First, let’s remind of what is the meaning of Pathophysiology?

What is the meaning of Immunopathology?

LABORATÓRIO DE BIOLOGIA CELULAR E MOLECULAR
Instituto de Ciências Biomédicas
Universidade de São Paulo
Instituto de Investigação em Imunologia - INCT

Immunopathology

Gustavo P. Amarante-Mendes
gpam@usp.br

Definition

Physiology of altered health, of abnormal states or diseases

Pathophysiology deals not only with the cellular and organ changes that occur with disease, but with the effects that these changes have on total body function.

Pathophysiology also focuses on the mechanisms of the underlying disease process and provides the background for preventive as well as therapeutic health care measures and practices.

Why it matters

Helps explain how immune system abnormalities contribute to disease, prognosis, and treatment strategies.

Guides development of therapies that modulate the immune response (e.g., immunosuppressants, biologics targeting specific immune pathways).

Definition

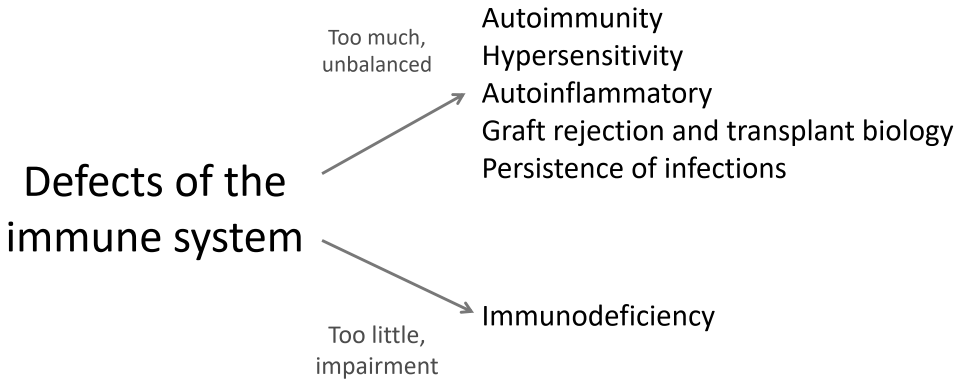
Immunopathology is the branch of pathology that studies diseases caused or driven by dysfunctions of the immune system.

Immunopathology examines how immune responses that are normally protective can become harmful, leading to tissue injury, dysfunction, or disease

Autoimmune diseases

Breakdown of tolerance: the adaptive immune system **(antibodies, T lymphocytes)** mistakenly attacks the body's own tissues (e.g., rheumatoid arthritis, type 1 diabetes)

Pathologies of the Immune System



Hypersensitivity reactions

Adverse immune responses to harmless antigens, classified into four categories

Autoimmune diseases

Rheumatoid arthritis (RA): autoantibodies (e.g., anti-citrullinated protein antibodies) and T-cell–mediated inflammation attack joints, causing synovitis and cartilage destruction.

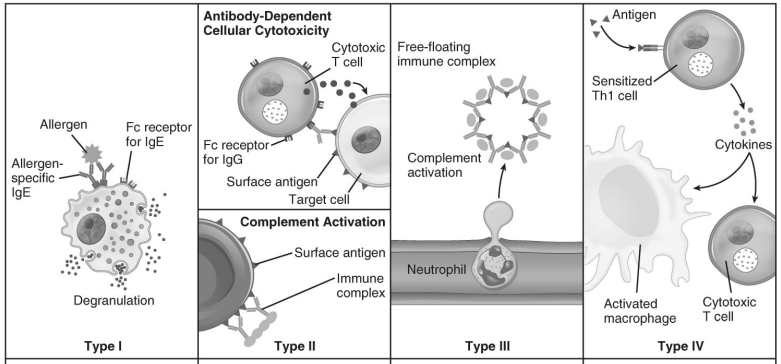
Type 1 diabetes mellitus (T1DM): autoimmune destruction of pancreatic beta cells by autoreactive T cells and autoantibodies, leading to insulin deficiency.

Systemic lupus erythematosus (SLE): autoantibodies against nuclear components (DNA, histones) form immune complexes that deposit in multiple organs (skin, kidneys, joints).

Hypersensitivity reactions

- **Type I (immediate, IgE-mediated)**:
  - Allergic rhinitis or hay fever in response to pollen.
  - Anaphylaxis after exposure to peanuts or bee venom.
- **Type II (antibody-mediated cytotoxic)**:
  - Immune hemolytic anemia: antibodies target red blood cells causing destruction.
  - Goodpasture syndrome: antibodies against glomerular basement membrane leading to kidney and lung involvement.
- **Type III (immune complex–mediated)**:
  - Serum sickness: formation of circulating immune complexes causing fever, rash, arthralgia.
  - Arthus reaction: local tissue necrosis and inflammation after intradermal antigen exposure in sensitized individuals.
- **Type IV (delayed-type, T cell–mediated)**:
  - Contact dermatitis from nickel or poison ivy.
  - Tuberculin skin test reaction (delayed hypersensitivity to Mycobacterium tuberculosis antigens).

Hypersensitivity reactions



IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

Autoinflammatory diseases

Familial Mediterranean Fever (FMF): caused by mutations in the MEFV gene (pyrin) leading to NLRP3-independent inflammasome–driven fever and serositis (pleura, pericardium, peritoneum).

Cryopyrin-associated autoinflammatory syndromes (CAPS): a spectrum including familial cold autoinflammatory syndrome and NOMID (Neonatal Onset Multisystem Inflammatory Disease) with gain-of-function mutations in NLRP3, driven by excessive IL-1β.

TNF receptor-associated periodic syndrome (TRAPS): due to mutations in the TNFRSF1A gene causing recurrent fevers and inflammatory episodes, with variable duration and organ involvement.

Autoinflammatory diseases

disorders of the innate immune system characterized by recurrent or chronic inflammation driven by **innate pathways** (e.g., inflammasomes) rather than autoantibody- or antigen-specific T-cell responses.

Graft rejection and transplant biology

Hyperacute rejection: preformed anti-donor antibodies (anti-ABO, anti-HLA, or other alloantibodies) causing rapid thrombosis of graft vessels (minutes to hours after transplantation).

Acute cellular rejection: host T cells infiltrating the graft tissue leading to graft dysfunction (weeks to months).

Chronic rejection: long-term immune and nonimmune injury causing gradual loss of graft function (months to years)

Graft rejection and transplant biology

Immune responses against transplanted tissues or organs.

Persistence of infections

Cytokine storm in severe viral infections:
Excessive production of cytokines (e.g., IL-6, TNF-α) causing systemic inflammation and organ damage.

Pulmonary immunopathology in influenza or SARS-CoV-2 infection:
Immune-mediated damage to alveolar epithelium and capillaries leading to acute respiratory distress syndrome (ARDS).

Autoimmune-like tissue injury post-infection:
Guillain–Barré syndrome following *Campylobacter jejuni* or viral infections, where antibodies cross-react with peripheral nerve components.

Persistence of infections

tissue damage caused by immune responses to pathogens (e.g., cytokine storms, immunopathology in viral infections).

Immunodeficiency

Primary (congenital) immunodeficiencies:
X-linked agammaglobulinemia: absence of B cells and B-cell–derived antibodies.

Severe combined immunodeficiency (SCID): defective T and B cell function leading to severe infections.

Secondary (acquired) immunodeficiencies:
HIV/AIDS: depletion of CD4+ T cells impairing cellular and humoral immunity.

Treatment-related immunosuppression (e.g., chemotherapy, organ transplantation): reduced lymphocyte function increasing infection risk.

Immunodeficiency

inadequate immune function resulting in increased susceptibility to infections or cancer

How immunodeficiency leads to tissue and cellular pathology

Increased or recurrent infections causing tissue damage

•**Defect type**: Humoral (antibody) deficiencies, cellular (T-cell) deficiencies, phagocyte defects, complement defects.

•**Pathophysiology**:

- Inadequate opsonization or microbial killing leads to frequent infections.
- Repeated inflammation causes collateral tissue injury (e.g., bronchiectasis from recurrent pneumonias; sinus damage; renal scarring from glomerulonephritis secondary to immune complex–driven processes).

•**Cellular consequences**:

- Chronic neutrophil recruitment with tissue destruction.
- Fibrosis from repeated healing attempts.

Dysregulated immune responses and autoimmunity

•**Defect type**: Regulatory failures (e.g., Treg defects), immune dysregulation syndromes (IPEX, ALPS).

•**Pathophysiology**:

- Loss of peripheral tolerance leads to autoreactive T and B cells.
- Autoantibody production and immune complex deposition cause tissue inflammation.

•**Tissue outcomes**:

- Autoimmune cytopenias (anemia, thrombocytopenia) with tissue destruction.
- Autoimmune nephritis, gastritis, dermatitis, and other organ-specific autoimmunity.

Impaired clearance of pathogens and reservoirs

•**Defect type**: Phagocyte disorders (e.g., CGD), NK cell defects, T-cell–mediated immunity deficits.

•**Pathophysiology**:

- Failure to eradicate intracellular pathogens allows organisms to persist and multiply within tissues.
- Granuloma formation as an attempt to wall off persistent agents, which can distort organ architecture.

•**Tissue outcomes**:

- Granulomatous inflammation in lungs, liver, skin, and lymphoid tissues.
- Abscess formation with necrosis.

Altered barrier integrity and mucosal vulnerability

- **Defect type**: Immunodeficiencies with poor mucosal immunity (e.g., IgA deficiency).
- **Pathophysiology**:
  - Reduced secretory IgA impairs defense at mucosal surfaces (GI, respiratory, genitourinary).
  - Microbial translocation and dysbiosis provoke systemic or localized inflammation.
- **Tissue outcomes**:
  - Chronic gastrointestinal symptoms, enteropathy, or inflammatory changes in mucosa.
  - Recurrent upper airway infections with sinusitis or bronchitis.

Impaired antibody-dependent cellular cytotoxicity and complement-mediated injury

- **Defect type**: Complement deficiencies (e.g., C3, C5-C9), antibody deficiencies.
- **Pathophysiology**:
  - Inability to form membrane attack complexes or to opsonize pathogens properly.
  - Persistent infections trigger chronic inflammation and tissue damage.
- **Tissue outcomes**:
  - Recurrent infections in mucosal surfaces leading to scarring.
  - Increased susceptibility to severe disseminated infections with organ involvement.

Specific organ- and pathway-focused examples

- **CVID and lung pathology**: Recurrent infections → bronchiectasis → loss of airways and gas exchange impairment.
- **CGD and granulomatous disease**: Neutrophil dysfunction → granuloma formation in abdomen, urinary tract, and lungs.
- **Hematopoietic stem cell transplant–related immunodeficiencies**: Graft-versus-host disease causing tissue injury in skin, liver, gut.
- **IFN-γ axis defects**: Susceptibility to mycobacterial infections with granulomatous inflammation in lymph nodes and lungs.

Nutritional and metabolic consequences

- **Defect type**: Chronic infection/inflammation, malabsorption due to GI involvement.
- **Pathophysiology**:
  - Ongoing inflammation affects appetite, absorption, and metabolism.
  - Malnutrition impairs immune function, creating a vicious circle.
- **Tissue outcomes**:
  - Growth delay in children.
  - Impaired wound healing and tissue regeneration.

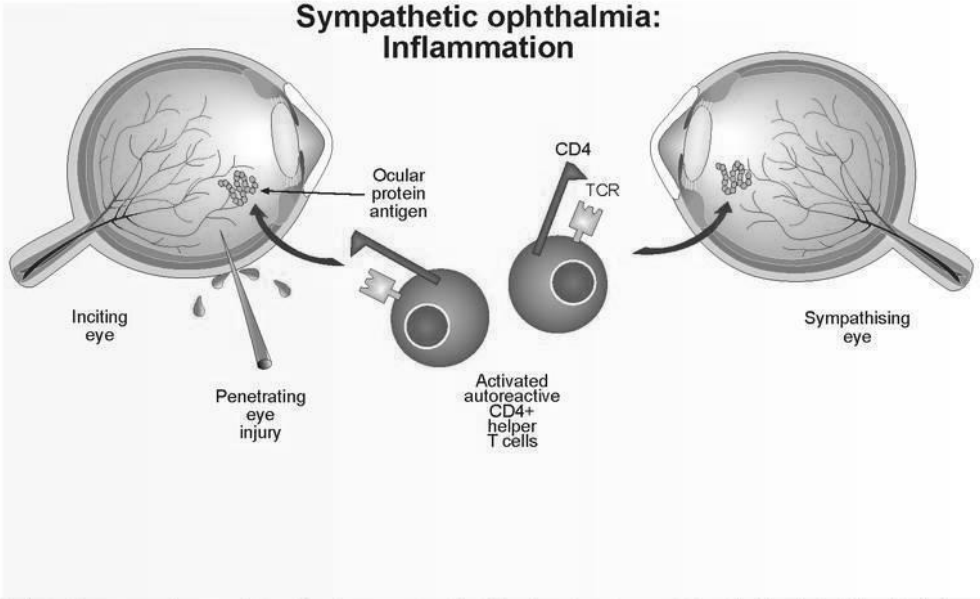
Possible mechanisms of autoimmune diseases

Conceptual framework: linking defects to pathology

- If defense against a pathogen is weak → more infections → tissue damage from inflammation.
- If clearance of dead cells and debris is defective → persistent inflammation and autoantigen presentation → autoimmunity.
- If regulatory checks fail → unchecked activation of immune cells → collateral tissue injury.
- If barrier immunity is compromised → microbial products trigger systemic inflammation and organ-specific injury.

Loss of tolerance

- **Central tolerance failure**: In the thymus or bone marrow, self-reactive T or B cells escape deletion.
- **Peripheral tolerance failure**: Regulatory T cell (Treg) dysfunction or insufficient peripheral anergy allows autoreactive cells to become activated.
- **Molecular mimicry**: Foreign antigens resemble self-antigens, leading to cross-reactive responses that target self



Activated immune cells upregulate cell surface receptors that allow them to extravasate from the blood circulation into inflamed tissue. Vascular endothelial cells also upregulate the ligands for these receptors to facilitate this process when stimulated by inflammatory cytokines such as IL-1 and TNF-α. Autoreactive CD4+ helper T cells penetrate the blood-retinal barrier of the damaged eye where they detect immunogenic ocular antigens and mount a pro-inflammatory immune response. Released cytokines recruit additional immune cells that overwhelm the immune privilege status of the eye and cause immune-mediated damage unless treated with anti-inflammatory drugs. Later, infiltration of autoreactive CD4+ helper T cells can promote inflammation of the undamaged eye (sympathetic eye), possibly due to upregulation of membrane receptors on local vascular endothelial cells by systemic cytokine stimulation.

Innate immune activation and dysregulation

•**Chronic innate activation**: Aberrant innate sensing (NLRP3 inflammasome, TLRs) leads to sustained cytokine production (IL-1β, IL-6, TNF-α).

•**Danger signals and tissue damage**: Damaged tissues release DAMPs that activate innate immunity and promote autoimmunity.

Genetic predisposition

•**HLA associations**: Certain HLA alleles present self-peptides more effectively, increasing risk (e.g., HLA-DRB1*04 in rheumatoid arthritis; HLA-B27 in spondyloarthropathies).

•**Non-HLA genes**: Variants in PTPN22, CTLA4, IL2RA, and other immune regulators influence threshold for activation, tolerance, or cytokine signaling.

•**Gene-environment interactions**: Infections, microbiome shifts, or toxins can interact with genetic susceptibility.

T cell–mediated autoimmunity

•**Autoreactive T cells**: CD4+ helper T cells (Th1, Th17, Tfh) drive inflammation and help B cells; CD8+ cytotoxic T cells can directly kill self-tissues.

•**Treg impairment**: Reduced number or function of Tregs fails to restrain autoreactive responses.

B cell–mediated autoimmunity

•**Autoantibody production**: B cells produce antibodies against self-antigens (e.g., anti-dsDNA, anti-CCP, ANA).

•**Antigen presentation**: B cells present self-antigens to T cells, sustaining autoreactivity.

•**T-bet and B cell subsets**: Skewed B cell differentiation contributes to pathogenic autoantibody production.

Barrier dysfunction and exposure

•**Barrier tissues**: Skin, gut, and mucosal barriers, when damaged, can expose self-antigens and promote systemic autoimmunity.

•**Microbiome shifts**: Dysbiosis can modulate immune tone and tolerance.

Epigenetic and metabolic influences

•**Epigenetic changes**: DNA methylation, histone modifications, and non-coding RNAs alter gene expression related to immunity.

•**Metabolic reprogramming**: Immune cell metabolism (glycolysis, oxidative phosphorylation) shapes activation and differentiation.

Tissue-specific factors and target organ susceptibility

•**Expression patterns**: Local antigen presentation, cytokine milieu, and resident immune cells shape organ-specific autoimmunity.

•**Hormonal and sex differences**: Higher prevalence in females; sex hormones can modulate immune responses.

Post-translational modifications and neoantigens

•**Citrullination, carbamylation**: Modified self-proteins become immunogenic (e.g., anti-CCP in rheumatoid arthritis).

•**Neoantigen formation**: Inflammation reveals or creates new self-epitopes that elicit responses.

THANK YOU!!

Environmental triggers

- **Infections**: Molecular mimicry or bystander activation can initiate autoimmunity.

- **Vaccination, drugs, toxins**: Rarely, can unmask or trigger autoimmune processes in susceptible individuals.