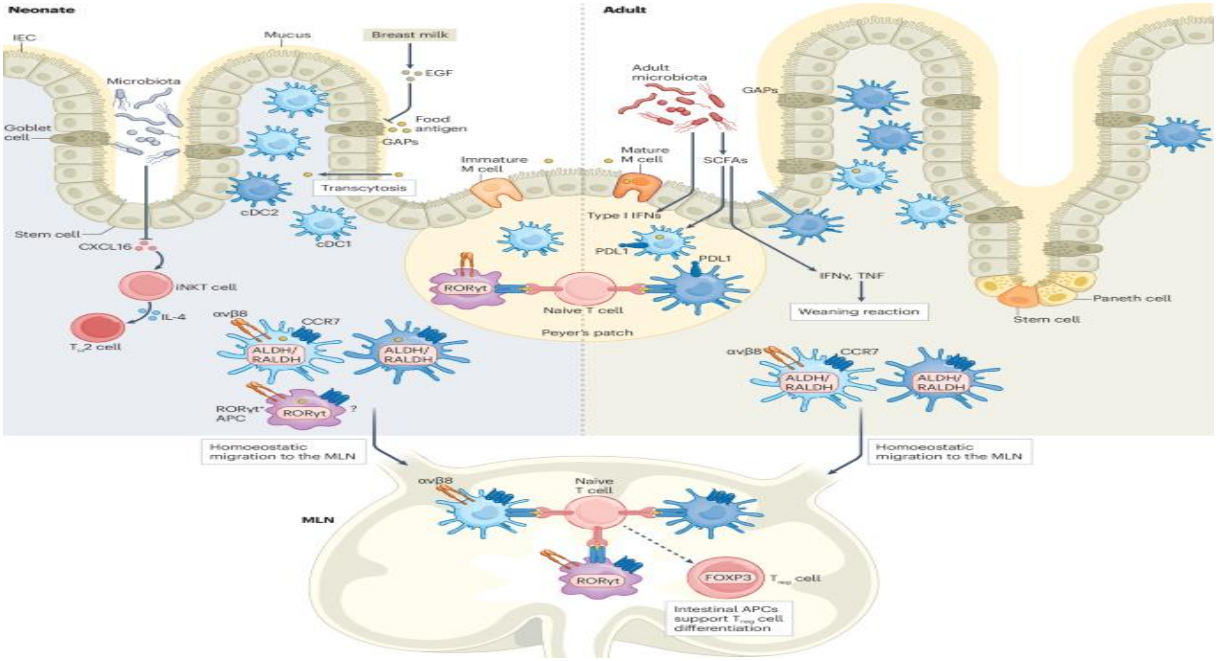


Figure 16 . Mechanism of immune tolerance to food antigens

1.2.1. Mechanisms of Oral Tolerance

Oral tolerance is primarily mediated by the gut-associated lymphoid tissue (GALT), where dietary antigens are sampled and processed. The dose of antigen exposure dictates the immune response:

Low-dose antigen exposure induces regulatory T cells (Tregs), which suppress effector T-cell activity via cytokines like IL-10 and TGF-β, promoting systemic tolerance.

High-dose exposure leads to clonal deletion or anergy of antigen-specific T cells, rendering them unresponsive.

Dendritic cells (DCs) and intestinal epithelial cells (IECs) play pivotal roles in antigen presentation. In steady-state conditions, DCs in the gut capture luminal antigens and migrate to mesenteric lymph nodes, where they induce Treg differentiation. This process is facilitated by retinoic acid, a metabolite of vitamin A, which enhances Treg stability.

Role of Antigen-Presenting Cells (APCs)

APCs, particularly DCs and macrophages, are central to distinguishing tolerance from allergy. In tolerant states, DCs exhibit a tolerogenic phenotype, characterized by low co-stimulatory molecule expression and high production of anti-inflammatory cytokines. These DCs instruct naïve T cells to differentiate into pTregs (peripherally induced Tregs), which suppress IgE-mediated allergic responses. Conversely, inflammatory signals (e.g., from infections or dysbiosis) reprogram DCs to promote TH2 polarization, driving IgE production and allergy.

Gut and Microbiota

The gut microbiota further modulates tolerance by metabolizing dietary fibers into short-chain fatty acids (SCFAs), which enhance Treg activity and reinforce epithelial integrity.

1.2.2. Breakdown of Tolerance: Allergy and Autoimmunity

Failure to establish or maintain oral tolerance results in food allergies or autoimmune disorders. For example:

Cutaneous sensitization (e.g., via skin exposure to peanut proteins) bypasses the gut's tolerogenic pathways, favoring TH2-driven IgE responses.

Dysbiosis (e.g., antibiotic-induced depletion of Clostridia species) reduces SCFA production, impairing Treg induction and increasing allergy risk.

In autoimmune conditions like celiac disease, gluten peptides trigger T-cell activation due to loss of tolerance, highlighting the interplay between genetic predisposition and environmental triggers.

2. Complex interactions between nutrition and immunity

The immune system and nutrition are inextricably linked, with diet serving as both a modulator of immune function and a substrate for immune cell activity. Nutrients provide energy and structural components for immune cells, regulate inflammatory pathways, and maintain the integrity of physical barriers such as the gut epithelium. Conversely, immune activation during infection or chronic inflammation alters metabolic demands, creating a dynamic interplay between nutrient availability and immune responsiveness. The gut microbiota, shaped by dietary intake, acts as a critical intermediary, metabolizing nutrients into bioactive compounds that influence systemic immunity. For example, fiber fermentation by gut bacteria produces short-chain fatty acids (SCFAs), which regulate T-cell differentiation and suppress pro-inflammatory cytokines. This review explores the multifaceted roles of macronutrients, micronutrients, dietary patterns, and food components in immune regulation, emphasizing their sources, mechanisms, and clinical relevance.

2.1. Macronutrients

Proteins are indispensable for immune competence, serving as the building blocks for antibodies, cytokines, and cell membrane receptors. Amino acids like glutamine, arginine, and cysteine are conditionally essential during immune challenges. Glutamine, abundant in eggs, dairy, and legumes, supports lymphocyte proliferation and intestinal epithelial repair by enhancing tight junction integrity. Protein-energy malnutrition leads to thymic atrophy, reduced CD4+ T-cell counts, and impaired phagocytic activity, increasing susceptibility to infections.

Dietary fats influence membrane fluidity, eicosanoid production, and inflammatory signaling. Omega-3 and monounsaturated fatty acids (MUFAs) exhibit distinct immunomodulatory effects across various immune cells. In neutrophils, MUFAs and n-3 polyunsaturated fatty acids (PUFAs) increase the expression of LFA-1, a beta2-integrin critical for cell adhesion and migration. In macrophages, FFA 18:3 (alpha-linolenic acid), an n-3 PUFA, enhances phagocytosis, enabling more efficient engulfment of pathogens, while also increasing the production of TNF-α, a pro-inflammatory cytokine. Dendritic cells respond to FFA 20:5 (eicosapentaenoic acid) by promoting lymph node infiltration and elevating the production of cytokines such as IL-12, IL-6, and IL-10, which play roles in both inflammation and resolution. T-cells are influenced by FFA 22:6 (docosahexaenoic acid), which modulates TH1 responses, while FFA 18:1 (oleic acid) regulates T-cell proliferation and activation. Mast cells demonstrate modulation of inflammasome components like NLRP3, as well as cytokines such as IL-1β, IL-6, and TNF-α, alongside altered activation levels.

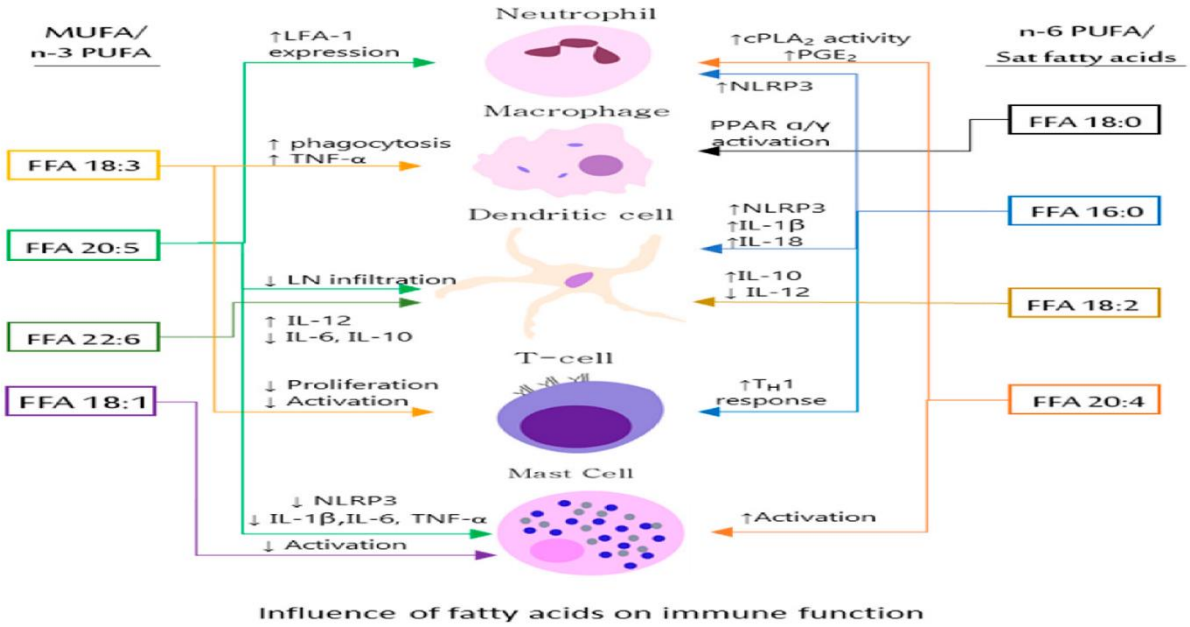
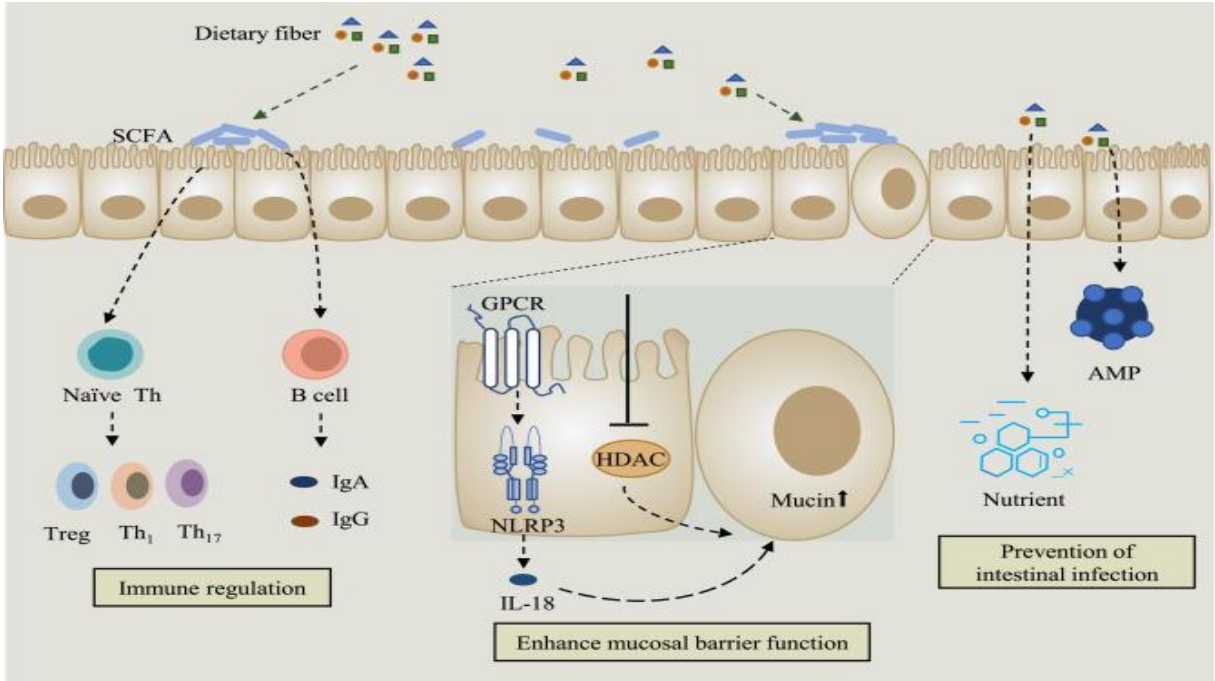


Figure 17 . Effects of fatty acids on immune function.

In contrast, omega-6 fatty acids and saturated fatty acids present more complex and often pro-inflammatory effects. Neutrophils exposed to n-6 PUFAs or saturated fatty acids show increased activity of cPLA2 and higher production of PGE2, both of which are key mediators of inflammatory responses. Macrophages treated with FFA 18:0 (stearic acid), a saturated fatty acid, activate PPAR α/γ pathways, influencing lipid metabolism and cellular processes. Dendritic cells exhibit heightened production of NLRP3, IL-1β, IL-10, and IL-12 when exposed to FFA 16:0 (palmitic acid), a saturated fatty acid linked to inflammatory signaling. T-cells modulate cytokine profiles under the influence of FFA 18:2 (linoleic acid), an omega-6 PUFA, which alters IL-10 and IL-12 levels. Finally, mast cells respond to FFA 20:4 (arachidonic acid), another omega-6 PUFA, by increasing their activation state, further contributing to inflammatory cascades. These findings highlight the contrasting roles of fatty acids in immune regulation, with omega-3s and MUFAs generally promoting resolution and homeostasis, while omega-6s and saturated fats tend to amplify inflammatory pathways.

Carbohydrates, particularly dietary fibers, are fermented by gut microbiota into SCFAs (acetate, propionate, butyrate). Butyrate, derived from inulin (chicory, onions) and resistant starch (beans, oats), fuels colonocytes, upregulates tight junction proteins (claudin, occludin), and promotes regulatory T-cell (Treg) differentiation via histone deacetylase (HDAC) inhibition. Conversely, refined sugars and simple carbohydrates trigger postprandial hyperglycemia, promoting Proteobacteria expansion and systemic inflammation.



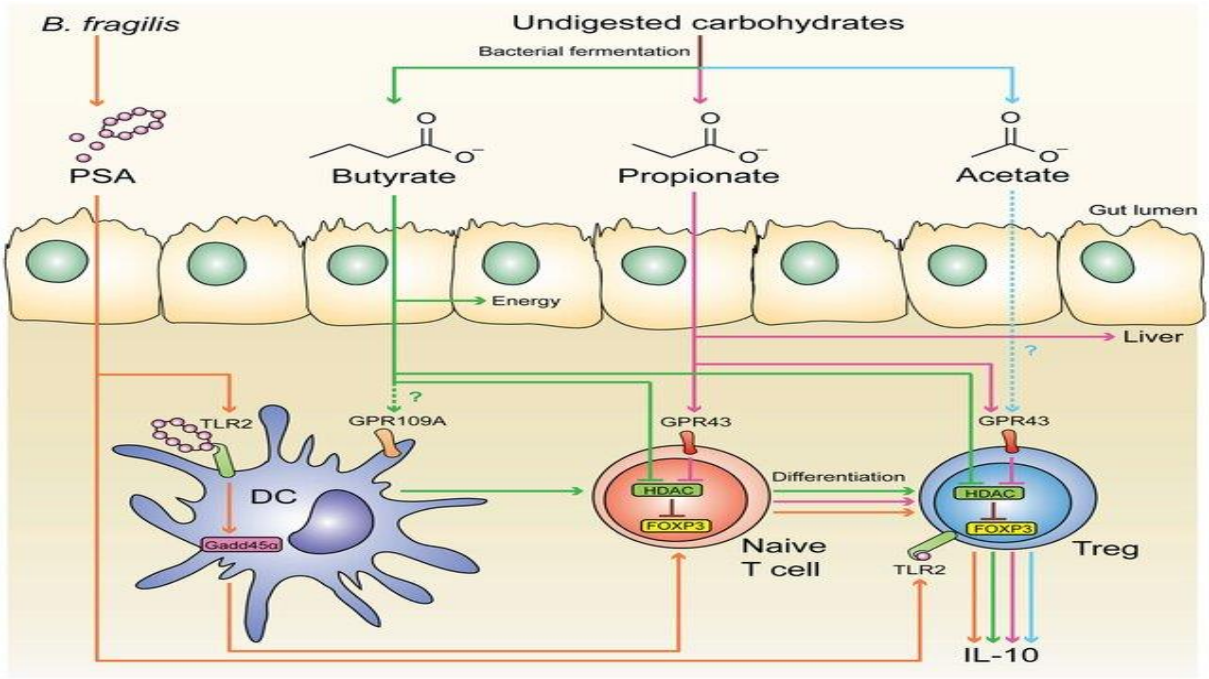


Figure 18 . Effects of dietary fibres on the immune system.

2.2. Micronutrients:

Vitamin A (retinol and β-carotene) maintains mucosal barriers and regulates T-cell differentiation. Retinoic acid (RA), synthesized from vitamin A in intestinal dendritic cells, RA exposure upregulates surface expression of α4β7 integrin and CCR9 receptor on lymphocytes to facilitate their guthoming. RA potentiates B-cell production of IgA. During T-cell differentiation, the presence of RA suppresses the differentiation and functions of Th17 cells while promoting FoxP3+ regulatory T cells (Tregs) differentiation.

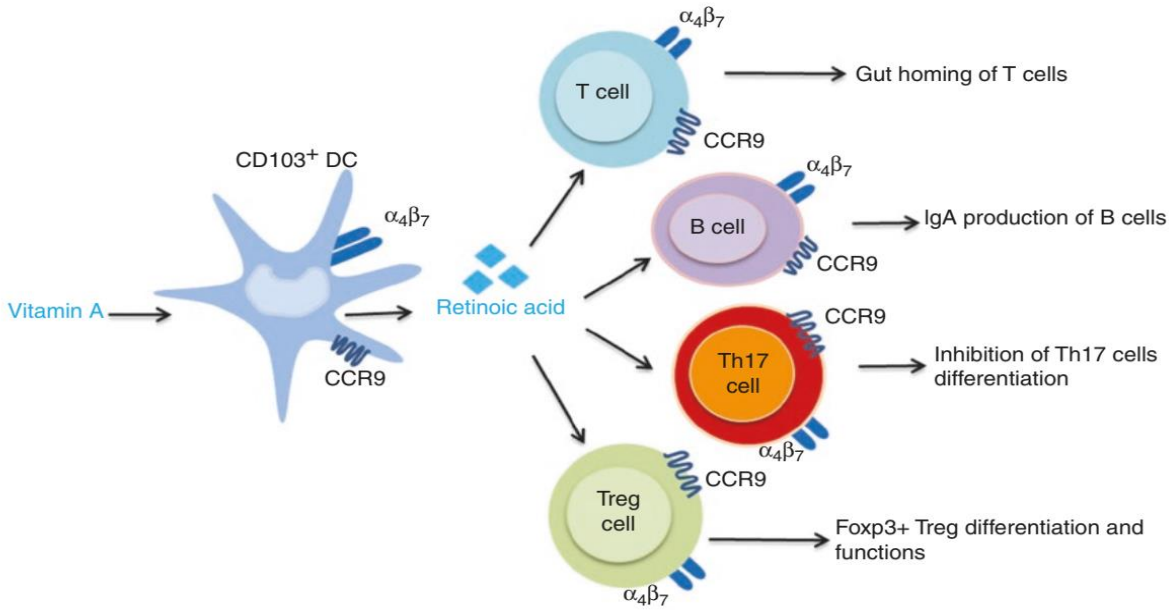


Figure 19 . Mechanism of action of vitamin A on the immune system.

Vitamin B: Vitamin B6 (Pyridoxine): Vital for immune cell metabolism, vitamin B6 supports lymphocyte proliferation, cytokine production (e.g., IL-2), and antibody synthesis. It aids glutathione production, protecting immune cells from oxidative stress. Deficiency leads to lymphopenia and impaired NK cell activity. Sources include poultry, fish, bananas, and chickpeas.

Vitamin B9 (Folate): Essential for DNA synthesis and methylation, folate enables T-cell and B-cell development and regulates immune gene expression. Deficiency causes hyperhomocysteinemia, linked to oxidative stress and autoimmune risks. Found in leafy greens, legumes, and fortified grains.

Vitamin B12 (Cobalamin): Works with folate in DNA synthesis and red blood cell formation. B12 deficiency reduces NK cell cytotoxicity and elevates pro-inflammatory cytokines. Sources are animal-based (meat, fish, dairy) or fortified plant milks.

Synergy: B6, B9, and B12 collaborate in one-carbon metabolism, critical for nucleotide synthesis, methylation, and redox balance. Their interplay supports immune cell function and reduces inflammation. Deficiencies are linked to autoimmune diseases and age-related immune decline.

Vitamin E, a fat-soluble antioxidant, plays a critical role in modulating immune function by influencing both innate and adaptive immunity. Its effects on immune cells are mediated through antioxidant activity, regulation of signaling pathways, and modulation of gene expression. Dietary sources of Vit E include nuts (e.g., almonds, sunflower seeds), leafy greens (e.g., spinach), vegetable oils (e.g., wheat germ, safflower), and fortified foods. Synthetic or natural supplements (e.g., α-tocopherol) are also common.

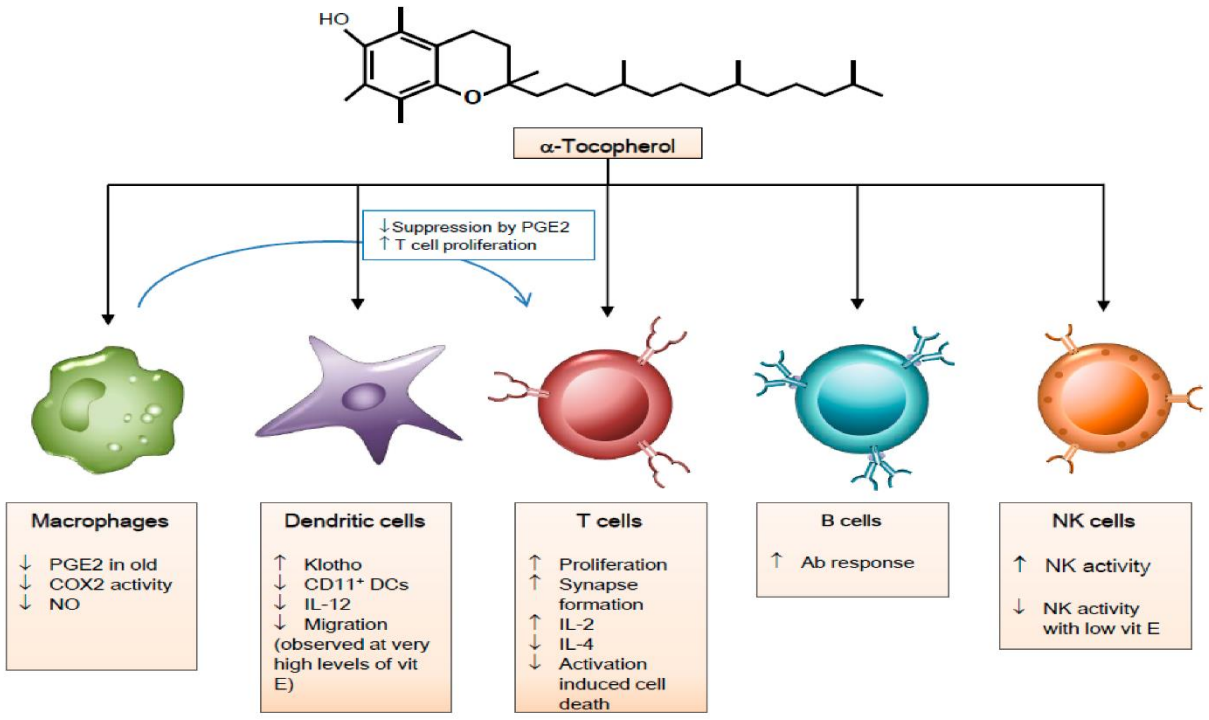


Figure 20 . Mechanism of action of vitamin E on the immune system.

Vitamin C orchestrates the function of the human immune system by supporting various aspects of both the innate and adaptive immune system, including epithelial barrier function, chemotaxis and antimicrobial activities of phagocyte cells, natural killer (NK) cell functions, and lymphocyte proliferation and differentiation.

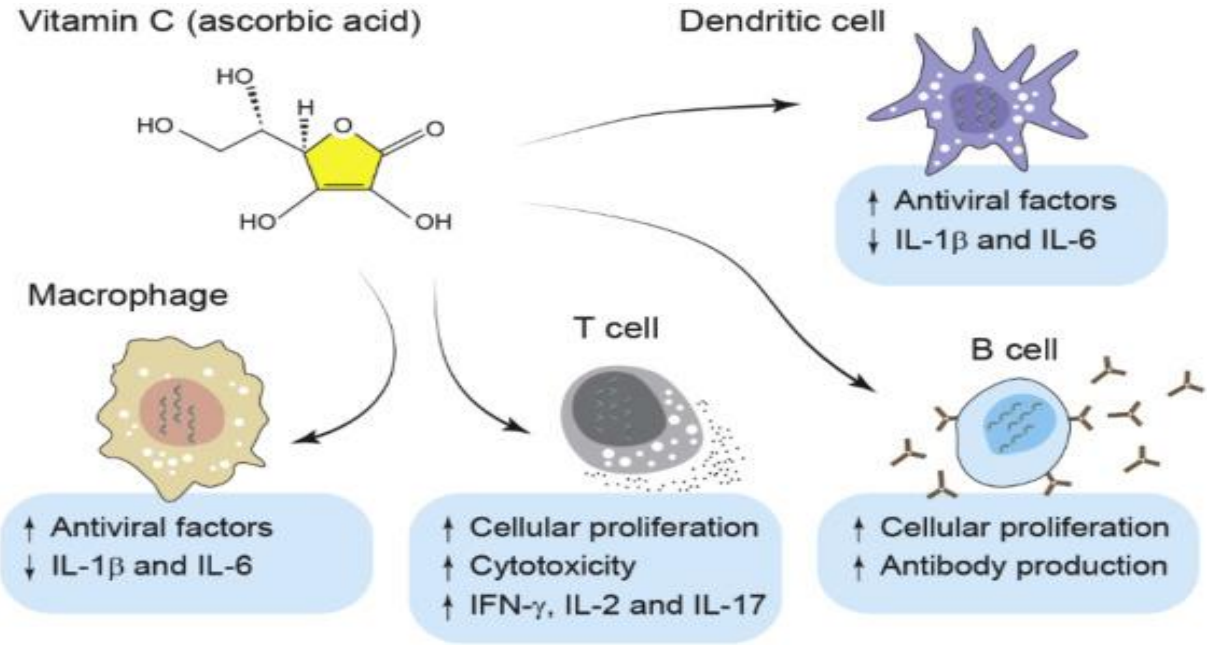


Figure 21 . Mechanism of action of vitamin C on the immune system.

Vitamin D (cholecalciferol) enhances innate immunity by inducing cathelicidin, an antimicrobial peptide, and modulates adaptive immunity by suppressing Th1/Th17 cells. Sourced from fatty fish, fortified dairy, and sunlight exposure, it reduces the risk of respiratory infections and autoimmune diseases like multiple sclerosis. Deficiency is linked to increased sepsis severity and impaired wound healing.

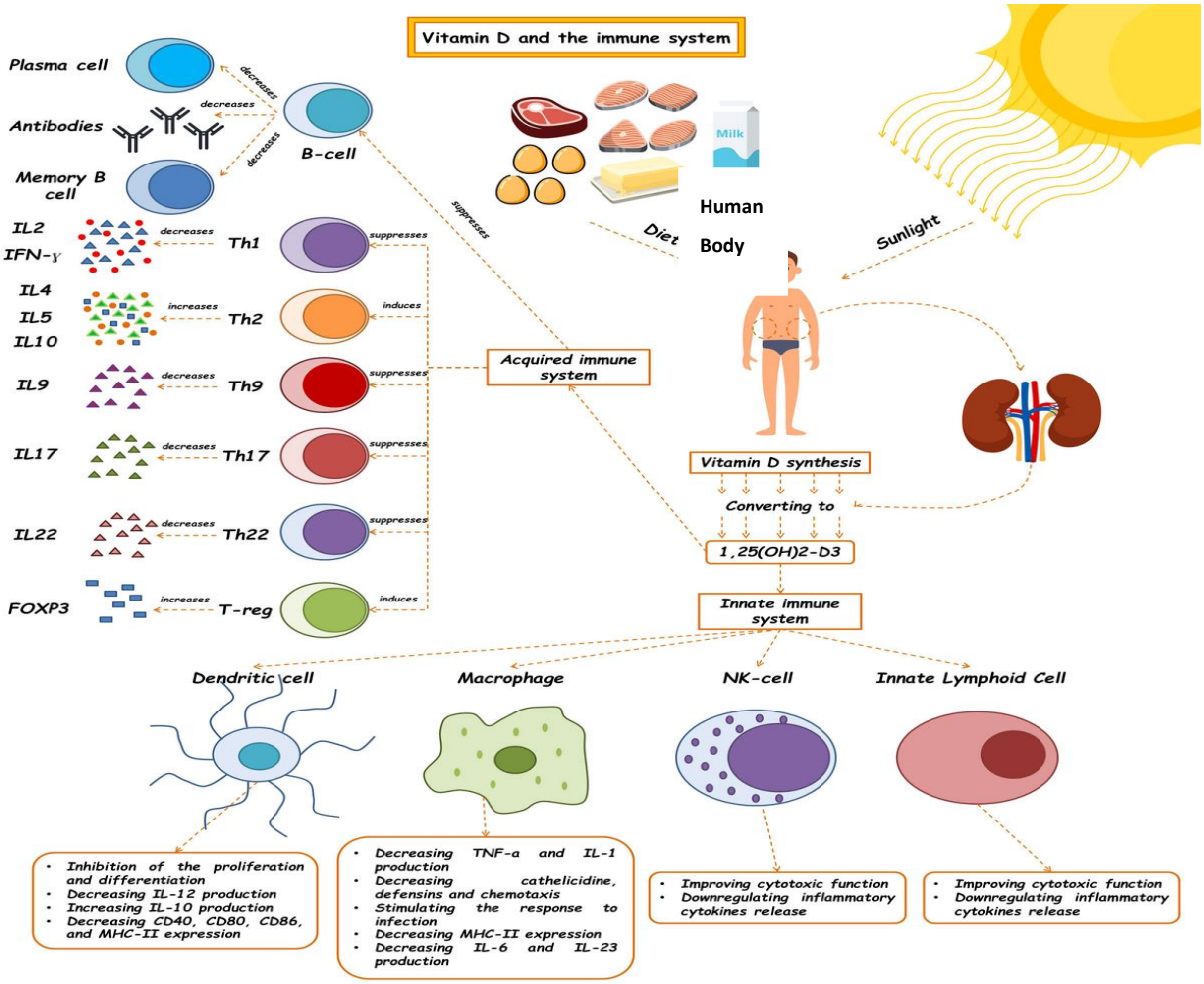


Figure 22 . Mechanism of action of vitamin D on the immune system.

Iron adequate intake from sources like heme iron (red meat, poultry, oysters, and liver) and non-heme iron (spinach, lentils, fortified cereals, and whole grains) plays a critical role in immune function by supporting the growth, differentiation, and activity of immune cells, including lymphocytes and macrophages. Adequate iron levels enhance oxygen transport via hemoglobin, ensuring energy for immune cell metabolism and pathogen defense. Iron deficiency impairs cytokine production, skewing immune responses toward TH2 dominance and reducing pathogen clearance. It also regulates intestinal immune homeostasis, as iron deficiency disrupts mucosal immunity and increases susceptibility to infections. Iron is a cofactor for enzymes like myeloperoxidase in neutrophils, which generate reactive oxygen species to combat pathogens.

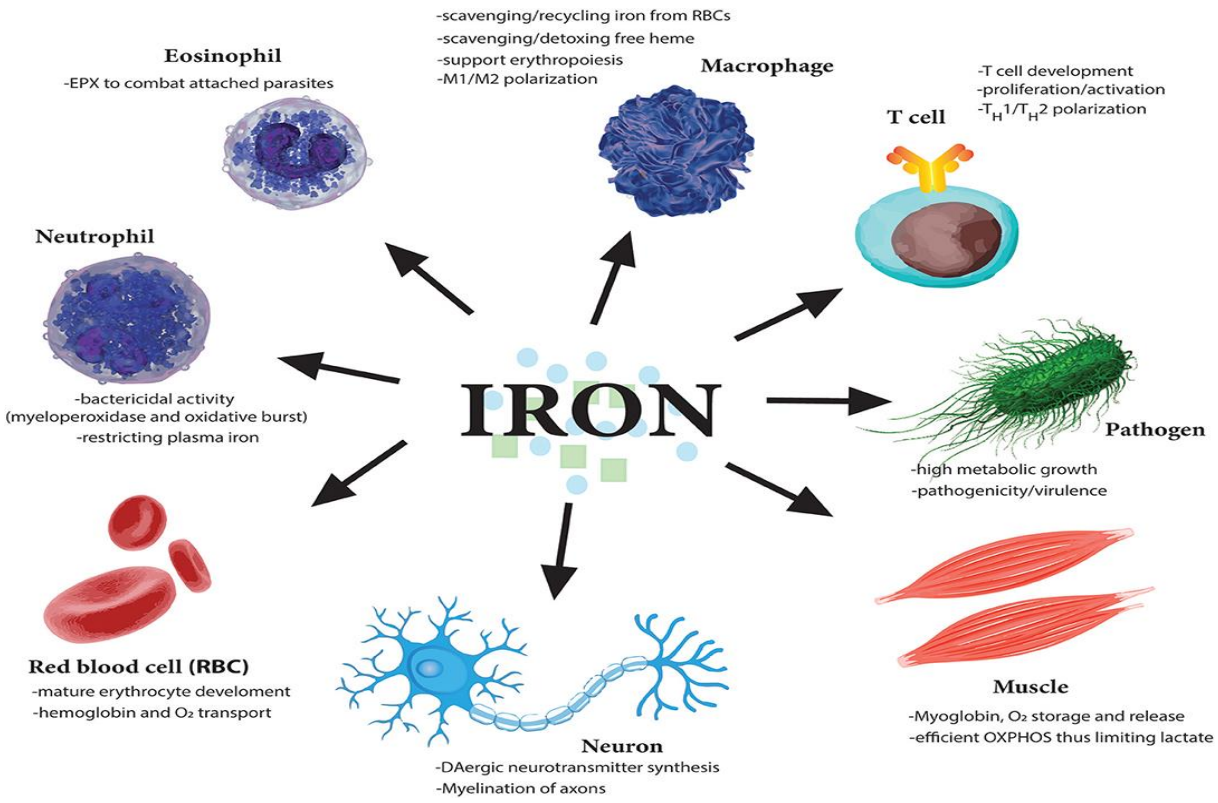


Figure 23 . **Mechanism of action of iron mineral on the immune system.**

Zinc, an essential cofactor for over 300 enzymes, plays a pivotal role in immune health, particularly in lymphocyte development, neutrophil function, and maintaining immune cell integrity. Dietary sources rich in zinc include oysters, beef, lentils, and pumpkin seeds. Balanced zinc homeostasis is vital, as both deficiency and excess disrupt immune function. Zinc deficiency leads to thymic involution, lymphopenia, and impaired phagocytosis, increasing susceptibility to infections. In children, supplementation reduces diarrhea and pneumonia incidence. Conversely, excessive zinc intake mimics deficiency, compromising innate and adaptive immunity. This dual impairment underscores zinc's role as a "gatekeeper" of immune regulation, governing zinc flux and signaling pathways critical for pathogen defense and preventing autoimmune disorders, chronic inflammation, and allergies. Zinc modulates immune cell processes, including T-cell activation, cytokine production, and neutrophil activity. It reverses immune deficits in conditions like Acrodermatitis Enteropathica, a genetic disorder causing severe zinc malabsorption, and mitigates age-related immune decline. By regulating zinc-dependent signaling, it helps balance pro-inflammatory and tolerogenic responses, highlighting its therapeutic potential for immune-related diseases.

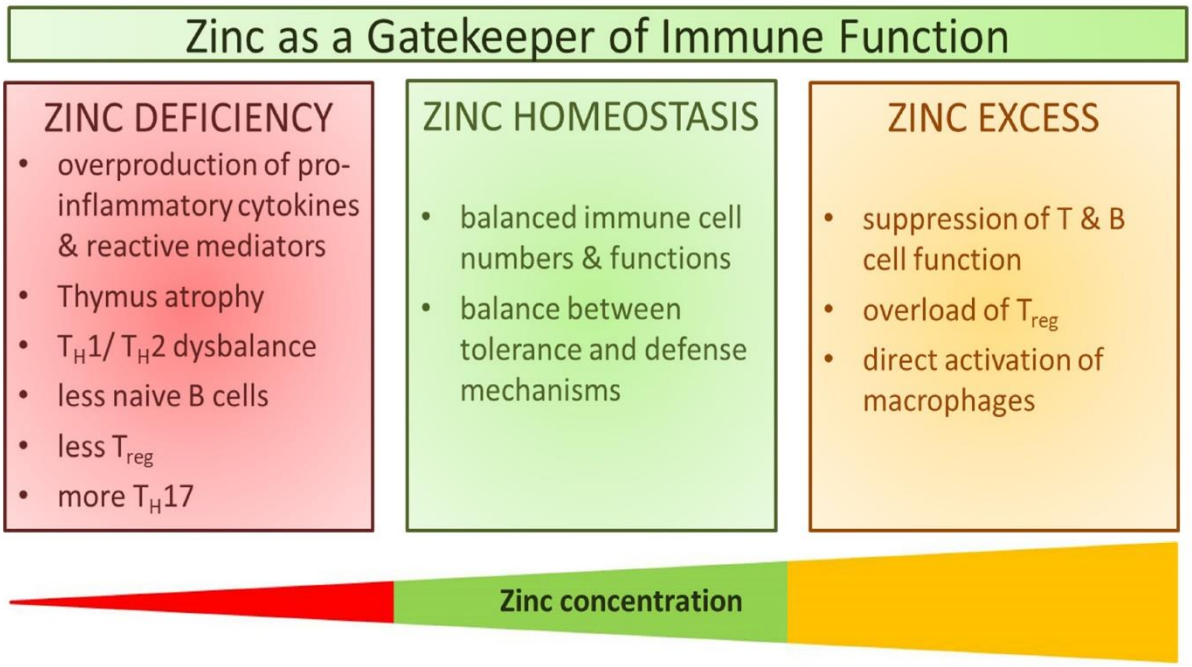


Figure 24 . **Mechanism of action of zinc mineral on the immune system.**

Selenium (Brazil nuts, seafood) supplementation of Se affects innate immunity; neutrophils, increasing of selenoproteins protect from oxidative stress; macrophages, increasing of migration and phagocytotic activity and switching to anti-inflammatory M2 type; NK cells, increasing lytic activity and pro-inflammatory cytokines. Se supplementation also affects adaptive immunity through recruiting Th1 T-lymphocytes, releasing pro-inflammatory cytokines. In contrast, Se deficiency affects humoral immunity; B-lymphocytes by decreasing amounts of IgG and IgM.

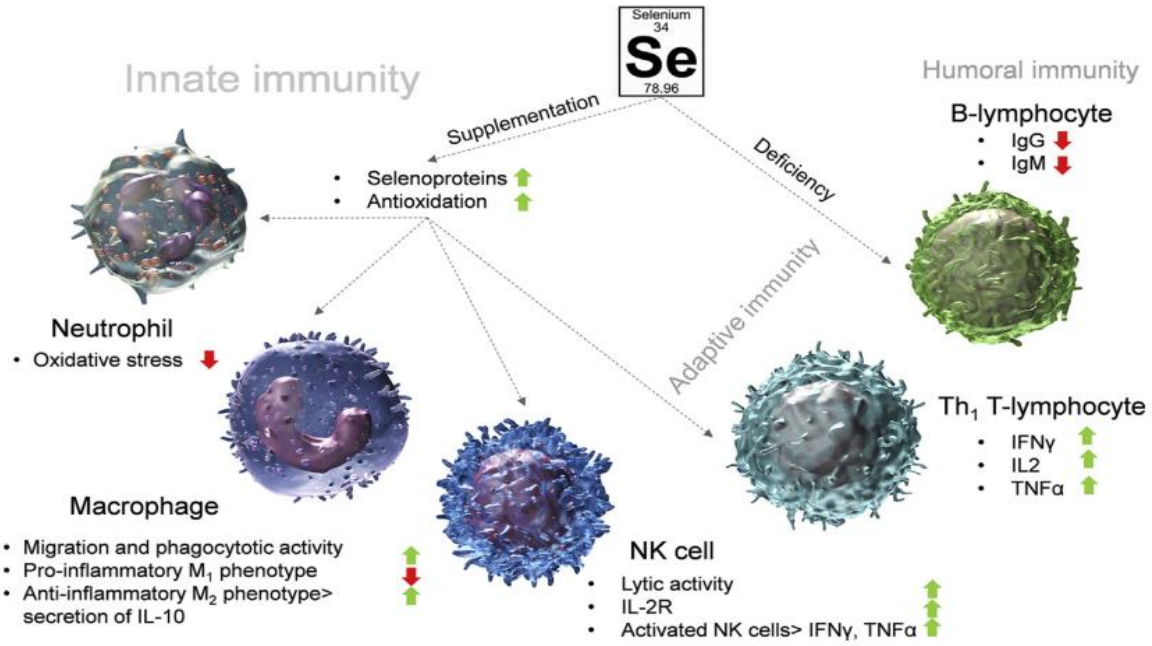


Figure 25 . **Mechanism of action of selenium mineral on the immune system.**

2.3. Gut Microbiota:

The gut microbiome metabolizes dietary components into immunomodulatory metabolites. Prebiotics (inulin, pectin) from garlic, bananas, and apples stimulate Faecalibacterium prausnitzii , a butyrate producer that suppresses NF-κB and IL-17. Probiotics (Lactobacillus, Bifidobacterium in yogurt) enhance IgA secretion and induce Tregs, reducing allergies. Dysbiosis—driven by low-fiber, high-fat diets—depletes Clostridia clusters XIVa and IV, promoting Th17-driven inflammation in inflammatory bowel disease (IBD). Antibiotic use or Western diets further disrupt this balance, increasing Proteobacteria and LPS-driven systemic inflammation.

2.4. Polyphenols and flavonoids

Polyphenols and flavonoids, abundant in plant-based diets, play a multifaceted role in modulating immune function through antioxidant, anti-inflammatory, and microbiota-regulating mechanisms. These compounds neutralise reactive oxygen species (ROS), thereby reducing oxidative stress that drives chronic inflammation and immune dysregulation 1. By interacting with receptors on immune cells, polyphenols activate intracellular signaling pathways that suppress pro-inflammatory cytokines such as TNF-α and IL-6, while promoting anti-inflammatory responses 3. For example, quercetin —found in onions and apples—inhibits NF-κB activation, dampening excessive inflammation, whereas resveratrol (red grapes, berries) enhances regulatory T-cell (Treg) activity, fostering immune tolerance 6. Polyphenols also strengthen gut barrier integrity by stimulating beneficial bacteria like *Lactobacillus* and *Bifidobacterium,* which produce short-chain fatty acids (SCFAs) that nourish colonocytes and regulate mucosal immunity. Additionally, unabsorbed polyphenols are metabolized by gut microbiota into bioactive compounds, such as urolithins from ellagitannins, which further modulate immune responses 8. Dietary sources like curcumin (turmeric) and epigallocatechin gallate (EGCG) (green tea) directly enhance macrophage phagocytosis and suppress autoimmune reactions, highlighting their dual role in defense and immune regulation. Regular consumption of polyphenol-rich foods—such as colorful fruits, vegetables, tea, and dark chocolate—thus supports immune resilience by balancing inflammation, fortifying gut health, and enhancing pathogen defense.

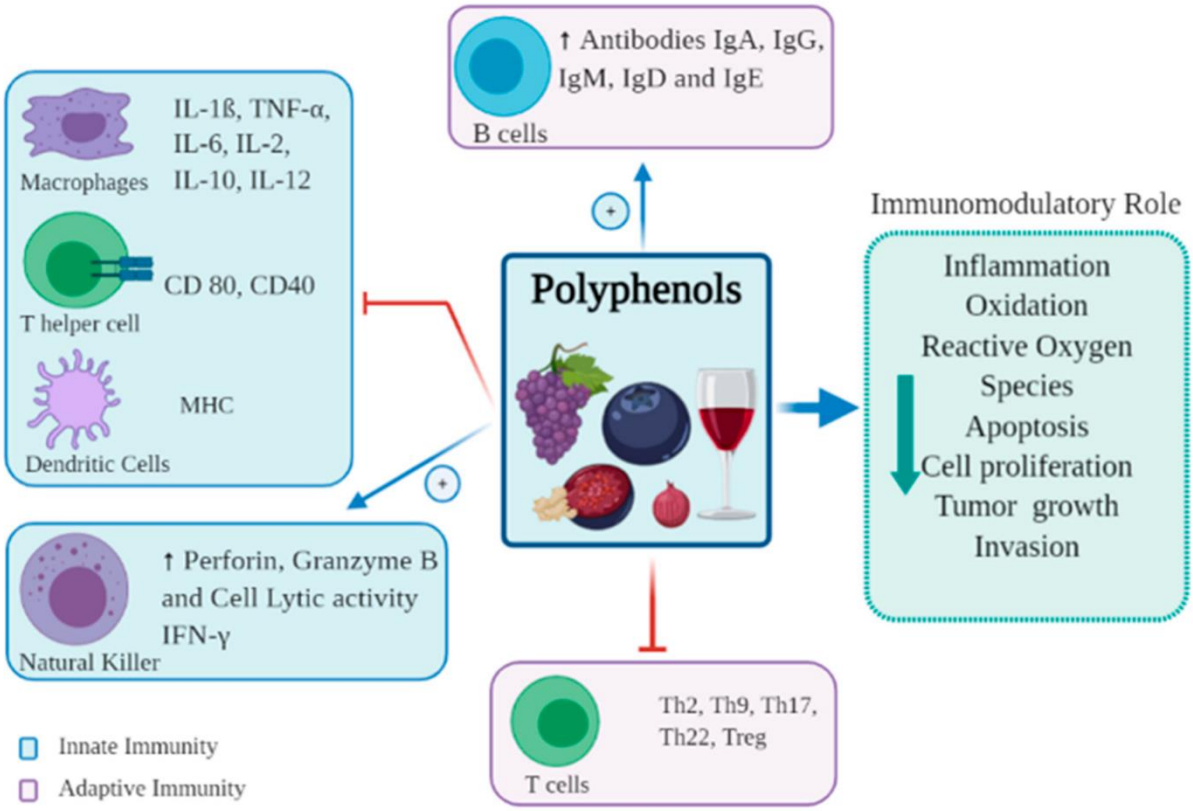


Figure 26 . Mechanism of action of polyphenols on the immune system.

3. Obesity and Immune Dysregulation

Obesity triggers systemic inflammation by promoting adipose tissue expansion, which releases pro-inflammatory cytokines such as TNF-α, IL-6, and leptin. This chronic low-grade inflammation alters immune cell behavior: macrophages in adipose tissue shift toward a pro-inflammatory M1 phenotype, while regulatory T cells (Tregs) decline, disrupting immune tolerance. For example, obese individuals exhibit impaired neutrophil chemotaxis and reduced phagocytic activity, increasing risks of bacterial infections like Staphylococcus aureus. Additionally, obesity exacerbates autoimmune diseases like rheumatoid arthritis by promoting Th17 cell activity, which drives tissue damage.

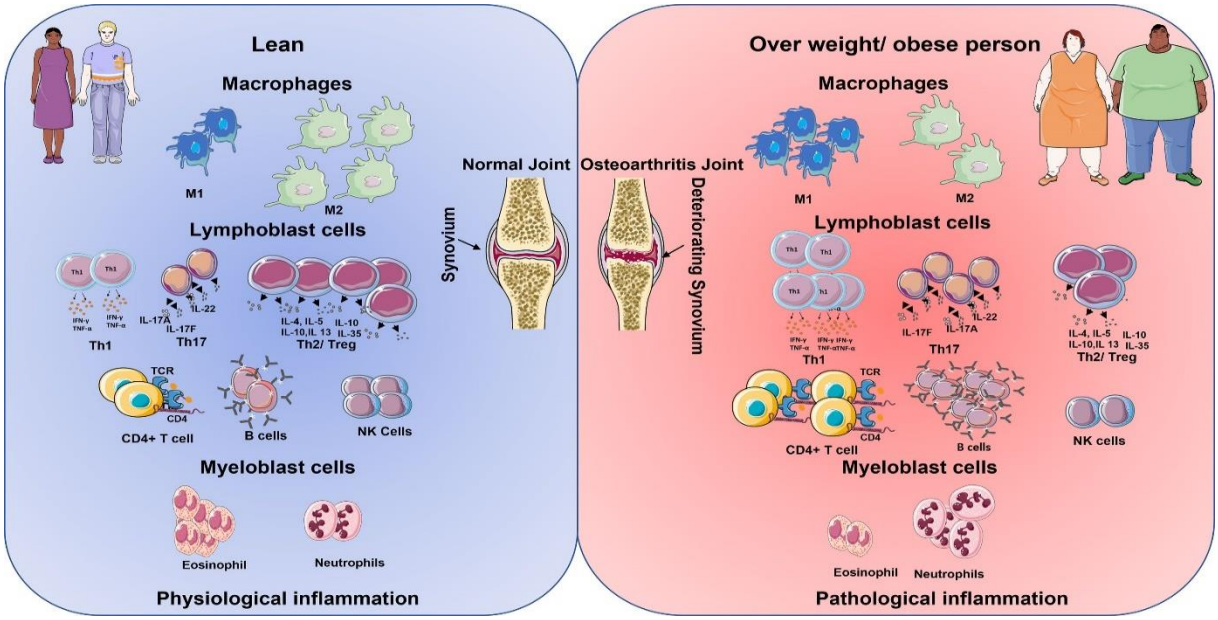


Figure 27 . Comparative overview of the immune systems of lean and overweight people.

3.1. Effects of Poor Dietary Control

Diets high in saturated fats, sugars, and processed foods directly impair immune competence. Saturated fats activate Toll-like receptor 4 (TLR4) on macrophages, mimicking bacterial infection and triggering inflammatory cascades. For instance, frequent consumption of sugary beverages correlates with elevated C-reactive protein (CRP) levels, a marker of systemic inflammation. High fructose intake disrupts gut barrier integrity, allowing lipopolysaccharide (LPS) translocation into the bloodstream, which fuels metabolic endotoxemia and insulin resistance. Trans fats, found in fried foods, reduce B-cell antibody production, weakening humoral immunity and vaccine efficacy. A diet low in fiber depletes beneficial gut bacteria like Faecalibacterium prausnitzii, reducing short-chain fatty acid (SCFA) production and compromising intestinal immune regulation.

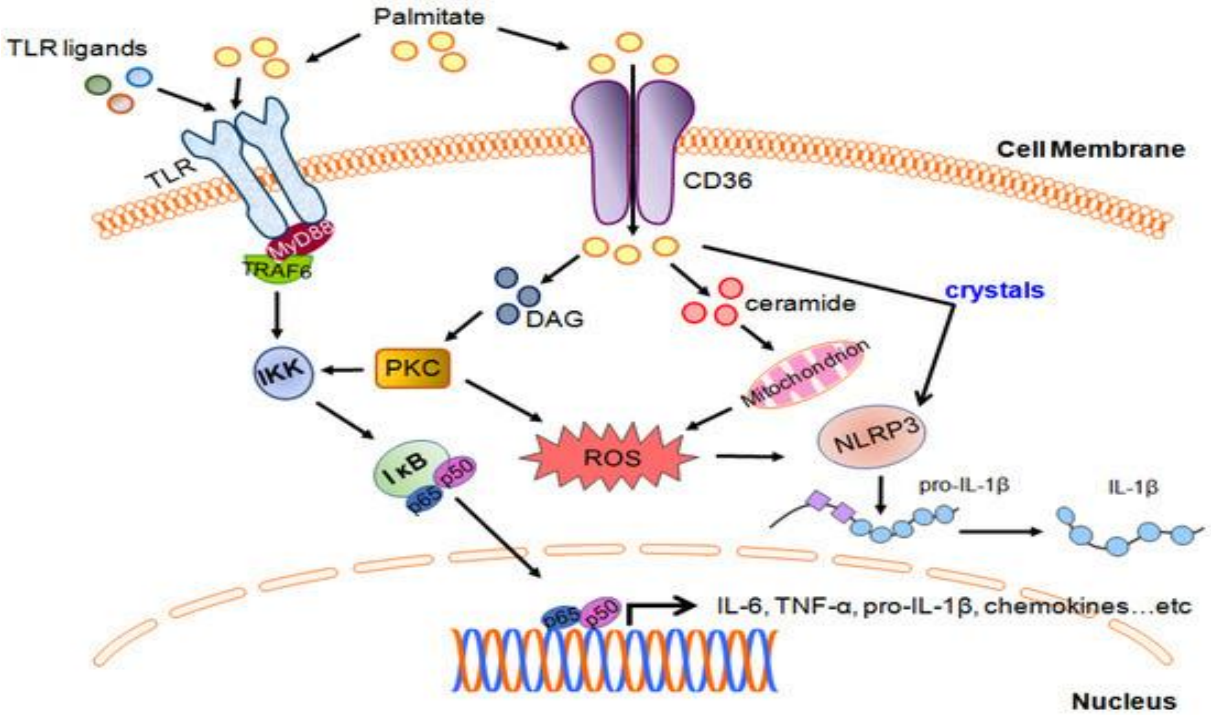


Figure 28 . Mechanism of palmitate-rich food on the immune system.

3.2. Synergistic Harm: Obesity and Poor Diet

The combination of obesity and poor dietary choices creates a vicious cycle of immune dysfunction. For example, obese individuals consuming a Western diet (high in red meat, refined carbs, and low in fiber) exhibit heightened Th1/Th17 responses, increasing autoimmune risks like psoriasis. In a study of postmenopausal women, high saturated fat intake amplified obesity-related T-cell exhaustion, worsening responses to influenza vaccination. Additionally, diets rich in advanced glycation end-products (AGEs), common in processed foods, promote oxidative stress and NF-κB activation, accelerating atherosclerosis and cardiovascular complications in obese individuals.

Obesity and poor diets collectively increase the burden of infectious and chronic diseases. For example, obese patients with diabetes face a 3.5-fold higher risk of severe sepsis due to impaired neutrophil function. During the COVID-19 pandemic, obesity emerged as a major risk factor for cytokine storms and ICU admission, driven by dysregulated IL-6 and TNF-α signaling. Public health strategies targeting dietary quality—such as reducing ultra-processed foods and increasing plant-based fiber—are critical to mitigating immune dysfunction and metabolic diseases.

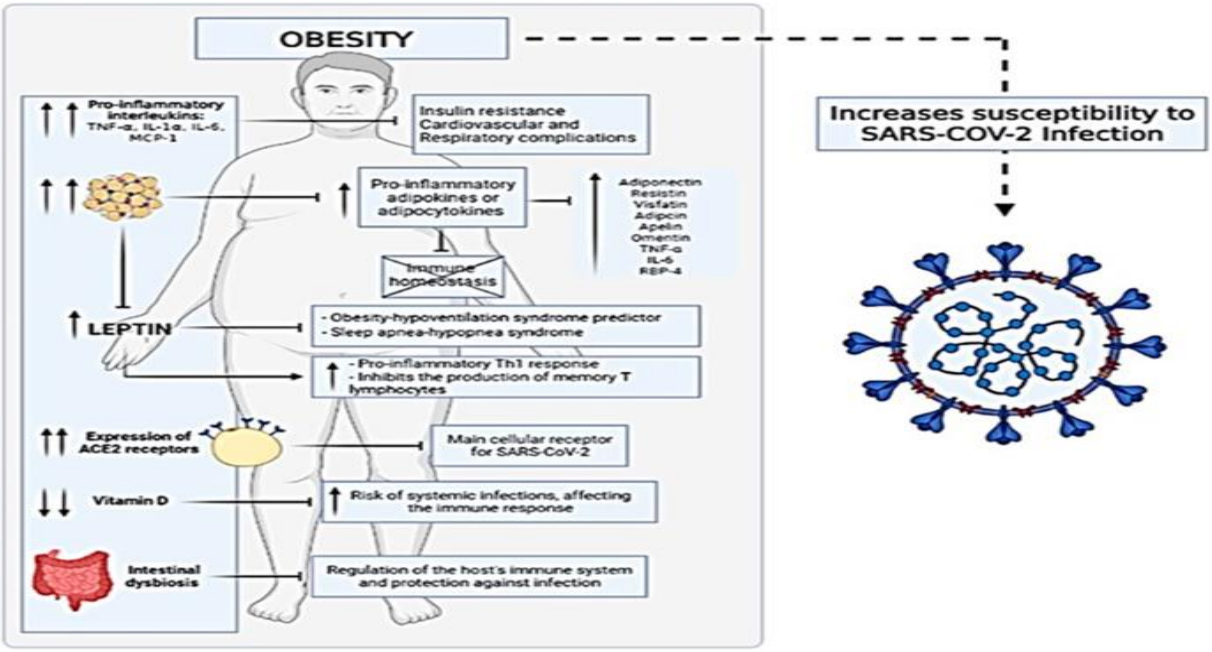


Figure 29 . Effect of obesity on the body's response to COVID infection.

3.3. Immune Disorders and Diet-Related Diseases Linked to Nutrient Deficiencies

Autoimmune disorders, which occur when the immune system mistakenly attacks healthy tissues, are often exacerbated by nutrient deficiencies. For example, Hashimoto's thyroiditis is linked to low selenium and vitamin D levels, as these nutrients regulate thyroid function and immune tolerance. Similarly, celiac disease, triggered by gluten intolerance, causes the malabsorption of iron, vitamin B12, and folate, leading to anemia and chronic inflammation. Rheumatoid arthritis (RA) involves joint inflammation worsened by deficiencies in vitamin D and selenium, which modulate inflammatory cytokines like TNF-α. Systemic lupus erythematosus (SLE) is associated with zinc and vitamin D deficiencies, which impair regulatory T-cell function, promoting autoantibody production. Inflammatory bowel disease (IBD) often coexists with iron and vitamin B12 deficiencies due to gut damage, resulting in fatigue and impaired immune responses.

Nutrient deficiencies directly undermine immune competence. Vitamin D deficiency weakens antimicrobial peptide production, increasing susceptibility to infections and autoimmune flares, as seen in multiple sclerosis. Iron deficiency anemia reduces oxygen delivery to immune cells, impairing neutrophil function and increasing risks of bacterial infections like Salmonella. Selenium deficiency exacerbates oxidative stress, worsening autoimmune thyroiditis and cardiovascular inflammation. Zinc deficiency causes thymic atrophy and reduced T-cell activity, elevating morbidity from diarrheal diseases and pneumonia.

Poor dietary patterns, such as high intake of processed foods, sugar, and gluten, deplete micronutrients and fuel inflammation. Low fiber intake disrupts gut microbiota, reducing short-chain fatty acid (SCFA) production needed for regulatory T-cell function, thereby promoting autoimmune dysregulation. Excess sugar and trans fats activate pro-inflammatory pathways (e.g., NF-κB), worsening conditions like RA and psoriasis.

Examples Highlighted:

Autoimmune Disorders: Hashimoto's thyroiditis (selenium/vitamin D deficiency), celiac disease (iron/B12 malabsorption), RA (vitamin D/selenium deficiency).

Diet-Driven Diseases: Iron-deficiency anemia (impaired immunity), selenium deficiency (thyroiditis), zinc deficiency (infection risk).

Synergy: Western diets (low fiber, high sugar) worsening IBD and psoriasis.

4. The Immune System's Role in Nutrient Absorption and Metabolism

The immune system profoundly influences nutrient absorption and metabolism, adapting these processes to meet dynamic physiological demands during health and disease. During an innate immune response, for example, amino acid uptake by skeletal muscles decreases, while the liver and immune cells increase their nutrient uptake to support inflammation and tissue repair. This metabolic shift ensures energy and substrates are redirected to immune cells, such as macrophages and lymphocytes, which require enhanced glucose and glutamine consumption to fuel phagocytosis, cytokine production, and proliferation.

Immune activation also alters nutrient storage and distribution. White adipose tissue (WAT), regulated by immune signals, releases fatty acids and glycerol during infection to meet heightened energy demands. Conversely, chronic inflammation—driven by poor diets high in saturated fats or sugars—disrupts insulin signaling, promoting metabolic syndrome and impairing nutrient uptake in peripheral tissues. For instance, obesity-induced inflammation increases leptin resistance, altering nutrient partitioning and exacerbating insulin resistance.

Micronutrient deficiencies further highlight this interplay. Zinc deficiency impairs T-cell maturation and antibody responses, reducing immune competence, while vitamin D deficiency disrupts calcium absorption and antimicrobial peptide production. In contrast, probiotics and fiber-rich diets enhance nutrient absorption by promoting gut microbiota diversity, which strengthens intestinal barrier function and modulates immune reactivity. For example, Lactobacillus strains

improve iron absorption by lowering gut pH, while short-chain fatty acids (SCFAs) from fiber fermentation enhance colonic nutrient uptake.

Chronic immune activation, such as in autoimmune diseases, also dysregulates metabolism. Rheumatoid arthritis patients often exhibit altered lipid profiles and reduced selenium levels, exacerbating oxidative stress and joint inflammation. Similarly, celiac disease triggers malabsorption of iron, B12, and folate due to immune-mediated gut damage, necessitating strict dietary management.

Examples:

Amino acid redistribution : Liver uptake increases during infection.

Zinc deficiency : Impairs T-cell function.

Probiotics : Enhance iron absorption via Lactobacillus.

Obesity : Alters WAT nutrient release, worsening insulin resistance.

Celiac disease : Causes malabsorption of iron and B12

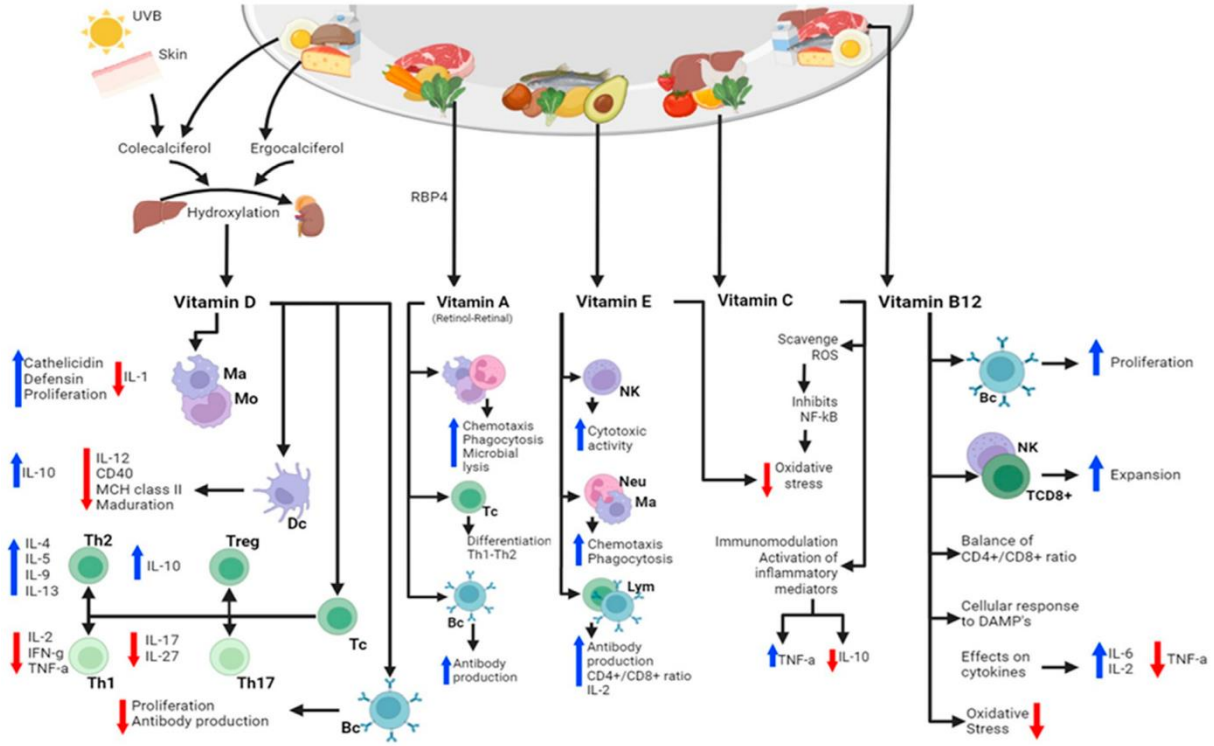


Figure 30 . Effects of different nutrients on the immune system.

Hypersensitivity

1. Introduction

Hypersensitivity reactions are exaggerated immune responses that can cause tissue damage and are classified into different types based on the immune mechanisms involved. These reactions can occur in response to various stimuli, including drugs, allergens, and environmental factors. Understanding the underlying mechanisms and causes of hypersensitivity is crucial for diagnosis, prevention, and treatment.

2. Immune Mechanisms in Hypersensitivity Reactions

Hypersensitivity reactions are primarily mediated by the immune system and can be classified into four types: Type I, Type II, Type III, and Type IV. Each type involves distinct immune pathways and effector molecules.

2.1. Type I Hypersensitivity (Immediate Hypersensitivity)

Type I hypersensitivity encompasses atopic conditions characterized by an overactive IgE-mediated immune response. These include allergic disorders such as asthma, rhinitis, conjunctivitis, and dermatitis, as well as reactions to foreign allergens like anaphylaxis, urticaria, angioedema, and food or drug allergies. Allergens triggering these reactions may be innocuous (e.g., pollen, dust mites, certain foods) or more dangerous, such as insect venoms. Symptoms manifest across multiple organ systems, including:

- Nasal: Allergic rhinitis (hay fever).
- Ocular: Conjunctivitis due to seasonal allergens like pollen or mold .
- Dermatological: Hives, atopic eczema, or erythema.
- Soft tissue: Angioedema.
- Respiratory: Asthma or hypoxia.
- Systemic: Life-threatening anaphylaxis .

Risk Factors

Genetic predisposition, environmental factors (e.g., pollution, socioeconomic conditions), geographic location, and the "hygiene hypothesis" contribute to susceptibility. The hygiene hypothesis posits that reduced early exposure to microbes in modern societies impairs immune regulation, potentially increasing allergy and asthma rates.

Etiology

Type I hypersensitivity involves two phases: sensitization and effector. During sensitization, asymptomatic antigen exposure primes the immune system. Upon re-exposure, pre-sensitized IgE

antibodies on mast cells and basophils trigger an inflammatory cascade. Common allergens include foods (nuts, shellfish), environmental agents (latex, pollen), animal dander, and medications (antibiotics).

Antigen-presenting cells (APCs) activate T-cells, which stimulate B-cells to produce IgE antibodies. These antibodies bind to mast cells and basophils. Re-exposure causes antigen crosslinking, degranulation, and release of mediators (histamine, leukotrienes, prostaglandins). This leads to vasodilation, bronchospasm, mucous secretion, and edema, culminating in localized (e.g., rhinitis) or systemic (anaphylaxis) reactions.

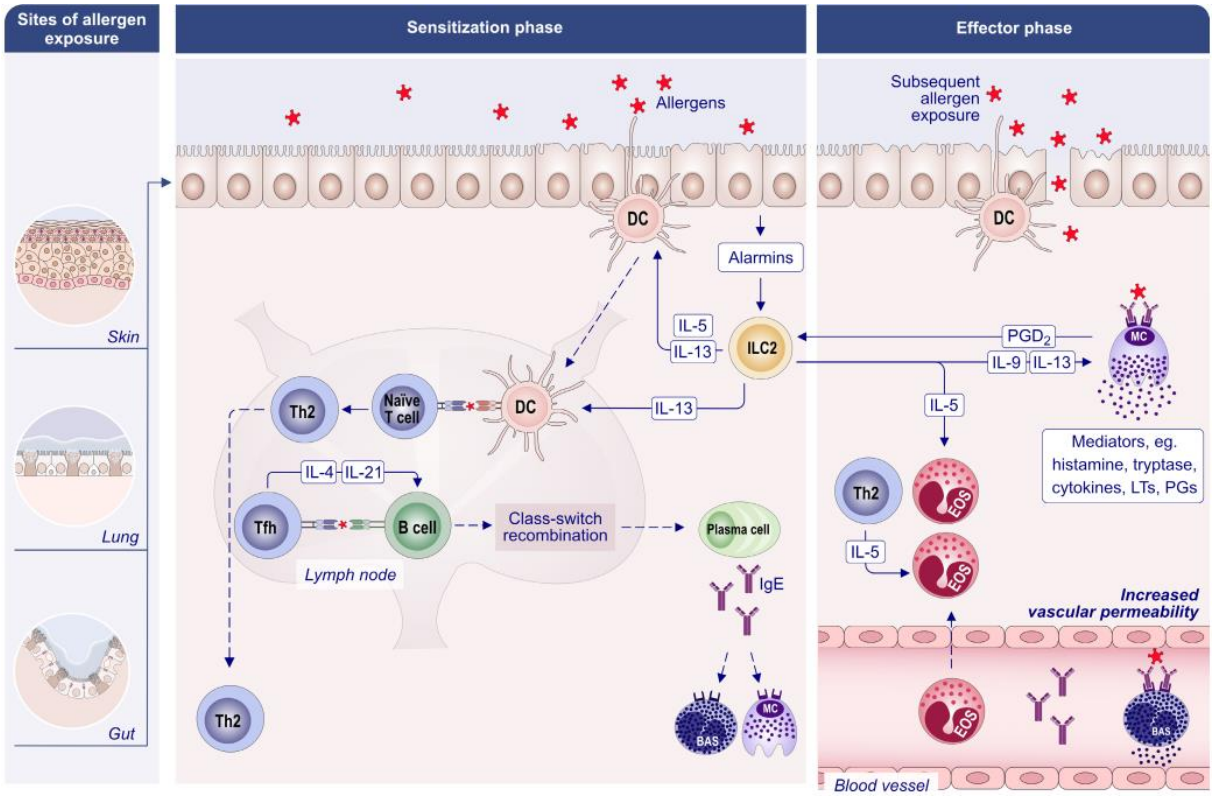


Figure 31 . Hypersensitivity I induction.

Allergens initially bind to epithelial cells in the respiratory tract, gastrointestinal system, or skin. During the sensitization phase, antigen-presenting cells (APCs), such as dendritic cells (DCs), process and present allergenic peptides to naïve T helper (Th) cells. Epithelial cells release alarmin cytokines—including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP)—which activate type 2 innate lymphoid cells (ILC2s). Activated ILC2s secrete type 2 cytokines (IL-5, IL-9, IL-13), amplifying the Th2 immune response. T follicular helper (Tfh) cells subsequently promote B-cell maturation, leading to the production of high-affinity allergen-specific IgE (sIgE). Mast cells (MCs) and basophils (BAS) express FcεRI receptors, which bind sIgE, completing the sensitization phase. Effector Phase and Symptom Onset Upon re-exposure, allergens crosslink sIgE bound to MCs and BAS, triggering degranulation. MCs reside in tissues (e.g., skin, airways), while BAS circulate in

blood. Preformed mediators like histamine, prostaglandins (PGD2), and leukotrienes (LT) induce vasodilation, bronchoconstriction, and mucus hypersecretion. Eosinophils (EOS) contribute to delayed allergic responses and chronic inflammation, bridging Type I and Type IVb hypersensitivity mechanisms. Conditions like asthma, allergic rhinitis (AR), atopic dermatitis (AD), and food/venom/drug allergies exhibit overexpression of T2 cytokines (IL-4, IL-5, IL-13) and elevated sIgE. Acute manifestations include anaphylaxis and urticaria/angioedema, often triggered by foods, medications, or insect stings. B, B lymphocyte; BAS, basophil; DC, dendritic cell; EOS, eosinophil; IL, interleukin; ILC2, type 2 innate lymphoid cell; LT, leukotrienes; MC, mast cell; PG(D2), prostaglandin (D2); sIgE, allergen-specific immunoglobulin E; Tfh, T follicular helper cell; Th naïve/2, T helper lymphocyte naïve/type 2; TSLP, thymic stromal lymphopoietin.

2.1.1. Clinical forms of type I hypersensitivity

Depending on the location of the antigen-antibody reaction (Ag-Ab reaction), two forms can be distinguished:

a) Reaction at the tissue level:

Allergic rhinitis (Ag-Ab reaction at the nasal mucosa, leading to increased vascular permeability, loss of plasma fluid on the mucosal surface, and local congestion, watery rhinorrhea, sneezing, and a sensation of nasal congestion).

Allergic or extrinsic bronchial asthma (Ag-Ab reaction at the bronchial mucosa causing bronchoconstriction through: bronchial muscle spasm, mucosal edema, and excessive secretion of sticky mucus, resulting in expiratory dyspnea, wheezing respiration called "wheezing", coughing, and expectoration).

Atopic dermatitis: It is characterized by the itch-scratch cycle: affected persons have the sensation of itch, followed by scratching and the subsequent creation of a rash.

Urticaria. Hives (the common term for urticaria), are pink or red itchy rashes, that may appear as blotches or raised red lumps (wheals) on the skin.

Allergic gastroenteritis: Some symptoms include diarrhea, nausea, vomiting, abdominal cramps, headaches, muscle aches and fever. Symptoms may range from mild to severe and typically last between one and ten days.

b) Reaction at the intravascular level:

Angioedema (Quincke's Edema) : subcutaneous edema (around the eyelids, lips, genitals), dyspnea, and intestinal colic.

Anaphylactic shock: intense vasodilation with vascular collapse, risk of death due to glottic edema causing asphyxiation = medical emergency.

2.2. Type II Hypersensitivity (Antibody-Dependent)

Type II hypersensitivity reactions are primarily drug-induced and often manifest as allergic cytopenias. However, they also play a critical role in autoimmune diseases such as immune thrombocytopenia, autoimmune hemolytic anemia (AIHA), autoimmune neutropenia, Goodpasture syndrome, hemolytic disease of the fetus and newborn (erythroblastosis fetalis), myasthenia gravis, pemphigus, and mismatched blood transfusion reactions. In drug-dependent Type II reactions, a drug or its metabolite binds to membrane proteins on host cells. This triggers the production of anti-drug antibodies, which form complexes with the drug-protein conjugate. These complexes activate complement or bind to Fcγ receptors on effector cells (e.g., NK cells, macrophages), leading to cytolysis. Similarly, in autoimmune Type II reactions, drug-anti-drug antibody complexes bind to self-antigens on cell membranes, activating complement or effector cells via Fc receptors, resulting in tissue damage. The mechanisms underlying IgG sensitization in these reactions remain unclear but may involve molecular mimicry. Classic examples include drug-induced lupus and hemolytic transfusion reactions due to ABO incompatibility.

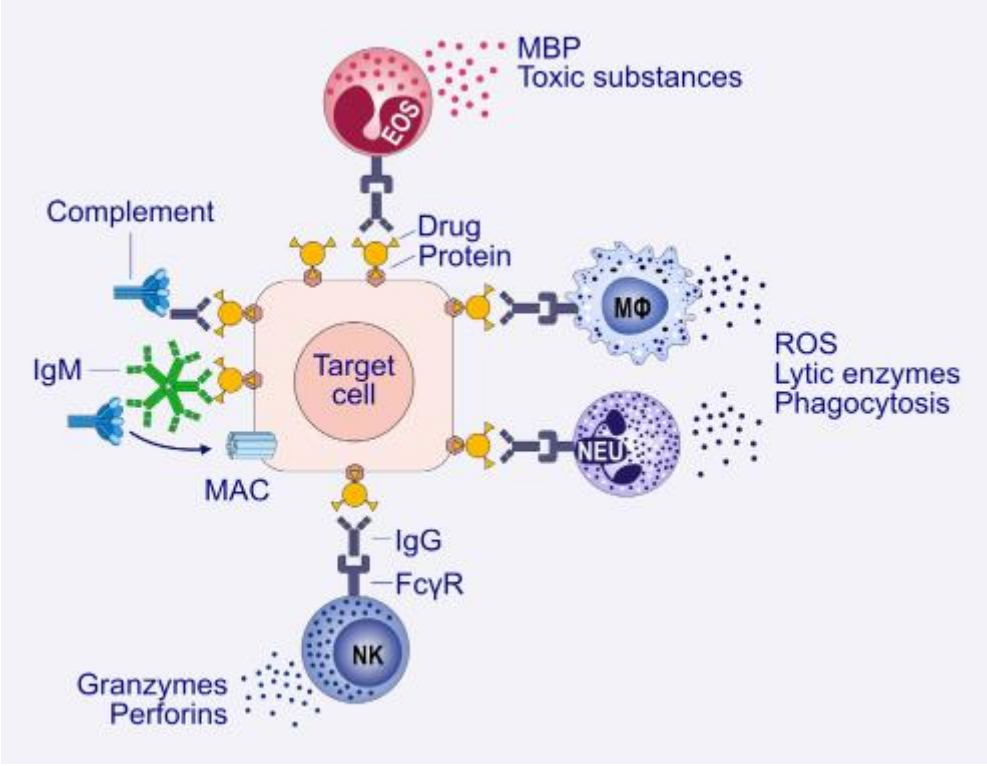


Figure 32 . Hypersensitivity II induction.

Drugs or their metabolites bind to membrane proteins on host cells, forming drug-protein complexes. Anti-drug antibodies (IgG or IgM) subsequently recognize these complexes, triggering complement activation via the classical pathway. This leads to membrane-attack complex (MAC) formation and cell lysis. IgG antibodies also bind to Fcγ receptors (FcγR) on macrophages (Mφ)

and neutrophils (NEU), stimulating phagocytosis, reactive oxygen species (ROS), and proteolytic enzyme release. Similarly, IgG-FcγR interactions on eosinophils (EOS) induce degranulation, releasing major basic protein (MBP) and ROS. Antibody-dependent cellular cytotoxicity (ADCC) may occur when natural killer (NK) cells or CD8+ T cells bind to IgG-coated target cells, further amplifying tissue damage. Collectively, complement activation and immune cell recruitment drive inflammation and cytotoxicity, characteristic of Type II hypersensitivity reactions. ADCC, Ab-dependent cellular cytotoxicity; EOS, eosinophil; FcγR, Fc fragment gamma receptor; IgG/M, immunoglobulin class G/M; MAC, membraneattack complex; Mφ, macrophage; MBP, major basic protein; NEU, neutrophil; NK, natural killer cell; ROS, reactive oxygen species.

2.2.1. Clinical forms of type II hypersensitivity

Transfusion reactions (incompatible transfusions within the ABO system):

The recipient's IgM antibodies (alpha and beta agglutinins) react with antigens (agglutinogens A and B) on the surface of the donor's red blood cells, causing rapid intravascular hemolysis through complement activation.

Goodpasture syndrome:

A glomerulonephritis (GN) caused by the formation of autoantibodies of the IgG class directed against intrinsic antigens of the glomerular basement membrane. This leads to local activation of the complement system and enzymatic destruction of the basement membrane via phagocytosis. The destruction releases new antigens into circulation, creating a vicious cycle of autoantibody amplification.

These autoantibodies may cross-react with structurally similar antigens of the pulmonary vascular basement membrane, leading to pulmonary vasculitis in some patients with glomerulonephritis.

Autoimmune hemolytic anemia:

When IgG anti-erythrocyte antibodies are produced, they react with antigens on the erythrocyte membrane. The sensitized red blood cells are phagocytosed by splenic macrophages (in warm antibody-mediated immune hemolytic anemia).

In cases where IgM anti-erythrocyte antibodies are generated, complement activation occurs along with C3b (opsonin) fixation on the surface of sensitized erythrocytes. This activates phagocytosis by hepatic macrophages (in cold antibody-mediated immune hemolytic anemia).

Drug-induced hemolytic anemia:

Penicillin (acting as a hapten) binds to the erythrocyte membrane, inducing the synthesis of IgG antibodies against the erythrocyte-drug complex. Sensitized erythrocytes undergo splenic erythrophagocytosis and complement-mediated cytolysis.

Erythroblastosis fetalis (hemolytic disease of the newborn):

Occurs in Rh incompatibility cases where the mother is Rh(-) and the fetus is Rh(+).

During the first pregnancy, fetal red blood cells bearing the Rh antigen come into contact with the Rh(-) mother's immune system at birth, leading to maternal sensitization (primary immune response with IgM anti-Rh antibody production).

In subsequent pregnancies with persistent incompatibility, a secondary immune response in the mother triggers the production of IgG anti-Rh antibodies, which cross the placenta into the fetal circulation, causing lysis of fetal erythrocytes. The baby is born with hemolytic anemia and is at risk of kernicterus if indirect bilirubin levels exceed 20 mg% (toxic accumulation in basal ganglia with neurological sequelae).

Pernicious anemia:

An autoimmune disease characterized by impaired absorption of vitamin B12 due to a lack of intrinsic factor. This deficiency is caused by the production of autoantibodies against gastric parietal cells (cells that produce hydrochloric acid and intrinsic factor).

Graves' disease:

Production of autoantibodies with stimulatory effects that bind to thyroid-stimulating hormone (TSH) receptors on the thyroid gland, leading to hyperthyroidism.

Myasthenia gravis:

Production of autoantibodies against acetylcholine receptors on the postsynaptic membrane of the neuromuscular junction, resulting in episodes of severe muscle weakness and hypotonia.

2.3. Type III Hypersensitivity (Immune Complex-Mediated)

Type III hypersensitivity reactions encompass conditions such as acute hypersensitivity pneumonitis (extrinsic allergic alveolitis), drug-induced vasculitis, serum sickness, and the Arthus reaction. These reactions are also linked to autoimmune disorders like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and post-streptococcal glomerulonephritis. The mechanism involves IgM or IgG antibodies binding to soluble antigens (e.g., drugs, venoms) to form immune complexes. When immune complex clearance is impaired—due to dysfunctional mononuclear phagocyte (MO) systems or excessive complex production (e.g., chronic infections, autoimmune/neoplastic diseases)—these complexes deposit in porous tissues such as small blood vessels, synovial joints, glomeruli, and alveoli. Tissue deposition activates the complement cascade, releasing chemotactic factors that recruit neutrophils (NEU). This triggers inflammation, oxidative stress, and proteolytic enzyme release, culminating in tissue damage.

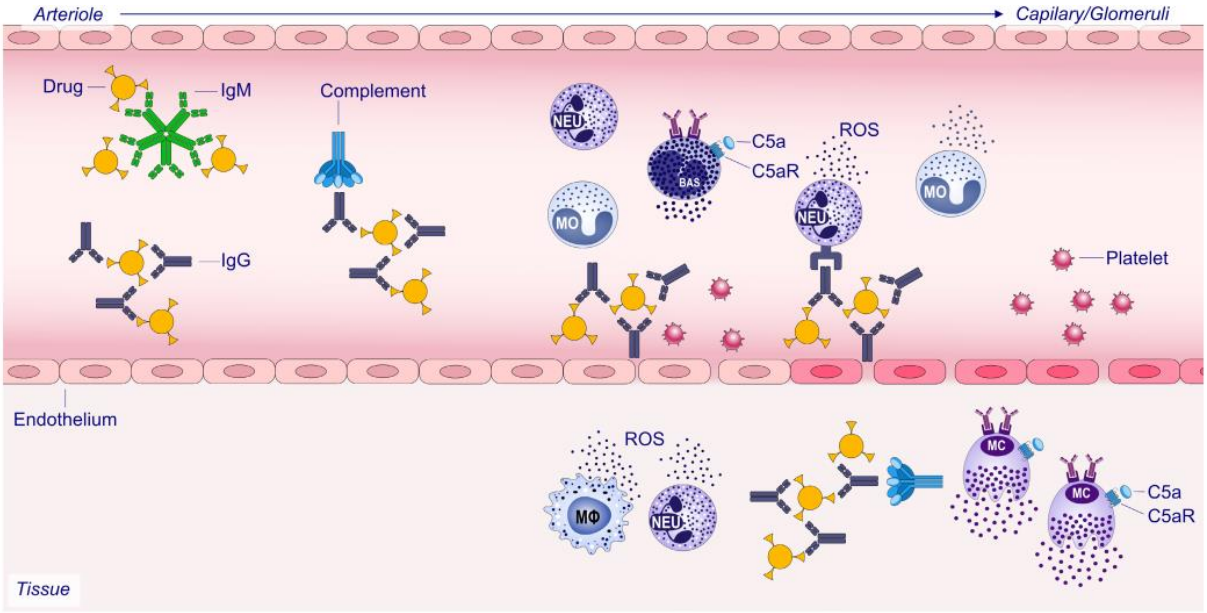


Figure 33 . Hypersensitivity type III induction.

Type III hypersensitivity encompasses conditions such as acute hypersensitivity pneumonitis, drug-induced vasculitis, serum sickness, and the Arthus reaction. These reactions involve IgM or IgG antibodies binding to soluble antigens (e.g., drugs, venoms) to form immune complexes. When clearance by the mononuclear phagocyte (Mφ) system is impaired, these complexes deposit in tissues like blood vessels, synovial joints, kidney glomeruli, and lung alveoli. Complement activation follows, increasing vascular permeability and triggering chemotaxis. Neutrophils (NEU) and macrophages (MO) are recruited, releasing proteolytic enzymes and reactive oxygen species (ROS), which propagate inflammation. Basophils (BAS) and mast cells (MC) further amplify inflammation by releasing mediators (e.g., histamine, cytokines) upon binding complement fragment C5a via C5a receptors. This cascade of events can lead to fibrinoid necrosis, thrombosis, and vasculitis. BAS, basophil; C5a(R), complement component 5a (receptor); MO, monocyte; MC, mast cell; Mφ, macrophage; NEU, neutrophil; IgG/M, immunoglobulin class G/M; ROS, reactive oxygen species.

2.3.1. Clinical forms of type III hypersensitivity

Depending on the location of the antigen-antibody reaction, two forms can be distinguished:

a. Systemic Reaction

(When immune complex deposition affects one or more tissues or organs, leading to the following conditions):

Serum Sickness

Caused by the therapeutic administration of animal antitoxin serum (e.g., horse-derived tetanus antitoxin) in humans. This induces the synthesis of specific antibodies directed against animal proteins (horse Ig, which is antigenic for humans).

Generalized lesions (vasculitis, arthritis, glomerulonephritis) peak between 8-14 days after exposure. The lesions then diminish as the immune complexes are phagocytosed and cleared from circulation.

Post-Streptococcal Glomerulonephritis

Occurs after streptococcal pharyngitis and is caused by the deposition of immune complexes in the glomerular basement membrane. This triggers local complement activation and lesions responsible for hematuria and proteinuria.

Drug-Induced Immune Anemia and Thrombocytopenia

Associated with drugs such as quinine, quinidine, and phenacetin.

Autoimmune Diseases

Includes systemic lupus erythematosus and rheumatoid arthritis.

b. Local Reaction

(When immune complexes are formed at the site of antigen entry, leading to the following conditions):

Arthus Reaction

A typical localized experimental form of Type III HS.

Cause : Repeated intradermal administration of low doses of antigen in laboratory animals (e.g., rabbits) increases circulating IgG levels.

Effects : Subsequent local administration of a high dose of antigen triggers local complement activation, resulting in an inflammatory infiltrate rich in neutrophils at the injection site. This leads to necrotizing vasculitis due to the destruction of the vascular basement membrane.

Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis)

Causes : Chronic inhalation of organic antigens leads to the development of granulomatous interstitial lung lesions. Both Type III and Type IV hypersensitivity reactions are involved in the pathogenesis.

Clinical Forms :

Farmer’s Lung : Caused by antigens found in moldy hay.

Bird Breeder’s Lung : Caused by antigens from pigeon droppings.

2.4. Type IV Hypersensitivity (Delayed-Type Hypersensitivity)

Type IV hypersensitivity is mediated by T cells and monocytes and typically occurs hours to days after antigen exposure. It involves the release of cytokines and chemokines, which recruit inflammatory cells to the site of antigen exposure. Examples include contact dermatitis, tuberculin reactions, and drug-induced hypersensitivity reactions.

2.4.1. Type IVa – T1 Immune Response

The hallmark clinical manifestations of type IVa reactions include allergic contact dermatitis, the chronic phase of hypersensitivity pneumonitis (also known as extrinsic allergic alveolitis), and celiac disease. These reactions also play a critical role in non-T2 endotypes of conditions such as asthma, allergic rhinitis (AR), chronic rhinosinusitis (CRS), and atopic dermatitis (AD). Additionally, type IVa mechanisms account for non-immediate allergic drug reactions, which occur when the drug undergoes haptenization by binding to a carrier protein.

Type IVa hypersensitivity encompasses a range of immune-mediated conditions driven by Th1 memory cells and their interactions with both innate and adaptive immune components. In allergic contact dermatitis (ACD), the triggering hapten, a small molecule, binds to host proteins such as epidermal proteins to become immunogenic through a process called haptenization. Antigen-presenting cells (APCs) present the hapten-protein complex to memory Th1 cells, which have been primed by prior cytokine exposure. Once activated, these Th1 cells produce pro-inflammatory cytokines like IFN-γ and TNF-α, recruiting and activating immune cells such as macrophages (Mφ), cytotoxic T cells (Tc), and natural killer (NK) cells. Macrophages generate reactive oxygen species (ROS), while Tc and NK cells release granzymes and perforins, causing inflammation and tissue damage. Innate lymphoid cells type 1 (ILC1s) further amplify the response by secreting large amounts of IFN-γ. Similarly, in the chronic phase of hypersensitivity pneumonitis, an immune response is mounted against inhaled airborne allergens, leading to inflammation in the lung parenchyma, granuloma formation, and eventual scarring (fibrosis) of lung tissue. Celiac disease, another condition associated with type IVa hypersensitivity, is mediated by gliadin-specific Th1 cells that induce intestinal inflammation upon the ingestion of gluten-containing cereals. Chronic inflammation damages intestinal villi and triggers the production of autoantibodies, such as anti-tissue transglutaminase antibodies (tTG-IgA), anti-endomysial antibodies (EMA-IgA), and anti-deamidated gliadin peptide antibodies (DGP-IgA and DGP-IgG), reflecting the mixed allergic-autoimmune nature of the disease.

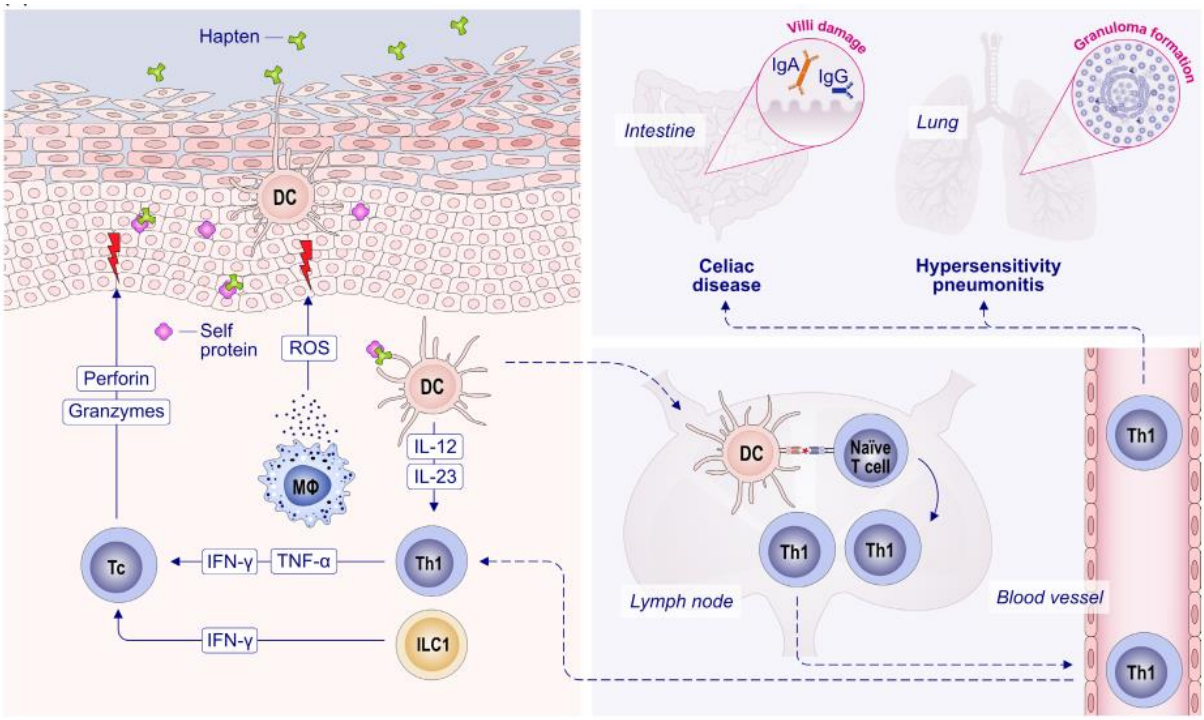


Figure 34 . Hypersensitivity type IVa induction.

ACD, allergic contact dermatitis; AD, atopic dermatitis; DC, dendritic cell; IFN-γ, interferon-gamma; IgA/G, immunoglobulin A/G; IL, interleukin; ILC1, type 1 innate lymphoid cell; Mφ, macrophage; ROS, reactive oxygen species; Th naïve/1/2, T helper lymphocyte naïve/1/2 type; Tc, cytotoxic lymphocyte; TNF-α, tumour necrosis factor-alpha.

2.4.2. Type IVb hypersensitivity

Type IVb hypersensitivity, associated with a T2 immune response, is most prominently expressed in classical allergic reactions characterized by chronic airway inflammation, as seen in conditions like allergic rhinitis (AR), chronic rhinosinusitis with nasal polyps (CRS), asthma, atopic dermatitis (AD), food allergies, eosinophilic esophagitis (EoE), and protein-contact dermatitis. The key players in this response include Th2 cells, innate lymphoid cells type 2 (ILC2s), natural killer T (NK-T) cells, eosinophils, and a subset of alternatively activated macrophages (Mφ). These mechanisms are evident in AR, AD, asthma (T2 endotype), CRS with nasal polyposis, EoE, and food allergies. In Type IVb reactions, Th2 cells take center stage, driven by cytokines such as IL-4, IL-13, IL-5, IL-9, and IL-31. These cytokines stimulate B cells to undergo class switching to produce IgE (via IL-4 and IL-13) and promote eosinophilia (via IL-5), leading to inflammation and tissue damage. IL-31, primarily secreted by Th2 cells, activates sensory neurons through IL-31 receptors, triggering the release of neuropeptides like CGRP and NGF, which contribute to neurogenic inflammation and itching. Th9 cells, differentiated under the influence of IL-4 and TGF-

β, further enhance the response by promoting specific IgE synthesis and mast cell (MC) proliferation.

The process is further amplified by ILC2s, MCs, and alternatively activated Mφs. ILC2s, dendritic cells (DCs), and Th2 cells, activated by alarmins such as IL-25, IL-33, or thymic stromal lymphopoietin (TSLP), collaborate to produce cytokines that disrupt epithelial barriers, recruit eosinophils and basophils, and modulate antigen-presenting cell (APC) function, reinforcing the chronic nature of Type IVb reactions. NK-T cells also contribute by secreting IL-4 and IL-13, which drive alternative activation of Mφs and perpetuate inflammation. Eosinophils migrate to inflamed tissues, releasing cytotoxic granules and activating cytokines and chemokines, all of which contribute to tissue damage, cell death, and sustained inflammation. At later stages, when IgE production is triggered, Type IVb overlaps with Type I hypersensitivity. For example, T2-high asthma is marked by eosinophilic infiltration of the airways and overexpression of Th2-dependent cytokines (IL-4, IL-5, and IL-13). Similarly, AD often presents with elevated serum IgE levels and strong associations with other allergic diseases like asthma and AR.

Food allergies can involve both IgE-dependent and IgE-independent pathways, reflecting mixed hypersensitivity responses. Delayed food-allergy-associated atopic dermatitis (occurring 6–48 hours post-exposure) and eosinophilic gastrointestinal disorders, such as EoE, represent IgE-independent manifestations driven by T2 cells (Type IVb hypersensitivity). The esophageal epithelium plays a critical role in these processes by producing members of the IL-1 cytokine family, including IL-33, IL-36, and TSLP, which regulate pro-inflammatory and anti-inflammatory responses. This balance ultimately influences the progression and severity of Type IVb hypersensitivity reactions.

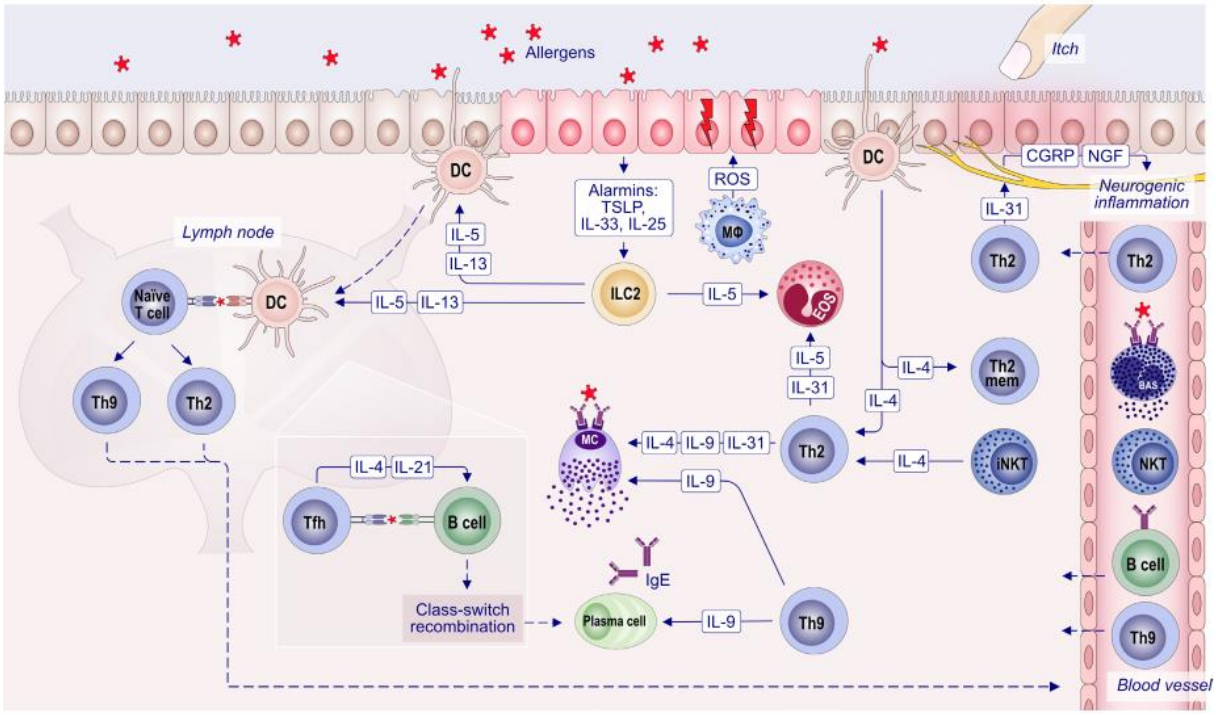


Figure 35 . Hypersensitivity type IVb induction.

AD, atopic dermatitis; AR, allergic rhinitis; APC, antigen-presenting cell; B, B lymphocyte; BAS, basophil; CGRP, calcitonin gene-related peptide; DC, dendritic cell; EOS, eosinophil; EoE, eosinophilic oesophagitis; (s) IgE, (allergen-specific) immunoglobulins class E; ILC2, type 2 innate lymphoid cell; IL, interleukin; (i)NKT, (invariant) natural killer T cells; Mφ, macrophage; MC, mast cell; Mf, macrophage; NGF, nerve growth factor; ROS, reactive oxygen species; Th0/2/9, T helper lymphocyte naïve/type 2 or 9; T2, type 2 immune response; Tfh, T follicular helper cell; TGF-β, tumour necrosis factor beta; Th mem, Th memory cells; TSLP, thymic stromal lymphopoietin. .

2.4.3. Type IVc – T3 immune response

Th17 cells, Tc17 cells, ILC3s, and other cells producing IL-17A and IL-17F have been linked to neutrophilic inflammation and the development of conditions such as atopic dermatitis (AD) and neutrophilic asthma. In type IVc hypersensitivity responses, Th17 cells, a subset of helper T cells, secrete cytokines from the IL-17 family. These cytokines regulate innate immune effectors and drive localized inflammation by promoting the release of proinflammatory cytokines and chemokines. This process recruits neutrophils (NEU) and amplifies the production of Th2 cytokines. Memory Th17 cells develop their characteristic phenotype when exposed to specific cytokines—IL-6, IL-21, IL-23, and TGF-β—provided by antigen-presenting cells (APCs). The primary effector cytokines produced by Th17 cells include IL-17A, IL-17F, IL-21, IL-22, and granulocyte-macrophage colony-stimulating factor (GM-CSF).

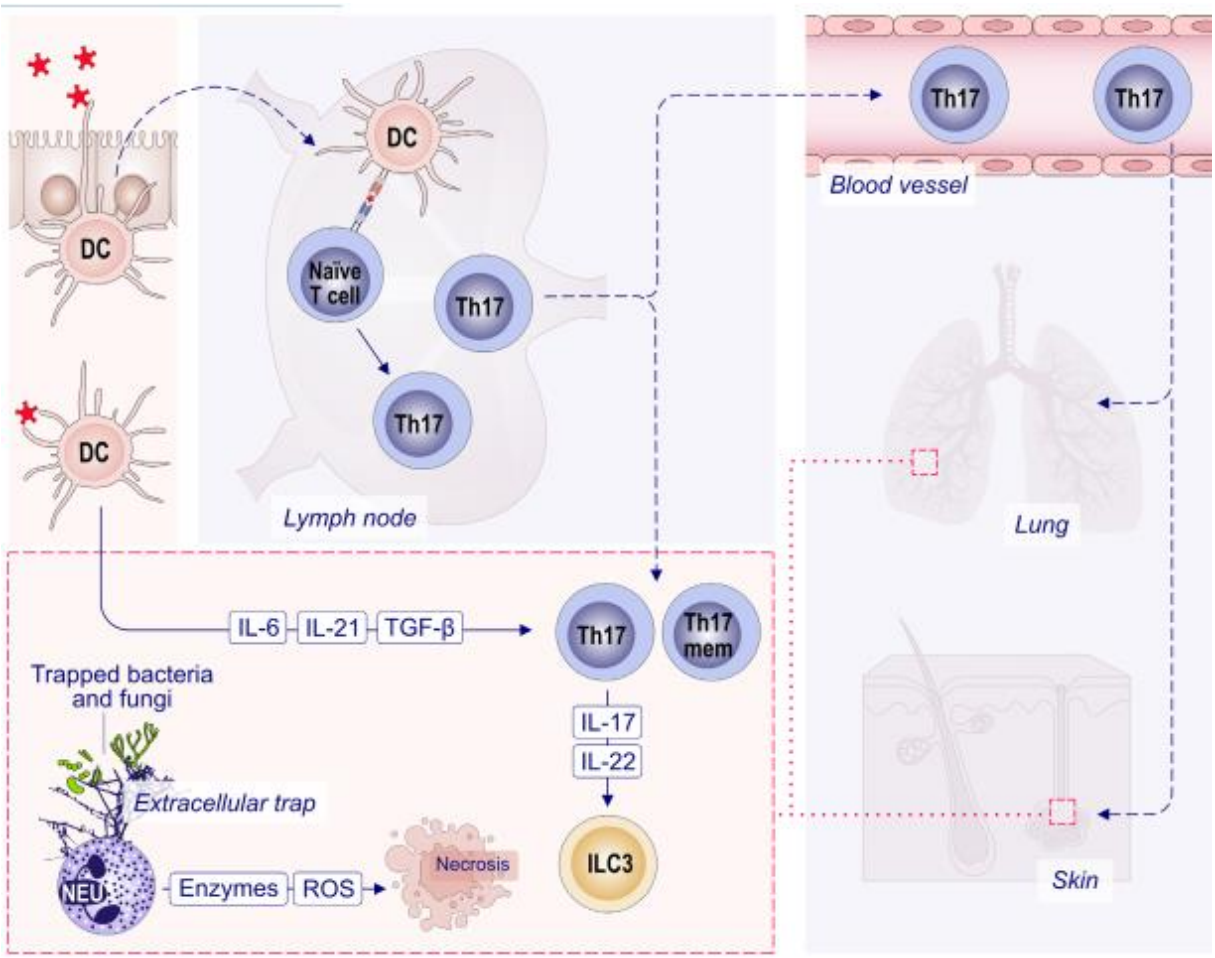


Figure 36 . **Hypersensitivity type IVc induction.**

Type IVc hypersensitivity plays a significant role in the pathogenesis of conditions such as atopic dermatitis (AD), chronic rhinosinusitis with nasal polyps, and neutrophilic asthma. In this type of hypersensitivity, Th17 cells and innate lymphoid cells type 3 (ILC3) are central players, producing cytokines from the IL-17 family. These cytokines drive inflammation by recruiting neutrophils and amplifying the production of Th2 cytokines. Certain bacterial and fungal components can stimulate Th17 responses, which may lead to tissue damage through mechanisms such as the "respiratory burst," enzyme release, or the formation of neutrophil extracellular traps (NETs). NETosis, a process where neutrophils release NETs to trap and kill pathogens, is a critical component of the immune response against bacteria and fungi. This mechanism is particularly relevant in diseases like AD and neutrophilic asthma.

In some cases of AD, normal serum IgE levels are observed, reflecting a more diverse immune profile involving Th1, Th17, and Th22 cells. These patients often exhibit more severe skin barrier dysfunction, making them more prone to irritant contact dermatitis. The interplay between these immune pathways highlights the complexity of type IVc hypersensitivity and its contribution to chronic inflammatory conditions affecting the skin and respiratory system. AD, atopic dermatitis; DC,

dendritic cell; IgE, immunoglobulin E; IL, interleukin; ILC3, type 3 innate lymphoid cell; NET, neutrophil extracellular trap; NET, neutrophil extracellular trap; NK, natural killer cell; ROS, reactive oxygen species; TGF-β, tumour necrosis factor-beta; Th naïve/2/17/22, T helper lymphocyte naïve/2/17/22 type; Th17 mem, memory Th17.

2.5. Type V – epithelial barrier defect

In certain cases, the inflammatory response seems to stem from a compromised skin or mucosal barrier rather than from an inherent immune system imbalance. The disruption of the epithelial barrier enables the activation of the underlying immune system, which can then lead to chronic inflammation. This loss of barrier function may arise from defects in various critical components, such as structural elements of the skin's stratum corneum, tight junction proteins in both skin and mucosa, protective antiproteases, antimicrobial product expression, and the transport of ions, protons, water, or antimicrobial substances, among other mechanisms. Activation of sensory nerves—which plays a role in triggering allergic symptoms—is also linked to barrier dysfunction. Furthermore, intestinal barrier dysfunction can occur due to mucus erosion caused by low-fiber diets. This understanding has led to the introduction of type V hypersensitivity to highlight the unique aspects of these pathological processes, particularly given their significance for personalized and precision medicine approaches to endotype and biomarker identification. These insights are especially crucial in the context of rapidly advancing biological treatments, including therapies targeting anti-alarmins.

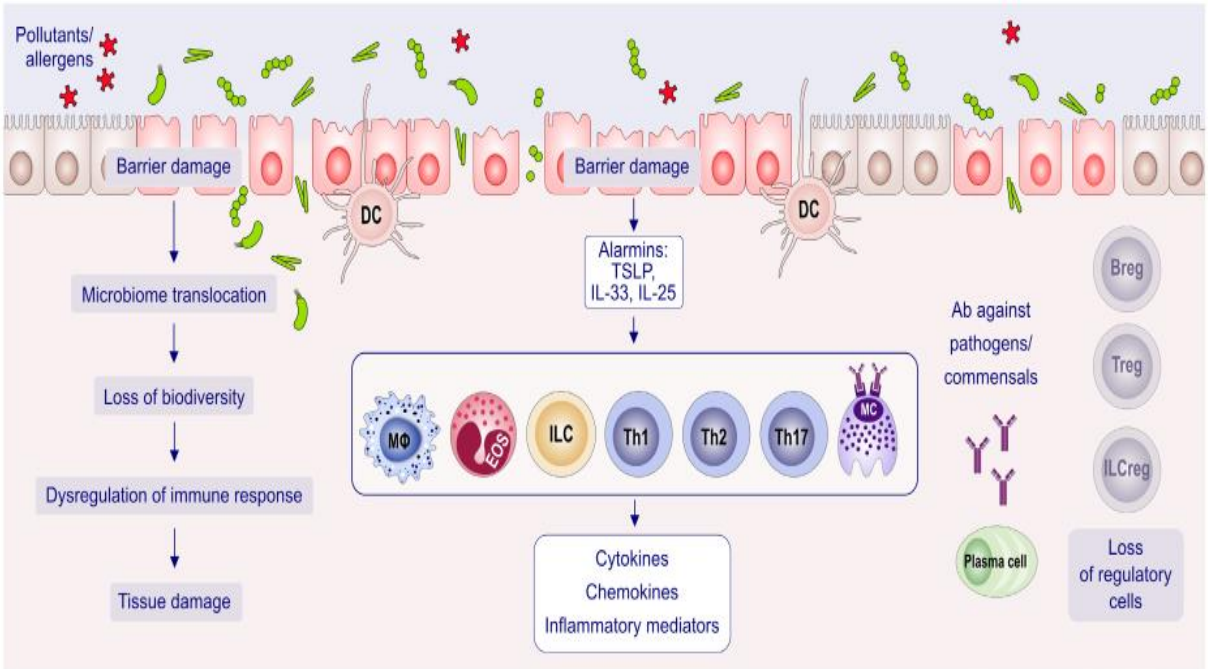


Figure 37 . Hypersensitivity type V induction.

Type V hypersensitivity involves a cascade of mechanisms that contribute to the pathogenesis of various inflammatory and allergic conditions, including asthma, chronic allergic rhinitis (AR)/allergic rhinoconjunctivitis (ARC), chronic rhinosinusitis (CRS), atopic dermatitis (AD), food protein-induced enterocolitis syndrome (FPIES), eosinophilic esophagitis (EoE), and celiac disease. Central to this process is the dysfunction of the epithelial barrier, often accompanied by microbial dysbiosis, which disrupts immune regulation.

This disruption manifests as an imbalance in immune responses, characterized by the overactivation of T helper type 1 (T1), T helper type 2 (T2), and T helper type 17 (T17) pathways. Simultaneously, there is a loss or impairment of regulatory immune cells, such as regulatory T cells (Tregs), regulatory B cells (Bregs), and regulatory innate lymphoid cells (ILCregs). These changes result in unchecked inflammation. Additional mechanisms include the formation of specific immunoglobulin E (sIgE) antibodies against inhaled or ingested allergens, activation of macrophages (Mφ), mast cells (MC), and basophils (BAS), and the release of proinflammatory cytokines, chemokines, and mediators such as histamine, leukotrienes, and reactive oxygen species (ROS). This cascade of events culminates in tissue damage, which is evident in the clinical manifestations of asthma, chronic AR/ARC, CRS, AD, FPIES, EoE, and celiac disease. Furthermore, immune responses to opportunistic pathogens and commensal microorganisms, such as Staphylococcus aureus, can exacerbate the condition. Microbiome translocation, where microbes cross the compromised epithelial barrier, triggers the production of IgE antibodies against these organisms, perpetuating the cycle of inflammation and tissue injury. Ab, antibody; AD, atopic dermatitis; AR/ARC, allergic rhinitis/rhinoconjunctivitis; BAS, basophil; Breg, B regulatory cells; CRS, chronic rhinosinusitis; DC, dendritic cell; EOS, eosinophil; EoE, eosinophilic oesophagitis; IL, interleukin; ILC, innate lymphoid cell; ILCreg, ILC regulatory cells; MC, mast cell; Mφ, macrophage; FPIES, food protein-induced enterocolitis syndrome; ROS, reactive oxygen species; sIgE, allergen-specific immunoglobulins class E; Th1/2/17, T helper lymphocyte type 1/2/17; Treg, T regulatory cells; TSLP, thymic stromal lymphopoietin.

2.6. Type VI – metabolic-induced immune dysregulation

Obesity serves as a key distinguishing factor for classifying and clustering asthma subtypes. Obese individuals with asthma, who are more often female, tend to develop adult-onset asthma and are at higher risk of corticosteroid resistance, hospitalization, and severe disease.

Obesity influences asthma through multiple mechanisms, including altered chest wall dynamics and direct or indirect effects on inflammatory responses. Direct effects involve the release of inflammatory mediators from adipose tissue, while indirect effects stem from dietary changes typical of obesity, such as high consumption of processed fats and low fiber intake. Increased body mass index (BMI) correlates with elevated levels of circulating inflammatory mediators, as well as

higher blood neutrophil and eosinophil counts. Obesity is also associated with elevated levels of acute-phase reactants, reactive oxygen species (ROS), chemokines, and innate proinflammatory cytokines, including those derived from adipose tissue like leptin. However, there is typically no significant increase in serum cytokines linked to T-cell polarization, such as TH2 cytokines. Adipose tissue plays a central role in this inflammatory process. Stressed and hypoxic adipocytes contribute to systemic inflammation by releasing inflammatory mediators, but activated tissue macrophages (Mφ) are particularly critical in driving both inflammatory responses and metabolic dysfunction associated with obesity. In obese asthmatics, the combination of asthma and obesity leads to an additive effect, characterized by heightened release of pro-inflammatory mediators and airway inflammation. This interaction also modifies the microbiome of the gut, nasal passages, oral cavity, and lungs, which is closely tied to inflammatory responses.

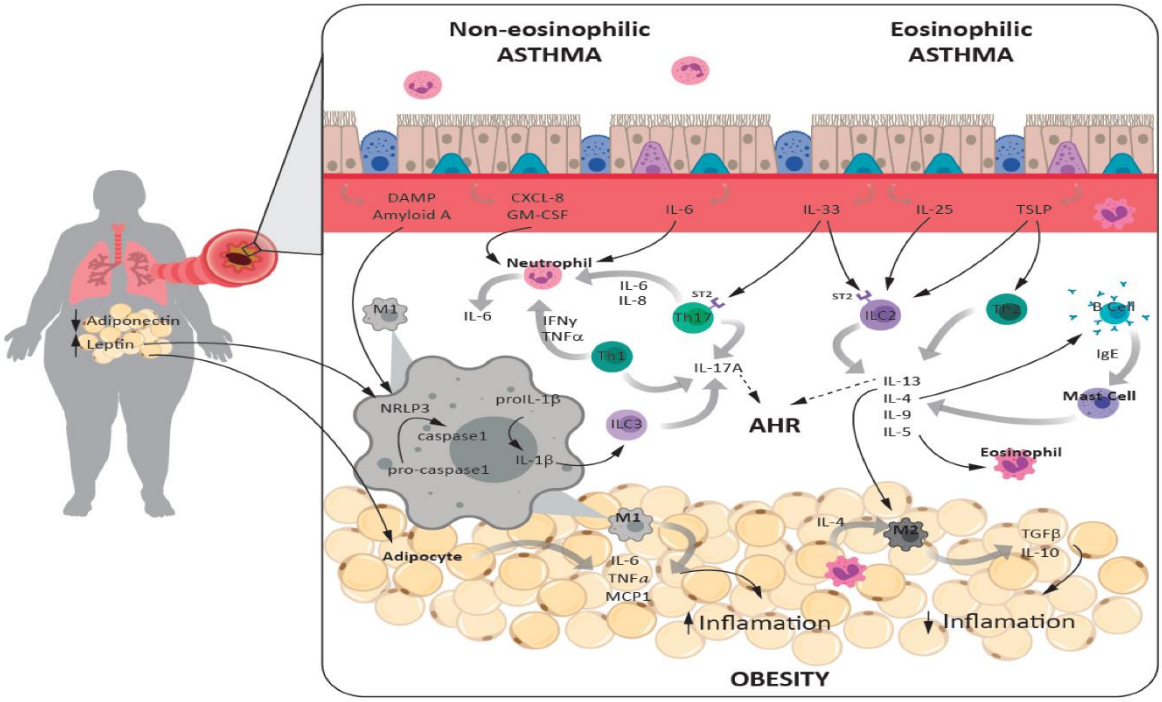


Figure 38 . Hypersensitivity type VI characteristics.

The connection between inflammatory processes in the asthma-obesity phenotype reveals a complex interaction. Eosinophilic asthma is driven by type 2 inflammation, involving Th2 cells, ILC2, and type 2 cytokines like IL-4, IL-5, and IL-13. This form of asthma can be allergic (when IgE is present) or non-allergic. In contrast, non-eosinophilic asthma, characterized by neutrophils in the airway lumen, is mediated by type 1 inflammation, with contributions from Th1, Th17 cells, and ILC3 releasing type 1 cytokines such as IL-17. Obesity-related inflammation arises from an imbalance in adipokines, particularly elevated leptin levels. Leptin triggers adipocytes to release inflammatory mediators and activates M1 macrophages through the NLRP3 inflammasome, a

multiprotein complex. Activation of NLRP3 in M1 macrophages within adipose tissue and the lungs leads to increased production of IL-1β, which activates ILC3 cells and promotes IL-17 secretion. This cascade contributes to airway hyperresponsiveness (AHR) in obese patients. In obesity, pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα play a role in asthma development. Conversely, cytokines that are typically pro-inflammatory in asthma, like IL-4, IL-13, and IL-33, help maintain a lean state by activating anti-inflammatory M2 macrophages. This highlights the dual and sometimes opposing roles of these cytokines in the context of obesity and asthma.

2.7. Type VII – direct cellular and inflammatory response to chemical substances

Type VII hypersensitivity reactions are observed in patients with allergic rhinitis (AR), allergic rhinoconjunctivitis (ARC), asthma, atopic dermatitis (AD), acute urticaria/angioedema, and drug allergies. Among these, idiosyncratic reactions include cross-reactive hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs). These reactions manifest in at least three distinct phenotypes, depending on the presence or absence of underlying respiratory or skin conditions:

- NSAIDs-exacerbated respiratory disease (NERD) , which occurs in individuals with rhinitis and/or asthma, with or without nasal polyposis.
- NSAIDs-exacerbated cutaneous disease , seen in patients with chronic spontaneous urticaria.
- NSAIDs-induced acute urticaria/angioedema , which affects otherwise healthy individuals.

Recently, additional phenotypes involving simultaneous respiratory and cutaneous symptoms following NSAID intake have been extensively described. The underlying mechanism of these reactions involves the inhibition of cyclooxygenase-1 (COX-1) and the release of eicosanoid mediators in susceptible individuals. This mechanism has also been proposed for NSAID-induced acute urticaria/angioedema.

Aspirin-exacerbated respiratory disease (AERD) is characterized by asthma, chronic rhinosinusitis with nasal polyposis, and pathognomonic respiratory reactions to aspirin.

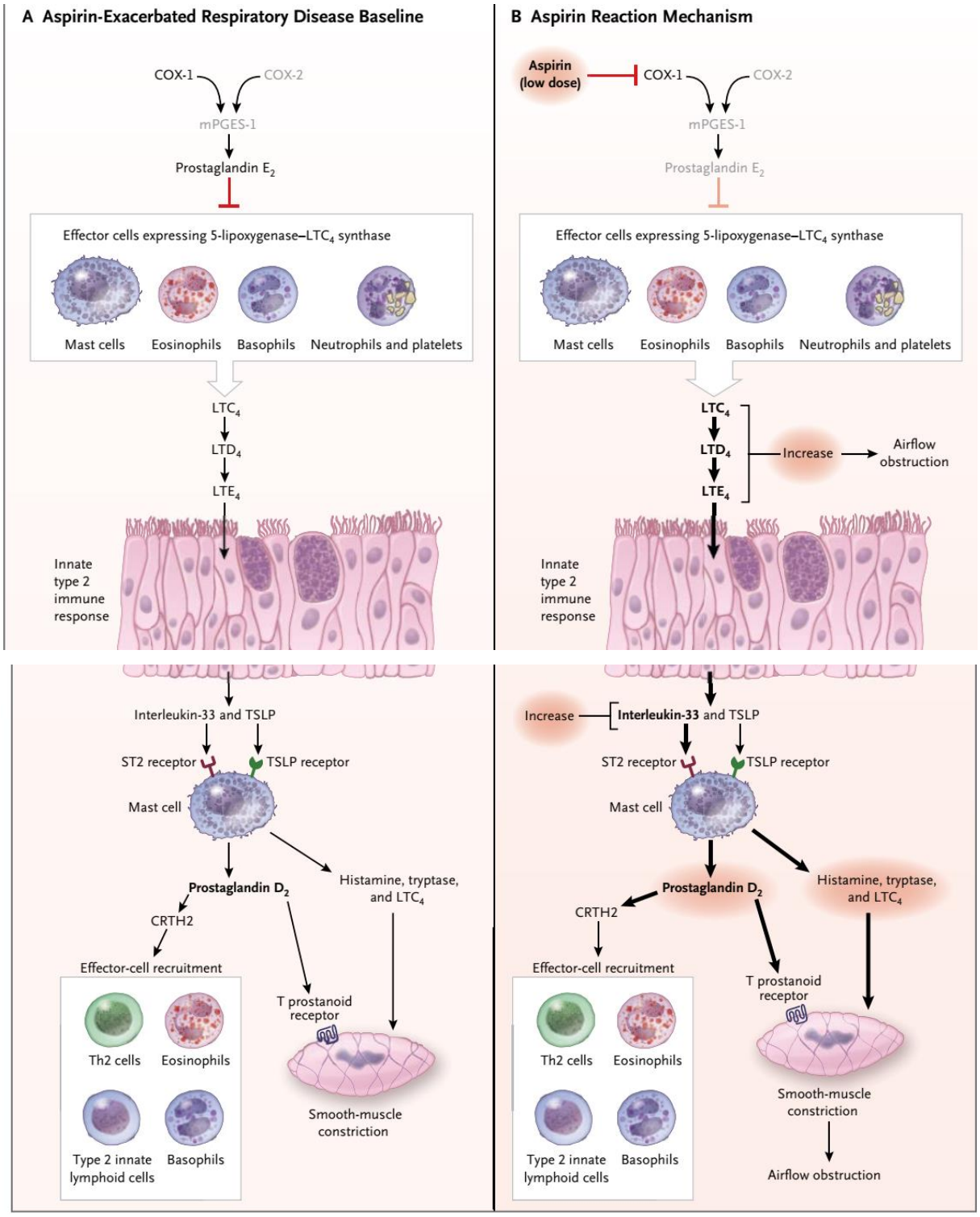


Figure 39 . Hypersensitivity type VII induction.

In Panel A , a deficiency in the function of the inducible cyclooxygenase (COX)-2–microsomal prostaglandin E2 synthase 1 (mPGES-1) system, which is responsible for producing prostaglandin E2, leads to the continuous synthesis of leukotriene C4 (LTC4). This occurs in effector cells that express 5-lipoxygenase and LTC4 synthase, including platelets that express LTC4 synthase and are attached to granulocytes expressing 5-lipoxygenase. Additionally, cytokines such as interleukin-33

and thymic stromal lymphopoietin (TSLP), released by structural cells, perpetuate inflammation and stimulate mast cells to release products like prostaglandin D2.

In Panel B , the use of aspirin or other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) reduces the remaining levels of prostaglandin E2. This depletion enhances the activation of 5-lipoxygenase, leading to increased production of LTC4. Cysteinyl leukotrienes trigger the release of interleukin-33, which activates mast cells. Bronchoconstriction results from the direct effects of cysteinyl leukotrienes, prostaglandin D2, and other mast cell-derived mediators. Prostaglandin D2 also recruits immune cells expressing CRTH2 (a receptor found on type 2 helper T cells) to respiratory tissues and induces bronchoconstriction through T prostanoid receptors. Abbreviations: LTD4 refers to leukotriene D4, LTE4 to leukotriene E4, and ST2 to suppression of tumorigenicity 2.

3. Diagnostic techniques of hypersensitivity

Diagnostic tests for allergies are essential tools to identify specific allergens triggering allergic reactions. The most common types of tests include skin tests, which are widely used due to their rapid results and cost-effectiveness. These include the Skin Prick Test (SPT), where small amounts of suspected allergens are introduced into the skin to observe any reaction, and the Intradermal Skin Test, which involves injecting a small amount of allergen under the skin. Another skin-based method is the Allergy Patch Test or Epicutaneous Test, often used for contact dermatitis. In addition to skin tests, blood tests are also utilized to measure IgE antibodies against specific allergens, offering an alternative for patients who may not be suitable for skin testing. Blood tests can also provide detailed component testing, helping to differentiate between genuine allergies and cross-reactive sensitizations.

Other less conventional methods, such as cytotoxic food testing, kinesiology, and hair analysis, exist but are not scientifically validated and are generally not recommended by clinical immunologists. For cases requiring more direct assessment, provocation tests may be conducted under medical supervision to confirm an allergy diagnosis.

While skin tests are preferred for their speed and affordability, blood tests offer a useful alternative in certain scenarios, such as when antihistamines cannot be discontinued or if there is extensive skin disease. Each test type has its pros and cons, and the choice depends on the patient's condition and the suspected allergens

4. Treatment of hypersensitivity

The treatment of hypersensitivity focuses on targeting various stages of the allergic reaction cascade to alleviate symptoms and prevent future episodes. Antihistamines are used to block

histamine receptors, reducing symptoms like bronchoconstriction, vasodilation, and increased vascular permeability. Mast cell stabilizers, such as cromolyn sodium, prevent degranulation and the release of inflammatory mediators. In severe cases like anaphylaxis, epinephrine is administered to counteract systemic effects. Steroids can stop mast cell contraction and reduce inflammation, while local phase inhibitors mitigate the effects of released mediators. For long-term management, desensitization or immunotherapy gradually exposes patients to small doses of the allergen to induce tolerance, often by promoting the production of blocking IgG antibodies that intercept allergens and prevent IgE-mediated reactions. Additionally, glutaraldehyde may activate T suppressor cells to reduce IgE production, further controlling hypersensitivity. These strategies collectively aim to manage acute symptoms and reduce sensitivity over time.

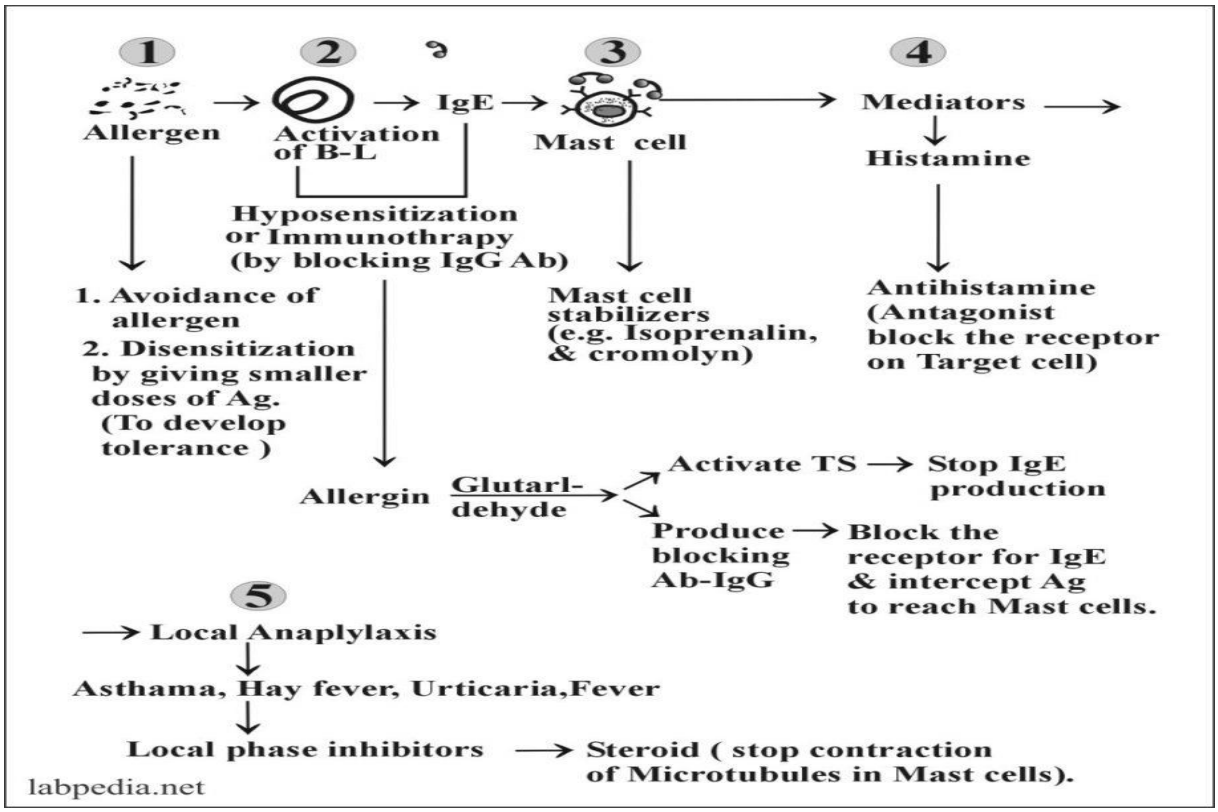


Figure 40 . Approaches for treatment of hypersensitivity.

4.2. Immunoregulatory Networks and Hypersensitivity

The immune system has regulatory mechanisms to prevent excessive or inappropriate immune responses. However, dysregulation of these mechanisms can contribute to hypersensitivity reactions.

4.2.1. Role of Regulatory T Cells (Tregs)

Regulatory T cells (Tregs) play a crucial role in maintaining immune tolerance and preventing autoimmune diseases. Insufficient Treg activity has been implicated in severe hypersensitivity

reactions, such as DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) and SJS/TEN. Enhancing Treg function may provide a potential therapeutic strategy for managing these reactions.

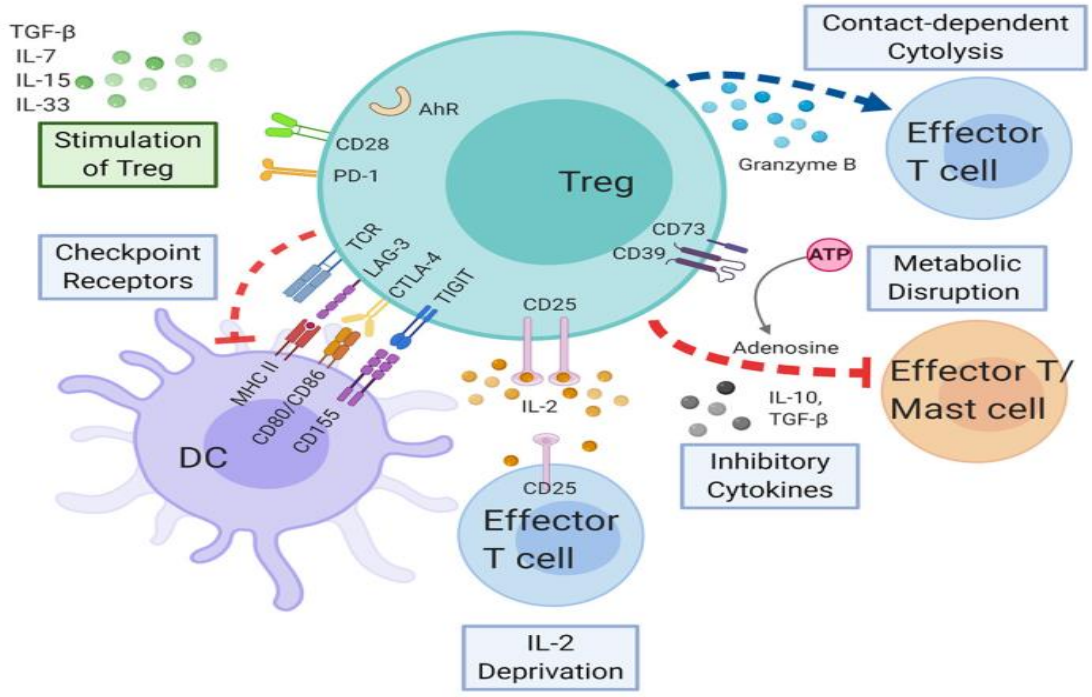


Figure 41 . Implication of Tregulatory cells in the treatment of hypersensitivity.

Regulatory T cells in delayed-type hypersensitivity. Tregs may exert immunosuppressive effect on APCs, effector T cells, and mast cells by the following mechanisms: coinhibitory receptors binding to cognate molecules on dendritic cells, secretion of inhibitory cytokines, e.g., IL-10 and TGF-b, metabolic disruption by depriving IL-2 binding and increasing adenosine binding to effector T cells, and contact-dependent cytolysis by granzyme B secretion. Likewise, cytokines and immunoregulatory molecules also modulate the Treg function. AHR, aryl hydrocarbon receptor; ATP, adenosine triphosphate; CTLA-4, cytotoxic T-lymphocyteassociated antigen 4; DC, dendritic cell; IL-2, interleukin 2; IL-7, interleukin 7; IL-10, interleukin 10; IL-15, interleukin 15; IL-33, interleukin 33; LAG-3, lymphocyteactivation gene 3; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; TCR, T cell receptor; TGF-b, transforming growth factor beta; TIGIT, T cell immunoreceptor with Ig and ITIM domains; Treg, regulatory T cell.

4.2.2. Co-Signaling Receptors

Co-signaling receptors, such as CTLA-4 and PD-1, regulate the balance between immune activation and tolerance. Dysregulation of these receptors can lead to excessive immune responses and hypersensitivity reactions. For example, immune checkpoint inhibitors (e.g., anti-CTLA-4 and anti-PD-1) used in cancer therapy can increase the risk of hypersensitivity reactions by enhancing T-cell activation.

Immunological targets and mechanisms of action of glucocorticoids

1. Introduction

Glucocorticoids are a class of steroid hormones that play pivotal roles in regulating metabolism, immune responses, and inflammation. These molecules are naturally produced in the adrenal cortex or synthesized synthetically for therapeutic use. They derive their name from their ability to regulate glucose metabolism, though their effects extend far beyond this function. The discovery of glucocorticoids dates back to the mid-20th century when researchers identified their anti-inflammatory properties. In 1948, the first synthetic glucocorticoid, cortisone, was used to treat rheumatoid arthritis, marking a revolutionary advancement in medicine. Since then, glucocorticoids have become indispensable in treating inflammatory and autoimmune diseases.

Key Functions

- Regulation of glucose metabolism by increasing gluconeogenesis in the liver.
- Modulation of immune responses to prevent overactivation and tissue damage.
- Suppression of inflammation through inhibition of pro-inflammatory pathways.

2. Nature and Origin of Glucocorticoids

2.1. Endogenous Production

Naturally occurring glucocorticoids, such as cortisol in humans, are produced by the adrenal glands in response to stress signals from the hypothalamic-pituitary-adrenal (HPA) axis.

The Hypothalamic-Pituitary-Adrenal (HPA) axis is a core neuroendocrine feedback loop that orchestrates the body's physiological response to stress, pain, and circadian cues. The cascade begins when neural inputs—such as emotional stress from the limbic system, circadian rhythms from the suprachiasmatic nucleus, or pain signals from peripheral nociceptors—stimulate the hypothalamus to secrete corticotropin-releasing hormone (CRH). This hormone signals the anterior pituitary to release corticotropin (ACTH) into the bloodstream, which subsequently prompts the adrenal gland to synthesize and secrete cortisol. Once released, cortisol exerts widespread metabolic, immune, and cardiovascular effects across target tissues. To maintain systemic homeostasis and prevent over-activation, the pathway concludes with a precise negative feedback mechanism, where elevated circulating cortisol levels directly inhibit the further release of both CRH from the hypothalamus and corticotropin from the anterior pituitary.

2.2. Circadian Rhythm:

Cortisol secretion follows a diurnal pattern, peaking in the early morning and declining throughout the day. This rhythm ensures optimal energy availability during active periods.

The circadian rhythm acts as the body's internal 24-hour master clock, coordinating the timing of physiological processes, metabolism, and behavior with the natural light-dark cycle.

In the context of the neuroendocrine pathways shown in the diagram, this rhythm is centrally regulated by the suprachiasmatic nucleus (SCN), a specialized region of the hypothalamus located directly above the optic chiasm. The SCN receives direct light inputs from the retina, allowing it to synchronize the body's internal chemistry with the external environment. One of its primary responsibilities is setting the baseline tone for the Hypothalamic-Pituitary-Adrenal (HPA) axis. Instead of being secreted at a constant rate, cortisol follows a strict circadian profile driven by this central clock:

The Morning Peak: Cortisol levels naturally rise sharply in the early morning hours, peaking roughly 30 to 45 minutes after waking (known as the cortisol awakening response). This surge helps mobilize energy reserves, increase blood pressure, and alertness to prepare the body for the day's demands.

The Nocturnal Trough: Throughout the day, levels gradually decline, reaching their lowest point around midnight, allowing the body to transition into restorative sleep and tissue repair.

When this circadian rhythm is disrupted—whether by chronic stress, shift work, or sleep deprivation—the SCN's control over the HPA axis becomes deregulated. This can lead to flattened cortisol curves (where morning levels are too low and night levels are too high), contributing to persistent fatigue, metabolic imbalances, and impaired immune function.

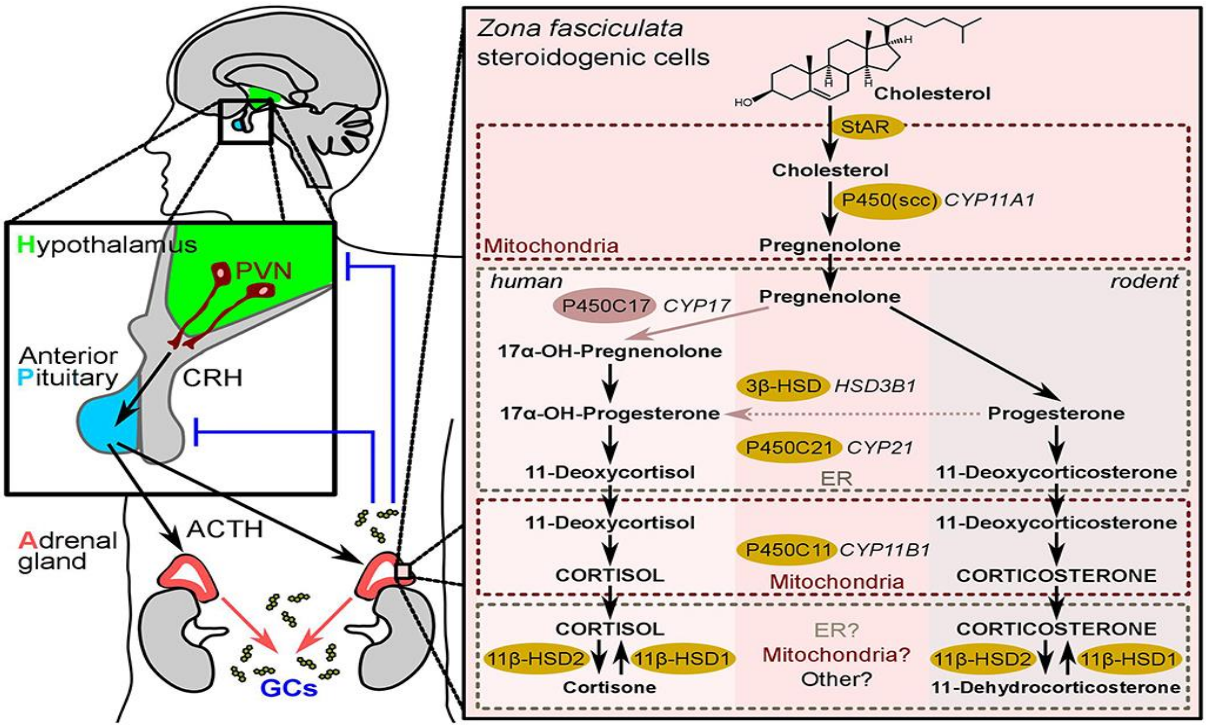


Figure 42 . Natural synthesis of glucorticoids in human body.

2.3. Synthetic Derivatives:

Synthetic glucocorticoids, including prednisone, dexamethasone, and hydrocortisone, mimic the actions of endogenous glucocorticoids but often have enhanced potency and longer durations of action.

- Examples of Synthetic Variants:
  - Prednisone: Used for its potent anti-inflammatory effects.
  - Dexamethasone : Known for its high receptor affinity and prolonged action.
  - Hydrocortisone : Often used in acute situations due to its rapid onset.
- Chemical Structure

Glucocorticoids share a four-ring steroid structure with specific functional groups that determine their biological activity. Modifications to the chemical structure can alter their potency, duration of action, and receptor-binding affinity.

3. Effects of Glucocorticoids

3.1 Anti-Inflammatory Effects

- Glucocorticoids exert their anti-inflammatory effects primarily by inhibiting the production of pro-inflammatory cytokines and chemokines, thereby attenuating the recruitment and activation of immune cells at sites of inflammation. This suppression operates through multiple molecular

mechanisms, most notably the inhibition of nuclear factor-kappa B, a pivotal transcription factor that orchestrates the expression of numerous inflammatory mediators including cytokines, chemokines, and adhesion molecules. By interfering with NF-κB signaling, glucocorticoids effectively block the transcriptional programs necessary for sustaining inflammatory responses. Additionally, these steroids reduce the expression of cyclooxygenase-2, the inducible enzyme responsible for converting arachidonic acid into prostaglandins during inflammatory states; this reduction in prostaglandin synthesis diminishes vasodilation, vascular permeability, and pain sensitization associated with inflammation. The clinical relevance of these immunomodulatory and anti-inflammatory properties is substantial, as glucocorticoids remain foundational therapies for a broad spectrum of chronic inflammatory conditions. They are widely employed in the management of asthma, where they suppress airway inflammation and bronchial hyperresponsiveness; in rheumatoid arthritis, where they mitigate synovial inflammation and joint destruction; and in inflammatory bowel disease, where they reduce mucosal immune activation and tissue damage. Through these convergent mechanisms, glucocorticoids provide essential therapeutic control over pathological inflammation across diverse organ systems.

3.2 Immunosuppressive Effects

Glucocorticoids exert broad immunosuppressive effects by impairing the function of multiple immune cell populations, including T cells, B cells, macrophages, and dendritic cells. On T lymphocytes, these steroids inhibit interleukin-2-driven proliferation and suppress the production of T-cell cytokines such as interferon-gamma and interleukin-17, thereby blocking clonal expansion and effector differentiation. B lymphocytes are similarly affected, as glucocorticoids suppress immunoglobulin synthesis and impair antibody-mediated immune responses. Macrophages exposed to glucocorticoids exhibit markedly reduced phagocytic activity and diminished capacity for antigen presentation, largely due to downregulation of major histocompatibility complex class II molecules and co-stimulatory signals. Dendritic cells also undergo functional impairment, losing their ability to mature fully and activate naive T cells. This collective dampening of adaptive and innate immune cell function underlies the critical therapeutic application of glucocorticoids in organ transplantation, where they help prevent allograft rejection by suppressing the recipient's immune recognition of donor tissues and blocking the cellular responses that would otherwise lead to graft destruction.

3.3 Metabolic Effects

- Beyond their well-established immune-modulating properties, glucocorticoids exert profound influences on metabolic homeostasis, specifically affecting glucose metabolism, protein catabolism, and lipid distribution throughout the body. In the liver, these steroids stimulate gluconeogenesis by upregulating key enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, which increases hepatic glucose output and raises circulating blood glucose levels. Concurrently, glucocorticoids induce peripheral insulin resistance in skeletal muscle and adipose tissue by interfering with insulin signaling pathways, reducing glucose transporter expression, and promoting lipolysis; the combination of enhanced hepatic glucose production and impaired peripheral glucose utilization frequently results in hyperglycemia and can precipitate steroid-induced diabetes mellitus with chronic exposure. Regarding protein and fat metabolism, glucocorticoids promote proteolysis in muscle tissue, leading to protein catabolism and muscle wasting, while simultaneously stimulating lipolysis and altering adipocyte differentiation. These effects on lipid metabolism produce a characteristic redistribution of body fat, with accumulation in the trunk, face, and neck and depletion in the extremities, contributing to the cushingoid phenotype observed in patients receiving long-term glucocorticoid therapy.

4. Mechanism of Action

4.1 Genomic Pathways

At the cellular level, the lipophilic steroid hormone cortisol diffuses across the plasma membrane into the cytoplasm of an endothelial cell, where its local availability is regulated by Type 2 11beta-hydroxysteroid dehydrogenase (11beta-HSD2) through conversion into its inactive form, cortisone. Free cortisol binds to the cytosolic glucocorticoid receptor (GR), triggering the dissociation of stabilizing heat shock proteins (HSPs) and inducing receptor phosphorylation. Once activated, this cortisol-GR complex operates through both rapid nongenomic activation in the cytoplasm to swiftly induce anti-inflammatory proteins, and slower genomic signaling within the nucleus via two distinct DNA-dependent pathways. In the first genomic pathway, known as transactivation, GR homodimers bind directly to glucocorticoid-responsive elements (GRE) on the DNA, driving the transcription and synthesis of anti-inflammatory proteins. In the second pathway, known as transrepression, the cortisol-GR complex directly interferes with pro-inflammatory transcription factors like NF-kappaB (activated by extracellular signals such as TNF-alpha or IL-1), physically blocking it from binding to its genomic targets, which halts mRNA production and effectively represses the synthesis of inflammatory proteins.

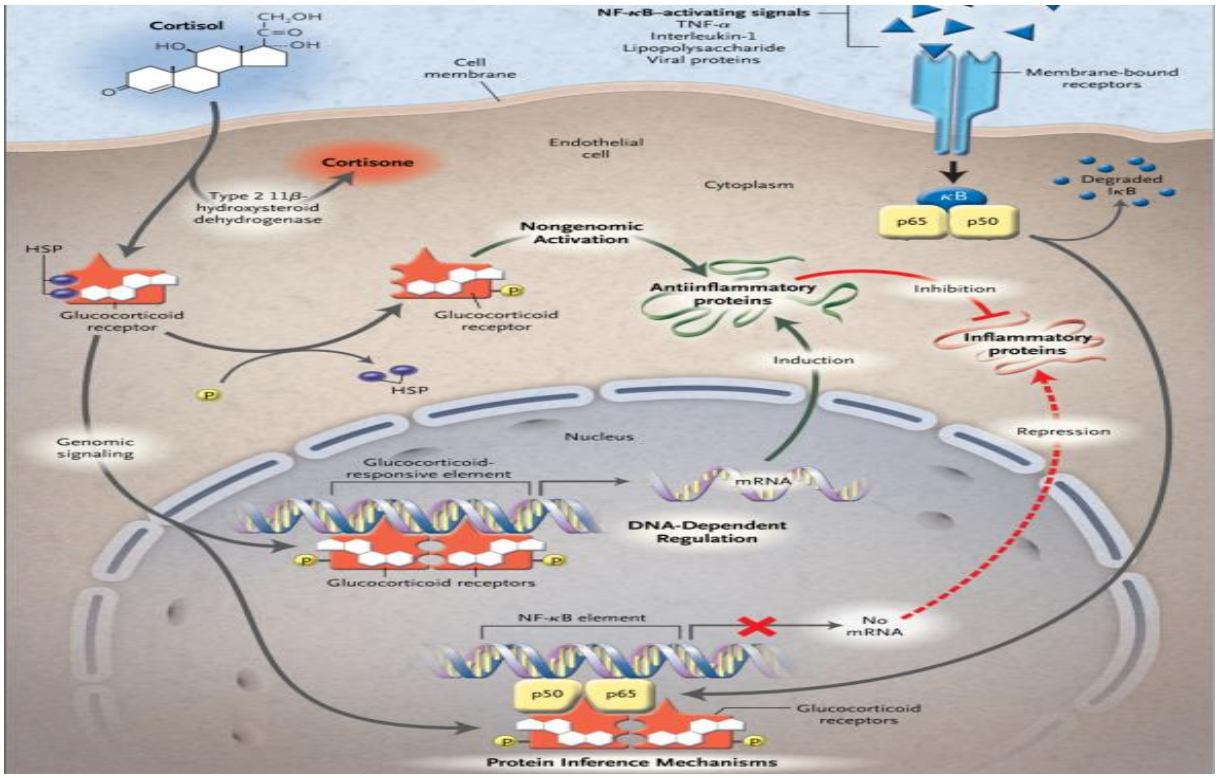


Figure 43 . **Genomic pathway of the glucocorticoids' inhibitory effect.**

4.2 Non-Genomic Pathways

At the molecular level, cortisol exerts master regulatory control over inflammation by multi-targeted disruption of both genomic transcription and enzymatic signaling cascades. The activated glucocorticoid receptor (GR) physically intercepts key inflammatory transcription factors, directly inhibiting NF-kappaB and c-Jun/Fos (AP-1) to halt the synthesis of downstream cytokines, adhesion molecules, and tissue-degrading metalloproteinases, while simultaneously utilizing negative GREs to actively repress genes like IL-1beta and CRH. Concurrently, the GR shuts down the arachidonic acid cascade by inducing Annexin I and MAPK phosphatase 1, which collectively deactivate MAPKs, Jun N-terminal kinase, and cytosolic phospholipase A_2alpha (cPLA_2alpha). This coordinated double-blockade completely starves the cell of lipid precursors and downregulates COX-2 expression, effectively halting the production of pro-inflammatory prostaglandins and leukotrienes to neutralize the inflammatory response at its source.

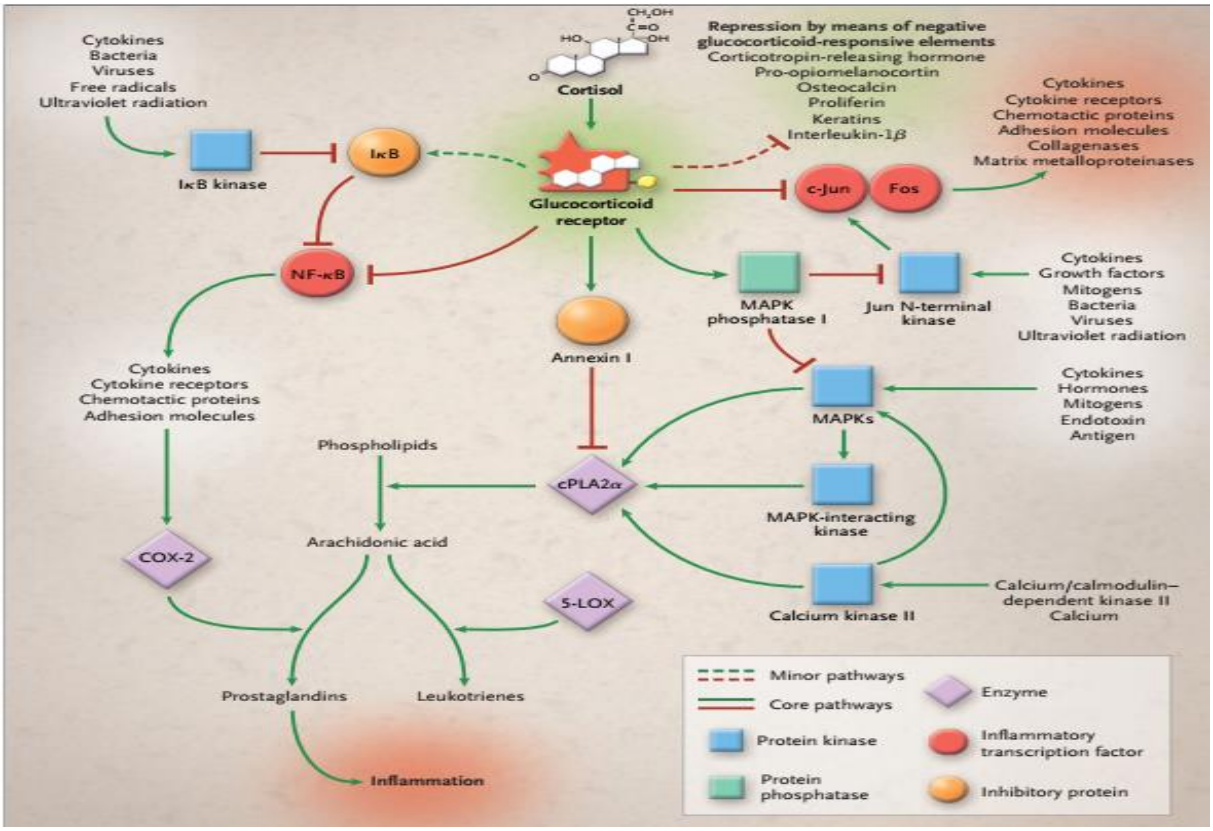


Figure 44 . **Non-genomic pathway of the glucocorticoids' inhibitory effect.**

Glucocorticoids suppress adaptive immunity by executing a coordinated, double-sided assault on the immunological synapse between dendritic cells (DCs) and CD4+ T cells. Within the DC, glucocorticoid receptor (GR) activation downregulates critical surface molecules required for antigen presentation and costimulation, specifically inhibiting MHC class II, CD1a, and CD80/CD86, while shifting the secretory profile away from pro-inflammatory signal-3 cytokines (IL-12, TNF) and toward the immunosuppressive IL-10. Simultaneously, glucocorticoids cross into the responding CD4+ T cell to deliver a direct intracellular brake; here, the activated GR paralyzes proximal downstream signaling by blocking the tyrosine kinases LCK and FYN, while structurally repressing the master transcription factors NF-kappaB, AP-1, and NFAT to completely halt T cell activation, proliferation, and downstream effector function.

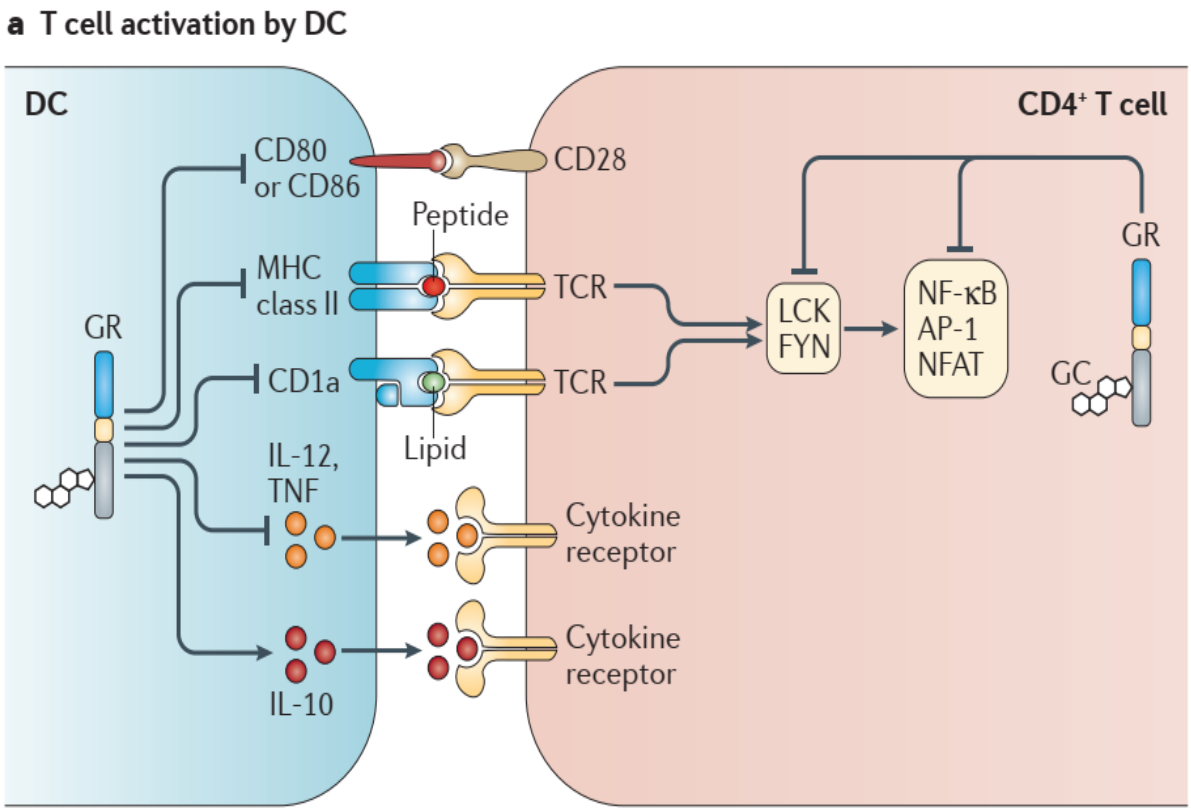


Figure 45 . Effect of glucocorticoids on immune cells interactions.

Glucocorticoids suppress adaptive immunity by executing a coordinated, double-sided assault on the immunological synapse between dendritic cells (DCs) and CD4+ T cells. Within the DC, glucocorticoid receptor (GR) activation downregulates critical surface molecules required for antigen presentation and costimulation, specifically inhibiting MHC class II, CD1a, and CD80/CD86, while shifting the secretory profile away from pro-inflammatory signal-3 cytokines (IL-12, TNF) and toward the immunosuppressive IL-10. Simultaneously, glucocorticoids cross into the responding CD4+ T cell to deliver a direct intracellular brake; here, the activated GR paralyzes proximal downstream signaling by blocking the tyrosine kinases LCK and FYN, while structurally repressing the master transcription factors NF-kappaB, AP-1, and NFAT to completely

5. Therapeutic Uses of Glucocorticoids

Glucocorticoids are widely employed in the treatment of various inflammatory diseases, including rheumatoid arthritis, asthma, and inflammatory bowel disease, owing to their potent anti-inflammatory properties. In rheumatoid arthritis, these agents effectively reduce synovial joint inflammation and alleviate pain, thereby slowing disease progression and improving functional outcomes. In asthma, glucocorticoids suppress airway inflammation and prevent bronchoconstriction by reducing mucosal immune cell infiltration and inflammatory mediator

release, which helps maintain airway patency and decreases the frequency and severity of exacerbations.

Glucocorticoids serve as foundational therapies in the management of autoimmune disorders by broadly suppressing aberrant immune activation and preventing tissue damage. In systemic lupus erythematosus, these agents are essential for controlling acute disease flares and preventing progressive organ damage, particularly to the kidneys, skin, and central nervous system, by dampening autoantibody production and immune complex deposition. Similarly, in multiple sclerosis, glucocorticoids are used to hasten recovery from acute relapses by reducing central nervous system inflammation and blood-brain barrier disruption. Beyond autoimmune indications, glucocorticoids play a critical role in organ transplantation, where they help prevent allograft rejection by suppressing the recipient's adaptive immune response against donor tissues, thereby reducing T-cell activation, cytokine production, and the cellular mechanisms that would otherwise lead to graft destruction.

6. Side Effects and Risks

Glucocorticoid therapy is associated with a spectrum of adverse effects that vary considerably depending on the duration and dose of treatment. During short-term use, patients commonly experience weight gain and fluid retention resulting from mineralocorticoid activity and altered renal sodium handling, alongside mood swings and insomnia that reflect the neuroactive properties of these hormones. Because glucocorticoids readily cross the blood-brain barrier, they directly influence central neurotransmitter systems, including serotonin, dopamine, and norepinephrine pathways, which can precipitate anxiety, irritability, or depression even during brief courses of therapy. With prolonged administration, the risk profile expands to include serious systemic complications such as osteoporosis, hypertension, diabetes, and infections, all of which stem from the cumulative metabolic and immunosuppressive actions of these drugs. Osteoporosis develops as glucocorticoids increase bone resorption by osteoclasts while simultaneously suppressing bone formation by osteoblasts and reducing intestinal calcium absorption, leading to progressive reductions in bone density and increased fracture risk. Concurrently, sustained immunosuppression impairs innate and adaptive immune defenses, rendering patients more susceptible to opportunistic infections, including bacterial, fungal, and viral pathogens that would otherwise be contained by a competent immune system. Beyond these adult concerns, antenatal administration of glucocorticoids to promote fetal lung maturation carries potential developmental implications, as

exposure during critical windows of immune system development may alter fetal programming and influence immune competence in early postnatal life.

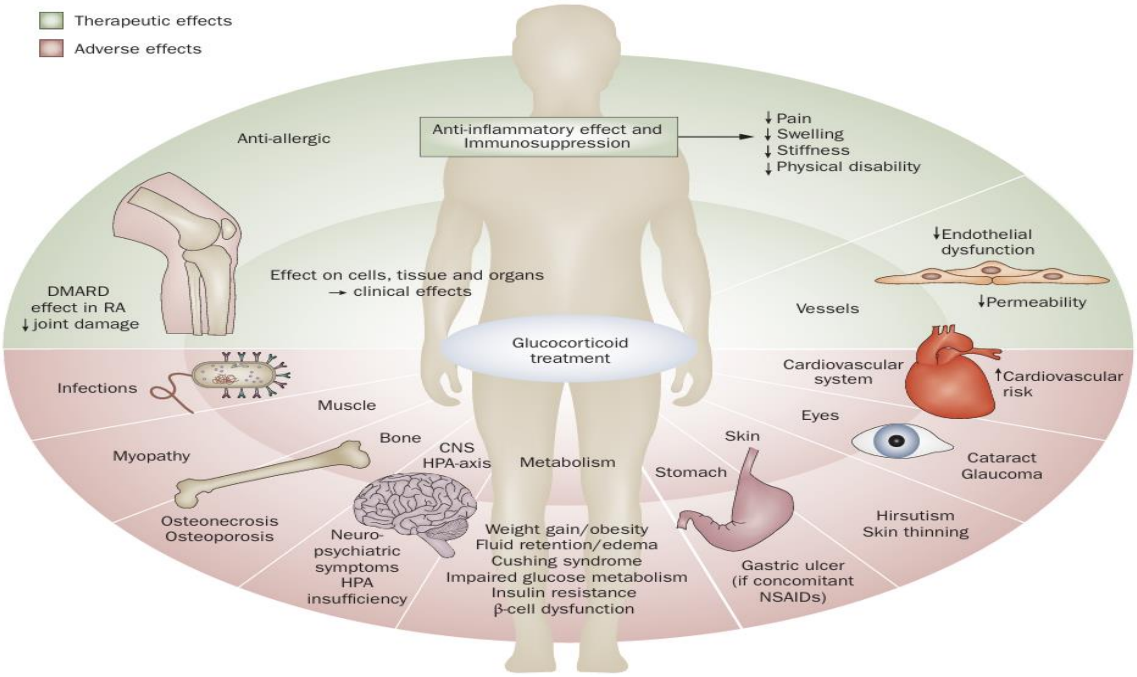


Figure 46 . Benefits and risks of using glucorticoid therapy.

7. Current Research and Future Directions

Current research in glucocorticoid pharmacology is increasingly focused on developing targeted therapeutic strategies that preserve the potent anti-inflammatory and immunosuppressive benefits of these agents while minimizing their extensive side effect profile. One promising avenue involves the design of selective glucocorticoid receptor modulators, which are engineered to dissociate the beneficial transrepression of pro-inflammatory genes from the harmful transactivation of metabolic target genes, thereby activating anti-inflammatory pathways while avoiding the detrimental metabolic, cardiovascular, and osteoporotic consequences associated with traditional glucocorticoid therapy. Complementing these biochemical approaches, significant advances in drug delivery systems aim to enhance the localized effects of glucocorticoids at specific sites of inflammation while reducing systemic exposure and toxicity. Among these innovations, nanoparticle-based delivery platforms have emerged as particularly promising, encapsulating glucocorticoids within biodegradable nanoparticles that preferentially accumulate at inflamed tissues and release their therapeutic payload in a controlled manner, thereby maximizing drug concentration at pathological sites while sparing distant organs from adverse effects.

Autoimmunity from toxic substances

I. Introduction

The immune system, composed of a diverse array of specialized cells, antibodies, and signaling molecules, serves as the fundamental defense mechanism that protects the body against invading pathogens including viruses, bacteria, and parasites. Central to its proper function is the ability to distinguish between self and non-self antigens: the immune system must recognize and tolerate the body's own normal tissues and components while simultaneously identifying and mounting effective responses against foreign substances, infectious agents, and altered self-components such as virus-infected or cancerous cells. However, this delicate system of recognition and regulation is not infallible, and instances of immune dysfunction can lead to significant pathological consequences. When the immune system reacts inappropriately against harmless external agents such as pollen, food proteins, or environmental antigens, it triggers allergic reactions characterized by excessive inflammation and tissue damage. Conversely, when the immune system fails to respond adequately to genuine microbial threats, the result is immunodeficiency, which leaves the individual vulnerable to recurrent, severe, or opportunistic infections. Most critically, when immune tolerance mechanisms break down and the immune system mistakenly identifies normal body components as foreign, it mounts destructive attacks against the body's own tissues and organs, leading to autoimmune diseases that can affect virtually any organ system and often result in chronic, progressive disability if left untreated.

Autoimmune diseases (AIDs) are conditions where the observed lesions result from the activation of our immune system's effectors against self-antigens of the organism. These diseases are defined based on specific clinical and biological criteria. They are complex and varied, broadly categorized into organ or tissue-specific autoimmune diseases and non-organ-specific autoimmune diseases, also known as systemic diseases.

Understanding the underlying mechanisms is crucial for developing new therapeutic strategies. It is important to differentiate between:

2. Physiological Autoimmunity:

No tissue damage occurs.

Natural autoantibodies are present at low levels in healthy individuals and are characteristically non-pathogenic, representing a normal component of the physiological immune repertoire rather than markers of autoimmune disease. These antibodies typically exhibit low affinity for their target antigens and belong predominantly to the immunoglobulin M class, which allows them to provide

broad, polyreactive recognition of common microbial structures and altered self-antigens without triggering harmful effector responses or tissue destruction.

3. Pathological Autoimmunity :

Tissue damage occurs, leading to autoimmune diseases.

In contrast to the benign natural autoantibodies present in healthy individuals, pathological autoimmunity is characterized by the production of high levels of autoantibodies that are actively pathogenic and drive tissue destruction, ultimately leading to clinically significant autoimmune diseases. These disease-associated autoantibodies differ fundamentally from their physiological counterparts in both quality and quantity, as they belong predominantly to the immunoglobulin G class rather than immunoglobulin M, and they exhibit high affinity for specific self-antigens due to affinity maturation and class-switching processes that occur during sustained adaptive immune activation. This combination of elevated titers, high-affinity binding, and pathogenic effector functions enables these autoantibodies to form immune complexes, activate complement cascades, and recruit inflammatory cells that directly damage normal tissues and organs..

4. Autoimmune Diseases and Toxic Substances

4.1. Role of Environmental Toxins

Environmental toxins represent a significant and increasingly recognized factor in the development and exacerbation of autoimmune diseases, as certain chemical agents possess the capacity to disrupt normal immune regulation and precipitate the loss of self-tolerance. Persistent organic pollutants, heavy metals, and various industrial chemicals have been epidemiologically and mechanistically linked to elevated risks of autoimmune conditions, where they may interfere with immune cell signaling, alter antigen presentation, or induce molecular mimicry that confuses the immune system's ability to distinguish foreign from self-antigens. Additionally, exposure to toxic materials such as organic solvents and pesticides can trigger acute autoimmune flares even after a single exposure event, particularly in individuals who carry a substantial cumulative body burden of these agents from prior environmental or occupational contact. This relationship between toxicant load and immune dysregulation underscores the importance of considering environmental health factors in both the prevention and clinical management of autoimmune disorders.

4.1.1. Mechanisms of Action

Toxic substances can induce autoimmune diseases through several mechanisms:

Disruption of Self-Tolerance **:**

Chemical agents can disrupt immune tolerance by interfering with the negative selection of lymphocytes within central lymphoid organs, thereby permitting autoreactive clones that would normally be deleted to escape into the periphery and subsequently attack the body's own tissues. Similarly, genetic defects in apoptosis-regulating molecules such as Fas and FasL impair programmed cell death pathways, preventing the physiological deletion of autoreactive lymphocytes during development and allowing these self-reactive cells to persist, expand, and ultimately initiate autoimmune pathology.

Altered Antigen Presentation :

Mutations in the autoimmune regulator gene, which is responsible for promoting the expression of tissue-specific self-antigens in the thymus during T-cell development, disrupt the presentation of self-peptides to developing lymphocytes and thereby prevent the negative selection of autoreactive T-cell clones. This failure of central tolerance underlies the pathogenesis of autoimmune polyendocrinopathy syndromes, where patients develop multi-organ autoimmune destruction targeting endocrine glands such as the parathyroids, adrenal cortex, and pancreatic beta cells. Separately, the abnormal expression of human leukocyte antigen class II molecules on cells that do not normally display these antigen-presenting structures, such as pancreatic beta cells or thyroid epithelial cells, can inappropriately activate autoreactive T-cells that recognize self-peptides presented in this ectopic context, thereby bypassing normal peripheral tolerance mechanisms and initiating organ-specific autoimmune destruction.

Epigenetic Modifications :

Environmental toxins can alter epigenetic expression patterns within immune cells, leading to immune dysregulation and promoting the development of autoimmunity. These chemical agents may induce changes in DNA methylation, histone modification, and microRNA expression that disrupt the normal regulatory programs governing immune tolerance, thereby increasing the susceptibility to autoimmune disease.

Molecular Mimicry :

Infections by microorganisms expressing antigens that structurally resemble self-antigens can trigger cross-reactive immune responses, wherein the antibodies or T cells generated against the pathogen also recognize and attack the body's own tissues. This phenomenon, known as molecular mimicry, represents a well-established mechanism by which microbial infections can precipitate autoimmune disease, as the immune system's attempt to eliminate the infectious agent simultaneously inflicts collateral damage on normal host components that share antigenic similarity with the pathogen.

Inflammation and Costimulation :

During inflammatory conditions, dendritic cells undergo maturation and can inappropriately present self-antigens to the immune system, thereby activating autoreactive T-cells that would normally remain quiescent. This breakdown in peripheral tolerance occurs because the inflammatory microenvironment provides co-stimulatory signals and cytokine cues that override the tolerogenic signals typically delivered by immature dendritic cells, effectively converting these antigen-presenting cells into initiators of autoimmune responses against the body's own tissues.

Cytokine Imbalance :

Dysregulation of cytokine networks represents a central pathogenic mechanism in autoimmune diseases, as the excessive and sustained secretion of pro-inflammatory cytokines creates a self-perpetuating cycle of immune activation and tissue destruction. In healthy individuals, cytokine production is tightly regulated to ensure appropriate inflammatory responses are initiated and then promptly resolved; however, in autoimmune conditions, this regulatory balance collapses, leading to elevated levels of mediators such as tumor necrosis factor-alpha, interleukin-1, interleukin-6, and interleukin-17 that drive the recruitment and activation of autoreactive lymphocytes, macrophages, and neutrophils. This chronic cytokine storm not only amplifies the effector functions of autoreactive immune cells but also disrupts the regulatory mechanisms that would normally restore tolerance, thereby perpetuating disease activity and contributing directly to the progressive organ damage characteristic of autoimmune pathology.

4.2. Risk Factors

Several risk factors significantly increase individual susceptibility to toxin-induced autoimmune diseases, creating a complex interplay between inherited traits, biological sex, and environmental exposures. Genetic predisposition plays a fundamental role, as polymorphisms in genes encoding major histocompatibility complex class I and II molecules, various cytokines, and key immune regulatory proteins contribute substantially to determining which individuals will develop autoimmune pathology following toxicant exposure. Gender represents another critical susceptibility factor, with women being disproportionately affected by autoimmune diseases compared to men, a disparity that is likely attributable to the immunomodulatory influences of sex hormones such as estrogen, progesterone, and testosterone on immune cell function and tolerance mechanisms. Additionally, occupational exposure constitutes a major environmental risk factor, as workers in industrial settings who encounter solvents, heavy metals, and other chemical agents through their employment face a markedly higher risk of developing autoimmune conditions due to repeated or high-level contact with these immune-disrupting substances.

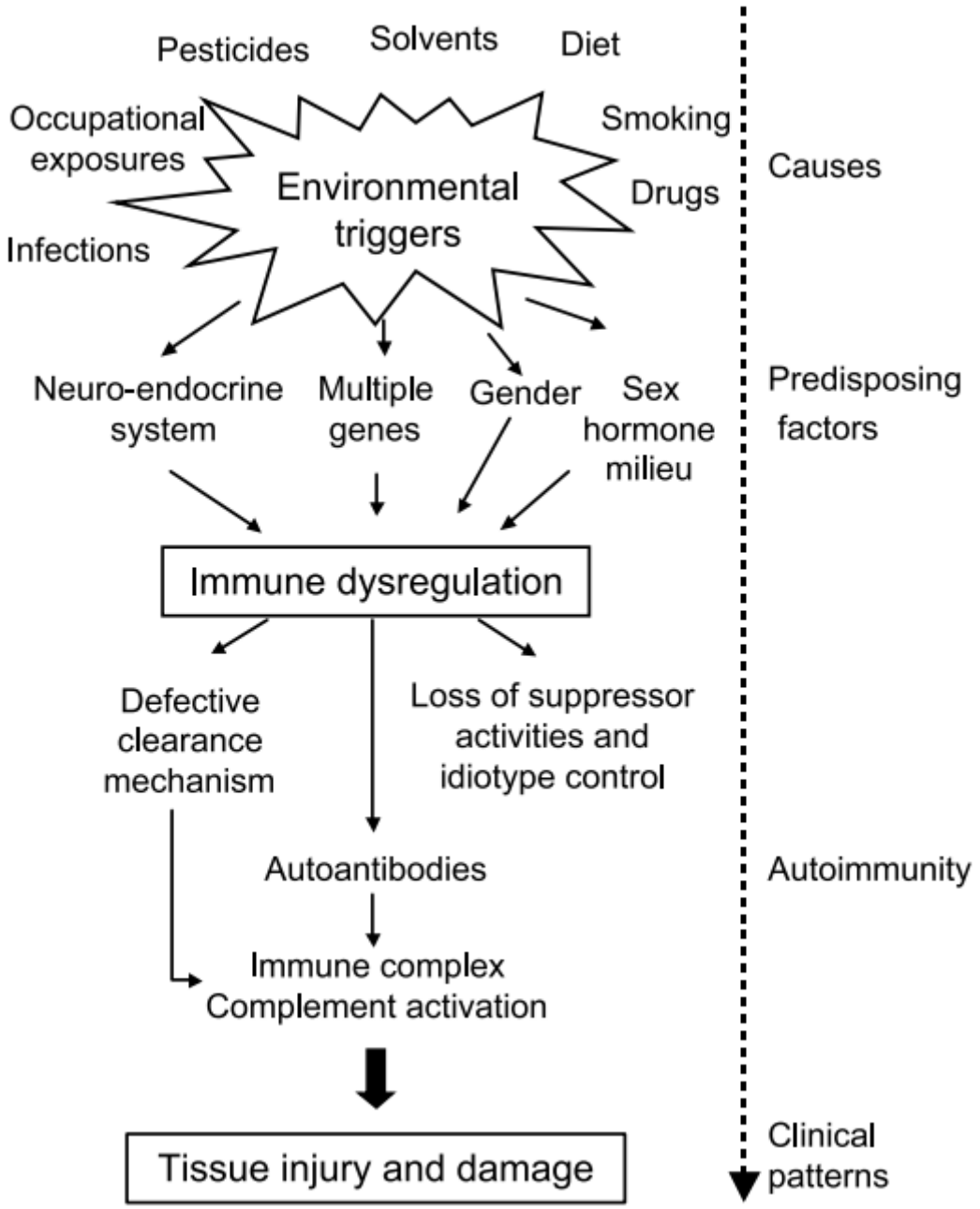


Figure 47 . Environmental autoimmune diseases associated risk factors.

4.3. Clinical and Biological Diagnosis

Autoimmune diseases are diagnosed through a comprehensive evaluation that integrates clinical manifestations with supportive laboratory findings, among which autoantibodies serve as critical diagnostic markers. These serological indicators include anti-nuclear antibodies, anti-DNA antibodies, and other disease-specific autoantibodies that help characterize the underlying immune pathology and distinguish between various autoimmune conditions. Systemic lupus erythematosus, widely regarded as a prototypical systemic autoimmune disease, exemplifies this diagnostic

approach through its characteristic presentation of high titers of immunoglobulin G autoantibodies and distinctive anti-nuclear antibody staining patterns that assist clinicians in confirming the diagnosis and assessing disease activity.

4.4. Therapeutic Strategies

The primary goals of autoimmune disease management are to control active disease, prevent future flares, and minimize the adverse effects associated with therapy. Conventional treatment strategies rely on broad immunosuppressive agents, particularly corticosteroids and general immunosuppressants, which dampen overall immune overactivity and reduce inflammation. In recent years, however, the therapeutic landscape has shifted increasingly toward targeted therapies, including biologics and small-molecule inhibitors that selectively disrupt specific immune pathways, thereby offering more precise control over disease mechanisms while potentially reducing the systemic toxicity associated with traditional immunosuppression.

4.5. Examples of Chemical-Induced Autoimmune Diseases

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE), canonically defined as an auto-immune disorder, can be considered as a chronic inflammatory illness with clinical manifestations encompassing various organs such as the blood vessels, brain, lungs, skin, kidneys and joints due to polymorphic biological alterations.

Drug-induced lupus (DIL) arises through a series of interconnected mechanisms where drugs or their metabolites disrupt immune regulation and promote autoimmune responses. First, reactive drugs or their metabolites interfere with central tolerance in the thymus, allowing autoreactive T helper (Th) cells to survive when they would normally be eliminated. This disruption increases the presence of these self-reactive cells in peripheral tissues, setting the stage for autoimmunity. Second, certain drugs or metabolites inhibit DNA methylation, a process critical for regulating gene expression. This inhibition leads to increased production of molecules like LFA-1 and B-cell stimulators, enhancing the responsiveness of lymphocytes and making them more likely to attack self-tissues. Third, some drugs or metabolites exhibit direct cytotoxic effects, causing cell death and generating cellular debris. Immature dendritic cells take up peptides from this debris, mature into antigen-presenting cells (APCs), and interact with autoreactive Th cells. This interaction activates lymphocytes and triggers the production of autoantibodies, further driving the autoimmune response. Fourth, drugs or their metabolites can bind to plasma or tissue antigens, rendering them immunologically active. This binding forms immune complexes through a process known as

haptenization, where drug-modified proteins are recognized as foreign by the immune system. these immune complexes are internalized by plasmacytoid dendritic cells, which respond by releasing type I interferons (IFNs). This alters the cytokine environment, promoting inflammation and amplifying the autoimmune cascade. Sixth, haptenized drug metabolites may directly bind to macrophages, impairing their ability to clear apoptotic or necrotic cellular debris. This impaired clearance allows autoantigens to persist, perpetuating the autoimmune response. Finally, certain drugs can activate neutrophils, leading to the production of reactive oxygen species (ROS). These ROS contribute to tissue damage and inflammation, exacerbating the autoimmune condition. Together, these mechanisms highlight the complex interplay between drugs, immune dysregulation, and the development of drug-induced lupus.

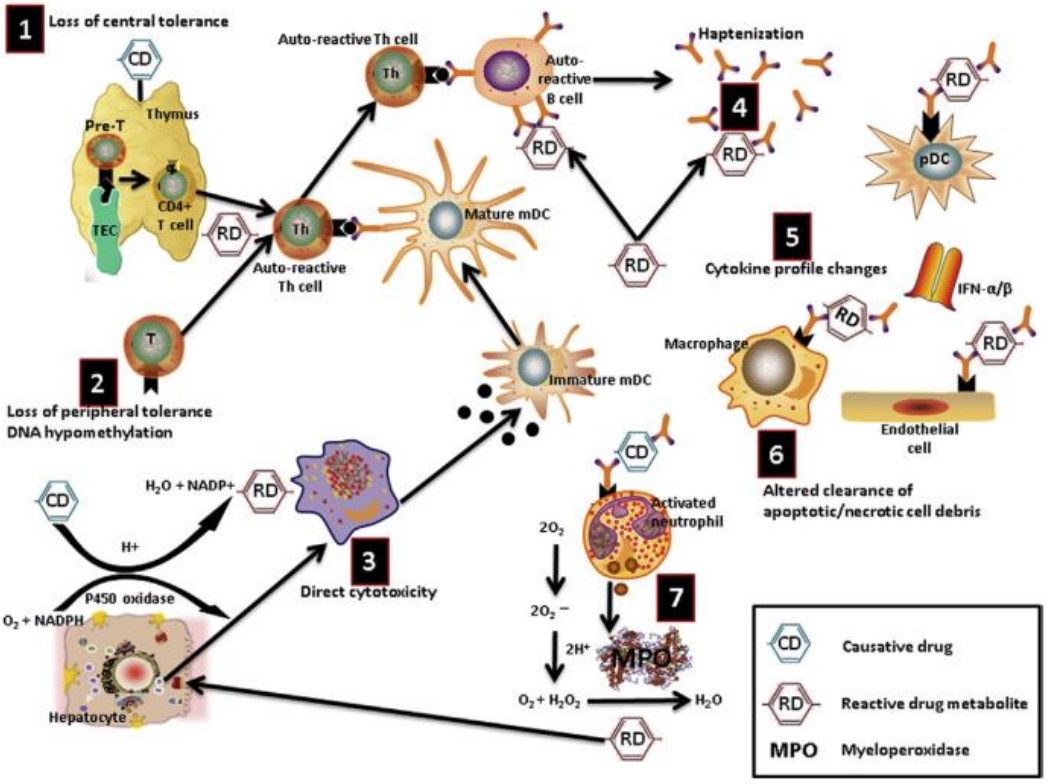


Figure 48 . **Systemic lupus erythematosus disorders induced by drugs.**

Silica particles are phagocytosed by macrophages via scavenger receptors, triggering a cascade of events that contribute to both tissue damage and autoimmunity. Upon uptake, silica induces oxidative stress in macrophages, leading to cell death through Fas/Fas ligand activation. This process results in the release or modification of self-antigens, which can then be presented by antigen-presenting cells (APCs) to T cells. The APCs also secrete proinflammatory cytokines such as TNF-α and IFN-γ, further amplifying the inflammatory response and contributing to lung fibrosis. The loss of macrophages due to silica-induced cell death reduces their anti-inflammatory clearance

function, exacerbating the inflammatory environment. Activated APCs stimulate T-cell activation and cytokine production, leading to a loss of tolerance and subsequent B-cell activation. This immune dysregulation results in the production of autoantibodies, which are characteristic of autoimmune diseases like SLE. Additionally, the blockage of regulatory T cells (Tregs), which normally suppress excessive immune responses, further perpetuates the autoimmune cascade. The overall process highlights how silica exposure can trigger chronic inflammation, disrupt immune tolerance, and ultimately lead to tissue damage and autoimmune exacerbation, underscoring the multifactorial nature of these conditions.

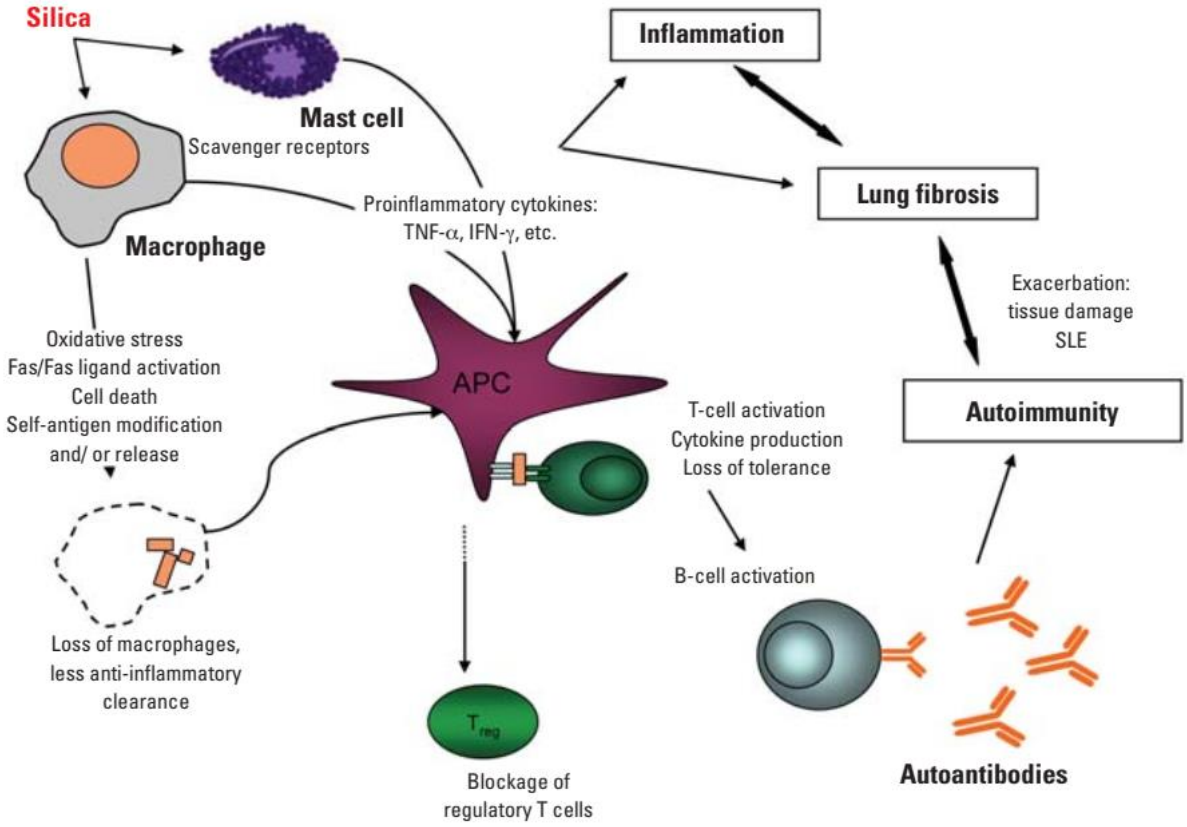


Figure 49 . Systemic lupus erythematosus disorders induced by silica.

Silicosis and silicone

Silica-induced activation of the inflammasome and subsequent production of interleukin-1 (IL-1) represent a critical mechanism linking silica exposure to inflammation and autoimmune responses. Upon exposure to crystalline silica, alveolar macrophages release IL-1α, which activates the nuclear factor-κB (NF-κB) pathway, leading to the transcription and translation of pro-IL-1β. The phagocytosis of silica crystals causes damage to phagosomes, releasing their contents into the cytoplasm. This event triggers the assembly and activation of the NALP3 inflammasome, a multiprotein complex composed of NALP3 (NACHT, LRR, and PYD domains-containing protein 3), the adapter protein ASC (apoptosis-associated speck-like protein containing a caspase

recruitment domain), and pro-caspase-1. Once activated, the inflammasome cleaves pro-IL-1β into its active, proinflammatory form, IL-1β, which amplifies the inflammatory response. Interestingly, immobilized silica crystals can also induce IL-1β production without evident lysosomal or phagosomal damage, suggesting alternative pathways for inflammasome activation. One such mechanism involves the efflux of intracellular potassium ions (K+), which may result from silica binding to membrane-associated proteins. However, it remains unclear whether K+ efflux alone is sufficient to activate the inflammasome in this context. Scavenger receptors on macrophages play a key role in recognizing and internalizing silica particles, facilitating their downstream effects. Together, these processes highlight the complex interplay between silica exposure, innate immune activation, and the development of inflammatory and autoimmune conditions, emphasizing the central role of the NALP3 inflammasome and IL-1β in disease pathogenesis.

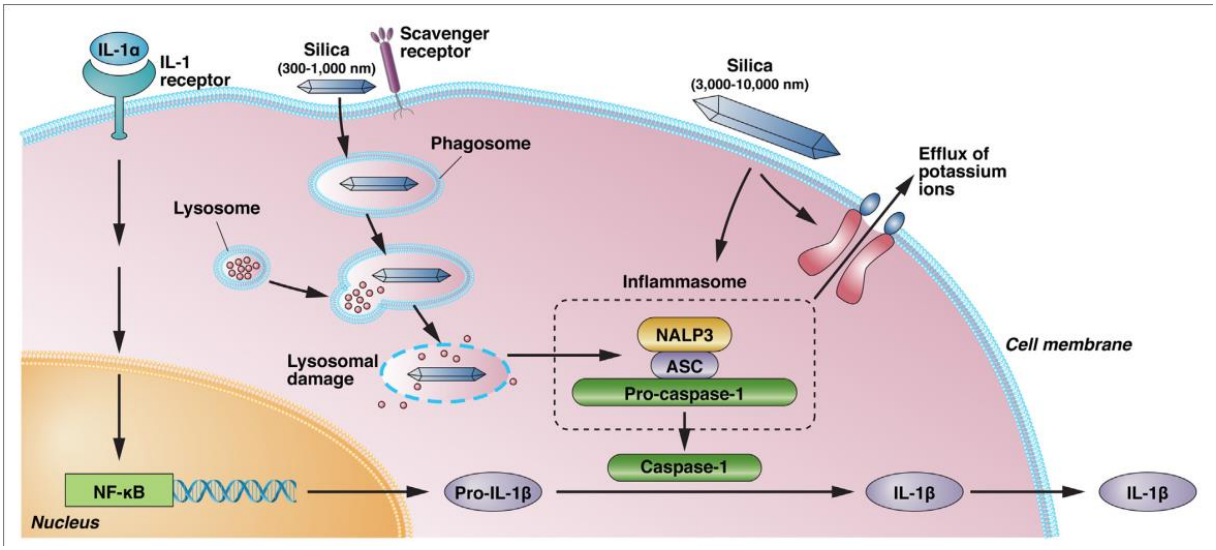


Figure 50 . Silicosis induction by silica.

The molecular and cellular components implicated in silica-induced inflammation and fibrosis reveal the complex mechanisms underlying silicosis, a condition characterized by inflammation, fibrosis, and the development of nodular lesions predominantly in the upper lobes of the lungs. These silicotic nodules, rich in collagen, represent a specific pathological response to crystalline silica exposure. Notably, the cellular and molecular processes driving inflammation differ from those mediating fibrosis. Key components essential for either acute or chronic inflammation and fibrosis are emphasized in red, while non-essential elements are marked in green (refer to accompanying details). Critical factors include TNF (tumor necrosis factor), IFN (interferon), MyD88 (myeloid differentiation primary response gene 88), IL (interleukin), NK (natural killer

cells), NKT (natural killer T cells), IRF (interferon regulatory factor), and TGF (transforming growth factor), each playing distinct roles in the disease progression.

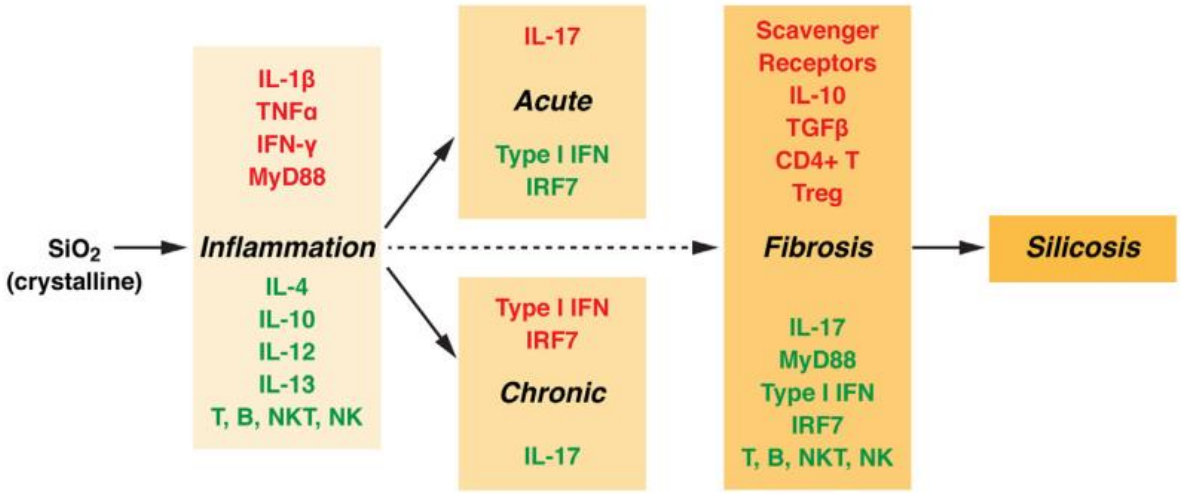


Figure 51 . Mechanism of induction of silicosis.

Rheumatoid arthritis

The process begins with (volatile organic compounds) VOC exposure, which triggers a surge in reactive oxygen species (ROS) generation, leading to oxidative stress. This oxidative stress activates transcription factors, initiating a series of downstream effects. These transcription factors promote the production of pro-inflammatory mediators, driving an inflammatory response that further amplifies immune activation.

Oxidative stress also plays a critical role by inducing modifications in proteins, mutations in DNA, and lipid peroxidation, all of which contribute to cellular damage and dysregulation. This damage can lead to the activation of T-cells and B-cells, resulting in the production of autoantibodies. Additionally, the figure highlights the involvement of Th1 cytokines and microphage activation , which reinforce the inflammatory response and perpetuate the cycle of immune dysregulation.

Epigenetic changes are also implicated in this process, as indicated by the dashed arrow connecting "Epigenetics" to other components, suggesting that VOC exposure may alter gene expression patterns, potentially exacerbating autoimmune responses. Ultimately, these interconnected pathways converge to drive the development of autoimmune diseases, emphasizing the multifactorial nature of the condition. The diagram underscores how environmental exposures like VOCs can trigger a cascade of molecular and cellular events, leading to chronic inflammation, immune dysregulation, and the onset of autoimmune pathology.

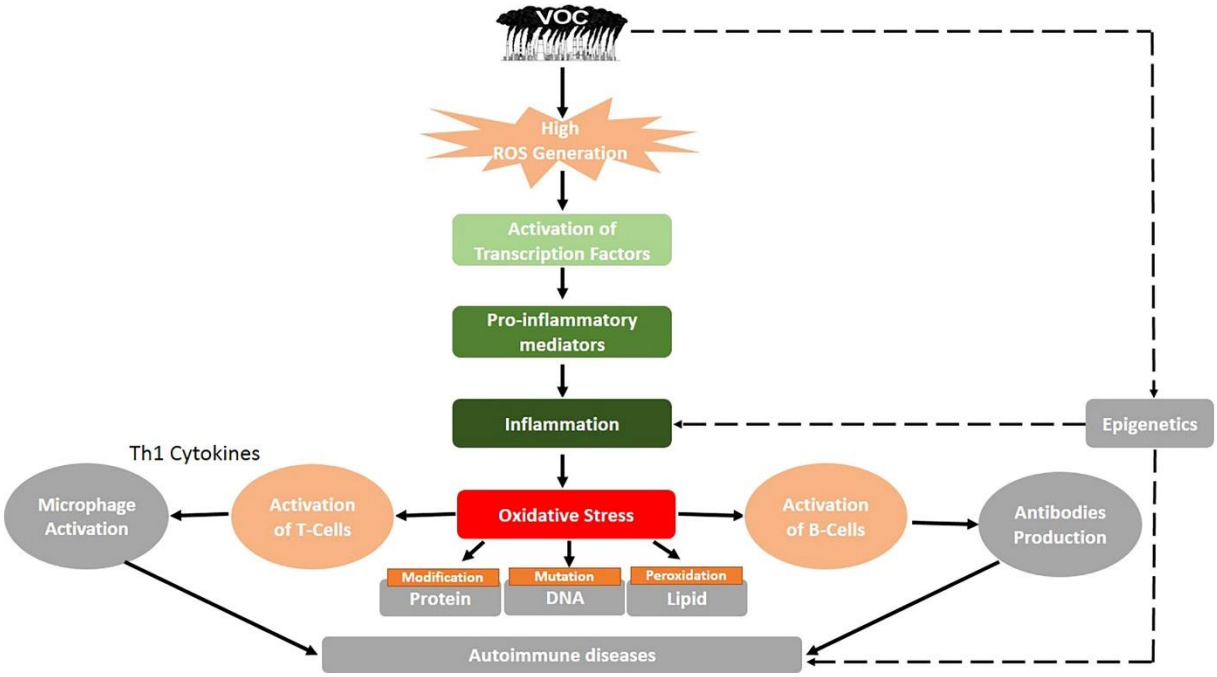


Figure 52 . Mechanism of induction of autoimmune diseases by volatile compounds.

A potential pathophysiological mechanism of tobacco smoke-induced rheumatoid arthritis (RA) involves oxidative stress and immune dysregulation. Oxidants present in tobacco smoke activate the transcription factor NF-κB, which reduces glutathione levels, leading to an increase in reactive oxygen species (ROS) and subsequent inflammation. Specifically, polycyclic aromatic hydrocarbons (PAHs) in tobacco smoke bind to aromatic hydrocarbon receptors on synovial cells, triggering the production of pro-inflammatory cytokines and chemokines. These molecules promote the activation of T-helper 17 (Th17) cells, which play a central role in RA pathogenesis. Th17 cells secrete IL-17, a cytokine that stimulates macrophages to produce IL-1, IL-6, and TNF-α—key mediators of inflammation. Over time, this acute inflammatory process transitions into chronic inflammation due to the influence of various factors, including hormonal and genetic predisposition.

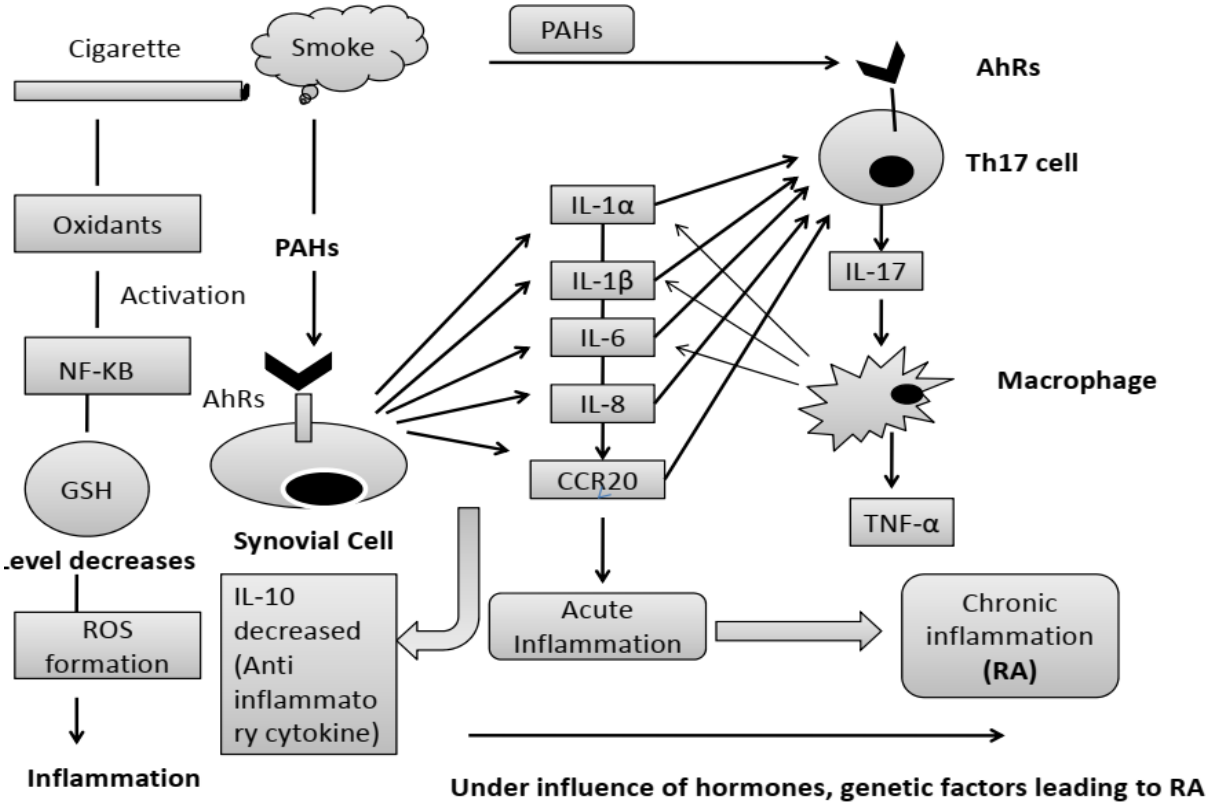


Figure 53 . **Mechanism of induction of rheumatoid arthritis by the smoke of cigarettes.**

Multiple sclerosis (MS) is a chronic neurological disease that is marked by inflammatory central nervous system (CNS) demyelination mediated by T cells specific for a myelin antigen. MS is categorized as an autoimmune disease (ADs) that in most cases, it starts by a relapsing onset, characterized by relapses, i.e. acute inflammatory demyelination. air pollutants, including particulate matter (PM), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and other toxic substances, can trigger systemic inflammation and neuroinflammation through the olfactory system. Upon inhalation, these pollutants enter the respiratory tract, where they are detected by immune cells like alveolar macrophages. This triggers the production of reactive oxygen species (ROS), leading to oxidative stress and activation of pro-inflammatory pathways. The olfactory system acts as a direct route for pollutants to bypass the blood-brain barrier, allowing them to travel along olfactory nerve fibers and reach the brain directly. In the lungs, pollutants activate immune cells such as neutrophils (Neu), monocytes (Mon), and Th17 cells, which release pro-inflammatory cytokines like IL-1, IL-6, TNF-α, and IL-8, amplifying the inflammatory response. Th17 cells, known for their role in autoimmune diseases, are prominently activated and produce IL-17, further driving inflammation. Systemically, inflammatory mediators disseminate through the bloodstream, affecting distant organs, while in the brain, microglia become activated, contributing to neuroinflammation. The figure also highlights an imbalance between Th1 and Th17 responses, with a prominent activation

of Th17 cells, which is critical in driving chronic inflammation and autoimmunity. Additionally, endothelial damage leads to vascular dysfunction and increased permeability, facilitating the entry of inflammatory cells into tissues, including the brain.

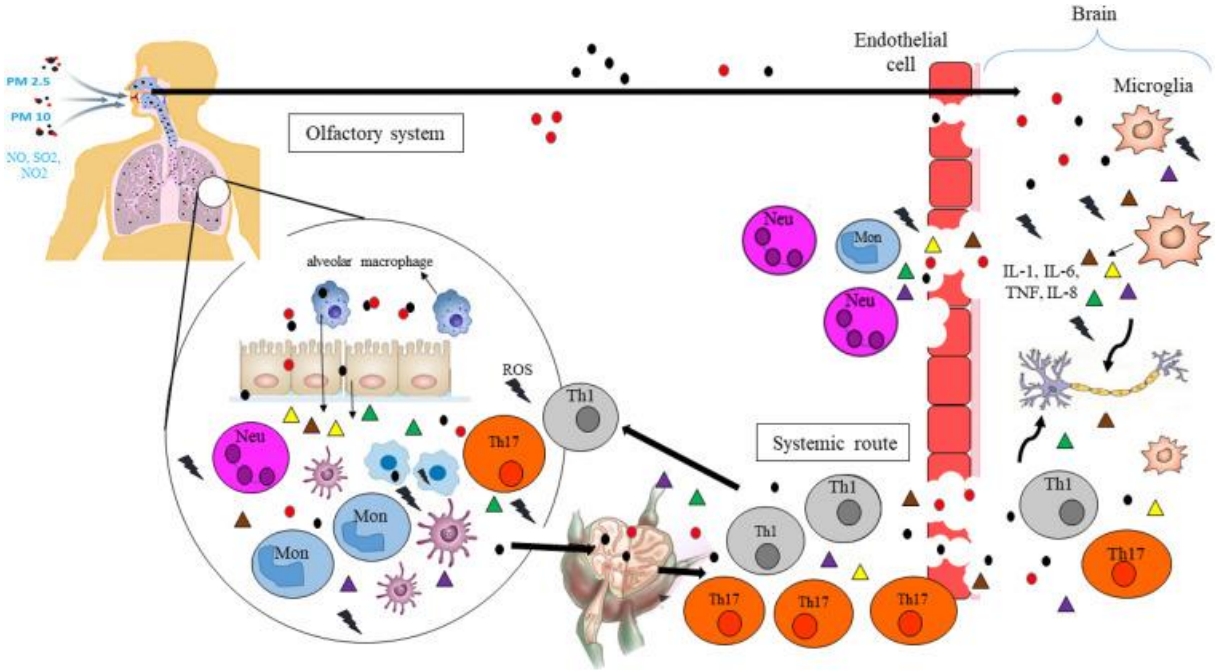


Figure 54 . Mechanism of action of inducing multiple sclerosis.

Targets and mechanisms of action of other immunosuppressants

1. Introduction

Immunosuppressors, also known as immunosuppressive agents or immunosuppressants, are drugs or substances that reduce or inhibit the activity of the immune system by interfering with various stages of immune cell activation, proliferation, or function. They are most commonly used in two major clinical scenarios: first, to prevent the rejection of transplanted organs by dampening the recipient's immune response against the foreign tissue; and second, to treat autoimmune diseases such as rheumatoid arthritis, lupus, Crohn's disease, and multiple sclerosis, where the immune system mistakenly attacks the body's own tissues. These agents span several drug classes, including corticosteroids like prednisone, calcineurin inhibitors such as cyclosporine and tacrolimus, antiproliferatives like azathioprine and mycophenolate mofetil, mTOR inhibitors including sirolimus, and biologic agents such as anti-TNF drugs and rituximab. Because their fundamental mechanism involves suppressing immune defenses, patients taking immunosuppressors face a significantly increased risk of infections and potentially a higher susceptibility to certain cancers, making careful medical supervision and monitoring essential throughout treatment.

Immunosuppressors are primarily used to prevent organ rejection in transplant recipients, where they dampen the recipient's immune response against the foreign graft to ensure long-term survival of the kidney, heart, liver, lung, or other transplanted organs. Beyond transplantation, they serve as cornerstone therapies for a broad spectrum of autoimmune and inflammatory disorders in which the immune system erroneously attacks the body's own tissues, including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease such as Crohn's disease and ulcerative colitis, multiple sclerosis, psoriasis, and various forms of vasculitis. They are also employed to manage severe allergic conditions that do not respond to conventional treatments, to treat certain hematologic disorders such as idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia, and to control graft-versus-host disease following allogeneic stem cell transplantation. In some cases, immunosuppressors are used in combination regimens to treat specific cancers or to manage severe inflammatory eye, skin, or lung diseases. Because these agents broadly diminish immune surveillance and response, their use requires careful risk-benefit assessment and ongoing monitoring to balance therapeutic efficacy against the heightened susceptibility to infections and other complications.

2. Mechanism of action

Immunosuppressors exert their effects through diverse molecular mechanisms that ultimately converge on reducing immune cell activation, proliferation, or effector function. Calcineurin inhibitors such as cyclosporine and tacrolimus block the phosphatase activity of calcineurin, thereby preventing the nuclear translocation of nuclear factor of activated T-cells (NFAT) and halting the transcription of interleukin-2 (IL-2) and other cytokines essential for T-cell activation and clonal expansion. Corticosteroids like prednisone diffuse into cells and bind to glucocorticoid receptors, forming complexes that translocate to the nucleus to suppress the transcription of pro-inflammatory genes—including cytokines, chemokines, and adhesion molecules—while upregulating anti-inflammatory mediators such as annexin-1. Antiproliferative agents including azathioprine and mycophenolate mofetil interfere with purine biosynthesis; mycophenolate specifically inhibits inosine monophosphate dehydrogenase, starving rapidly dividing lymphocytes of guanosine nucleotides and arresting their proliferation. mTOR inhibitors such as sirolimus and everolimus bind to FK-binding protein-12 to form a complex that inhibits the mammalian target of rapamycin (mTOR), a critical kinase regulating cell growth, protein synthesis, and metabolic activation in response to IL-2 and other growth signals, thereby blocking T-cell and B-cell proliferation. Biologic agents operate through highly targeted mechanisms—for instance, anti-TNF antibodies like infliximab bind and neutralize tumor necrosis factor-alpha, preventing it from activating its receptors on immune and stromal cells, while monoclonal antibodies such as basiliximab block the IL-2 receptor alpha-chain (CD25) on activated T-cells, starving them of the IL-2 signal required for survival and expansion. By disrupting these specific signaling nodes, immunosuppressors collectively diminish T-cell-mediated cytotoxicity, antibody production, and inflammatory cascade propagation, though this pharmacologic immune dampening simultaneously elevates the risk of opportunistic infections and malignancy.

2.1. Effect on lymphocyte T cells

Immunosuppressive agents precisely intercept these molecular stages to inhibit T-cell proliferation and prevent tissue rejection or autoimmune damage. Calcineurin inhibitors, such as cyclosporine and tacrolimus, work by blocking the activation of the transcription factor NFAT, while corticosteroids penetrate the nucleus directly to suppress inflammatory factors like NF-kappaB. Concurrently, Anti-TNF agents neutralize extracellular inflammatory cytokines (TNF-alpha) before they can bind to their receptors (TNF). Biologic therapies also interfere externally; CTLA-4-Ig blocks the co-stimulatory Signal 2, Anti-CD25 R monoclonals block the IL-2 receptor,

and depleting antibodies like Anti-CD52 or polyclonal antilymphocyte sera clear the T cells entirely. Finally, this therapeutic regimen is completed by JAK inhibitors and mTOR inhibitors, which disrupt the internal downstream signaling required for growth, alongside anti-metabolites that halt nucleotide synthesis during the S phase of the cell cycle, effectively arresting clonal expansion.

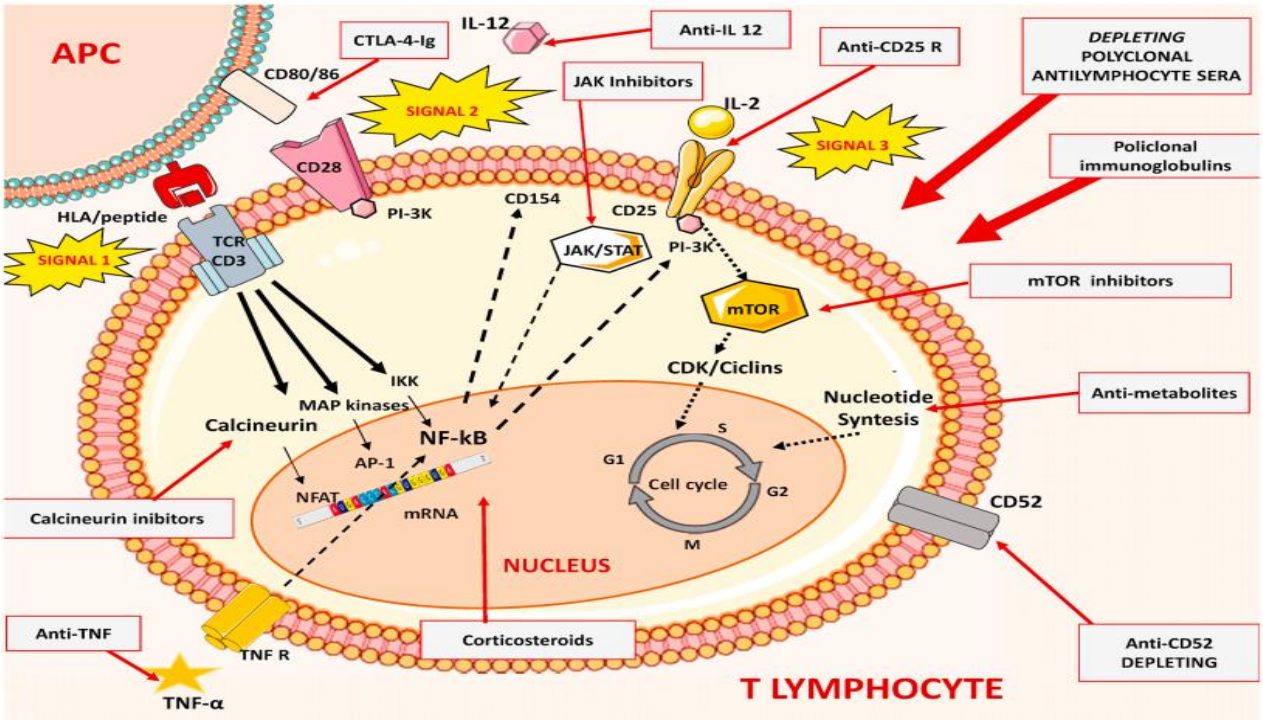


Figure 55 . Mechanism of action of immunosuppressors on T cell.

2.2. Effect on antigen-presenting cells

At the surface level, OKT3 and ATG act as direct antagonists targeting the CD3 complex, thereby blocking the initial antigen-recognition signal (Signal 1), while therapies like CTLA-4-Ig physically interfere with the essential costimulation pathway. Further downstream, intracellular signaling cascades are blocked by Cyclosporine and Tacrolimus, which specifically inhibit calcineurin, preventing it from dephosphorylating and translocating the transcription factor NF-AT into the nucleus. Concurrently, Corticosteroids (Steroids) exert a broad genomic effect by diffusing across membranes and entering the nucleus directly to suppress the transcription of messenger RNA (mRNA) required for cytokine synthesis, effectively choking off the production of Interleukin-2 (IL-2).

For therapies targeting the subsequent autocrine amplification loop, Anti-CD25 monoclonal antibodies (mAbs) function by physically occluding the IL-2 receptor on the cell surface, ensuring that any escaped or circulating IL-2 cannot bind to propagate further growth signals. If the receptor is engaged, downstream signal transduction is stopped by Sirolimus and Everolimus, which act as targeted TOR inhibitors, preventing the activation of the Cyclin/CDK complexes that drive the cell

out of its resting phase. On a broader cellular level, Alemtuzumab targets the surface CD52 antigen to induce peripheral T-cell depletion entirely. Finally, inside the nucleus, anti-metabolites such as MMF, Azathioprine, and Aza disrupt de novo nucleotide synthesis, arresting the cell cycle directly at the S phase and completely preventing the proliferation of the immune response.

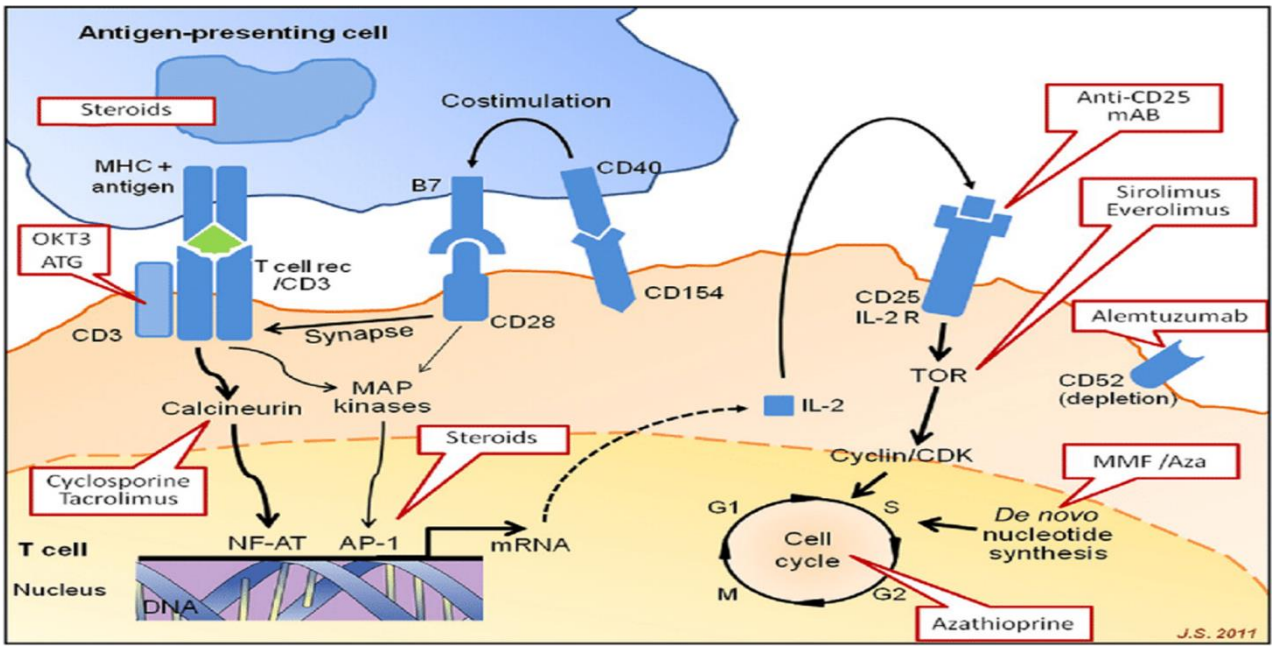


Figure 56 . Mechanism of action of immunosuppressors on APC cells.

2.3. Effect on B-cell activation

At the level of cellular interaction, the vital costimulatory crosstalk between CD4+ T cells and B cells is disrupted by alpha-CD40mAb (ASKP1240), which blocks the CD40L–CD40 link required for robust B-cell activation. For direct B-cell depletion or regulation, monoclonal antibodies like α-CD20mAb (including rituximab, ocrelizumab, ofatumumab, and veltuzumab) bind to surface CD20, whereas alpha-CD22mAb (epratuzumab) targets CD22 to modulate B-cell signaling. Additionally, pan-reactive biologicals like Alemtuzumab target the CD52 antigen to deplete peripheral lymphocyte populations entirely. To curtail B-cell survival and maturation into antibody-secreting cells, therapies also target essential soluble survival factors and intracellular machinery. The signaling pathways driven by the B-cell activating factor (BAFF) and APRIL are intercepted by alpha-BAFFmAb (belimumab) or the soluble chimeric receptor TACI-Ig (atacicept), neutralizing these ligands and choking off essential survival signals to mature B cells. For downstream cells that have already differentiated, the proteasome inhibitor Bortezomib acts directly inside the Plasma cell to jam the proteasome complex, preventing the activation of the transcription factor NF-kappaB and ultimately inducing plasma cell apoptosis to halt antibody production. Finally, to suppress the destructive terminal effector mechanisms triggered by remaining antibodies, alpha-C5mAb

(eculizumab) blocks C5 convertase from cleaving the complement protein C5, completely halting the assembly of the pro-inflammatory anaphylatoxin C5a and the cytolytic C5b-9 Membrane Attack Complex (MAC) along the cell wall.

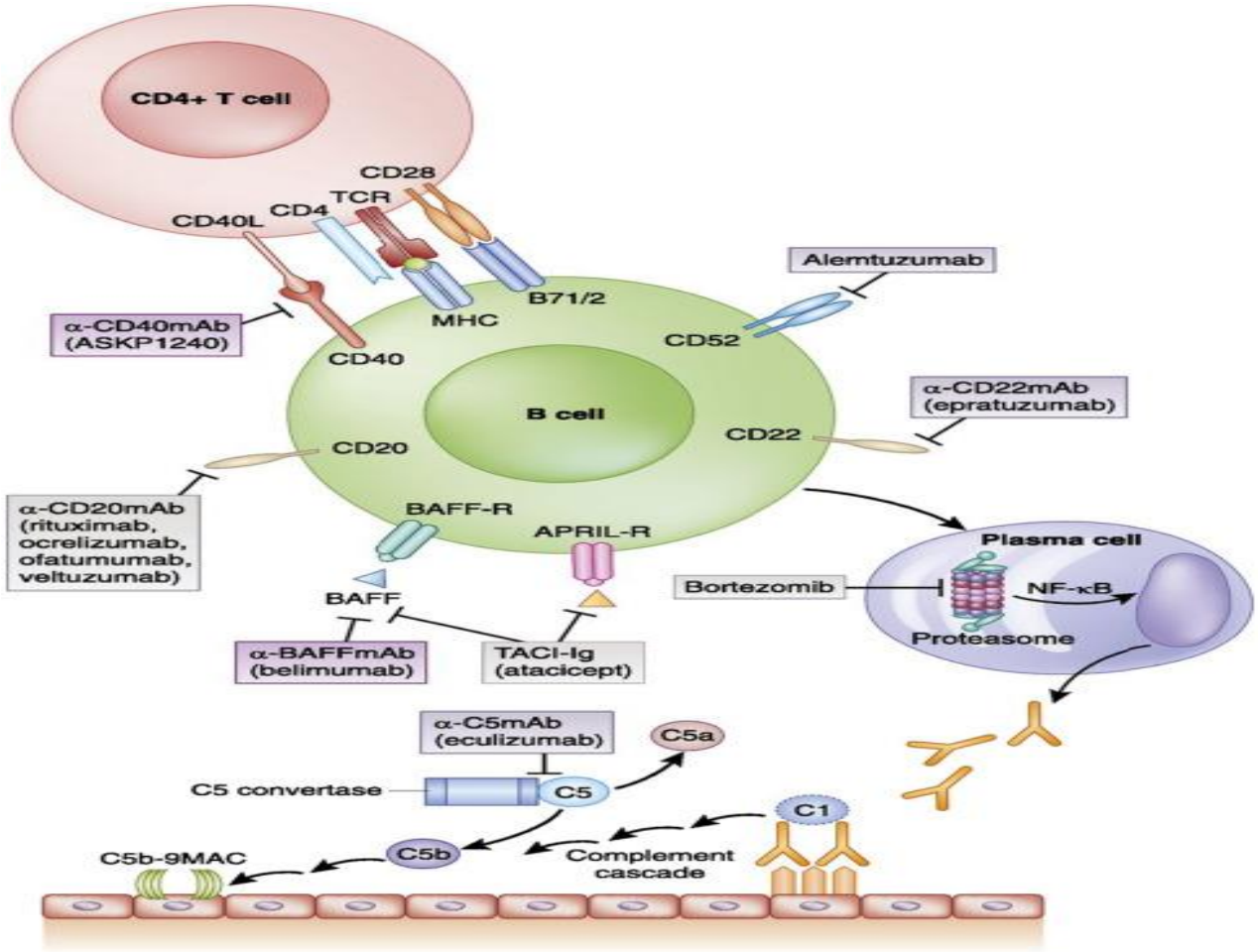


Figure 57 . **Mechanism of action of immunosuppressors on B-cells.**

2.4. Description of the most used immunosuppressants

Immunosuppressive agents systematically disable the immune response by disrupting cellular communication, intracellular signaling cascades, gene transcription, and metabolic replication pathways within lymphocytes. At the extracellular level, polyclonal antilymphocyte sera and specialized monoclonal antibodies like Anti-CD52 (Alemtuzumab) and Anti-CD20 induce direct, widespread peripheral depletion of target T and B cell populations, while intravenous immunoglobulins exert pleiotropic immunomodulatory masking effects. For intact cells, the essential initial activation signals are intercepted at the surface membrane; costimulation blockade therapies (such as chimeric CTLA-4 proteins) downregulate the critical CD28–B7 costimulatory signal, and α-CD40 mAbs block the CD40L–CD40 axis to choke off cooperative T-and-B-cell crosstalk.Further down the cascade, when surface receptors are engaged, small molecule drugs

target internal transduction mechanics to block nuclear communication. Calcineurin inhibitors (such as Cyclosporine A and Tacrolimus) bind directly to calcineurin to block its phosphatase activity, preventing the key transcription factor NF-AT from translocating into the nucleus. Concurrently, Corticosteroids act as powerful steroid hormones that exert broad pleiotropic effects by binding to cytoplasmic receptors and entering the nucleus directly to inhibit the genomic transcription of major pro-inflammatory genes, effectively cutting off early cytokine production like Interleukin-2 (IL-2). If cytokines are successfully secreted, therapies target the subsequent autocrine expansion loop. Anti-IL2 R monoclonal antibodies bind to and internalize the CD25/IL-2 receptor subunit, rendering the cell blind to circulating growth factors. For signals that breach the membrane, mTOR inhibitors (Sirolimus and Everolimus) form an intracellular complex with FKBP12 to bind and inhibit the mTOR kinase, successfully halting downstream Cyclin/CDK activation. Finally, to prevent literal cell division, antimetabolite agents (such as Azathioprine, Methotrexate, and Mycophenolate Mofetil) act as competitive or non-competitive inhibitors of nucleic acid synthesis, interfering directly with DNA replication during the S phase of the cell cycle to halt clonal proliferation. Meanwhile, downstream differentiated structures are neutralized by proteasome inhibitors like Bortezomib, which jam plasma cell machinery to stop antibody production, and alpha-C5 mAbs (Eculizumab), which arrest the terminal complement cascade to prevent full inflammatory lysis.

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