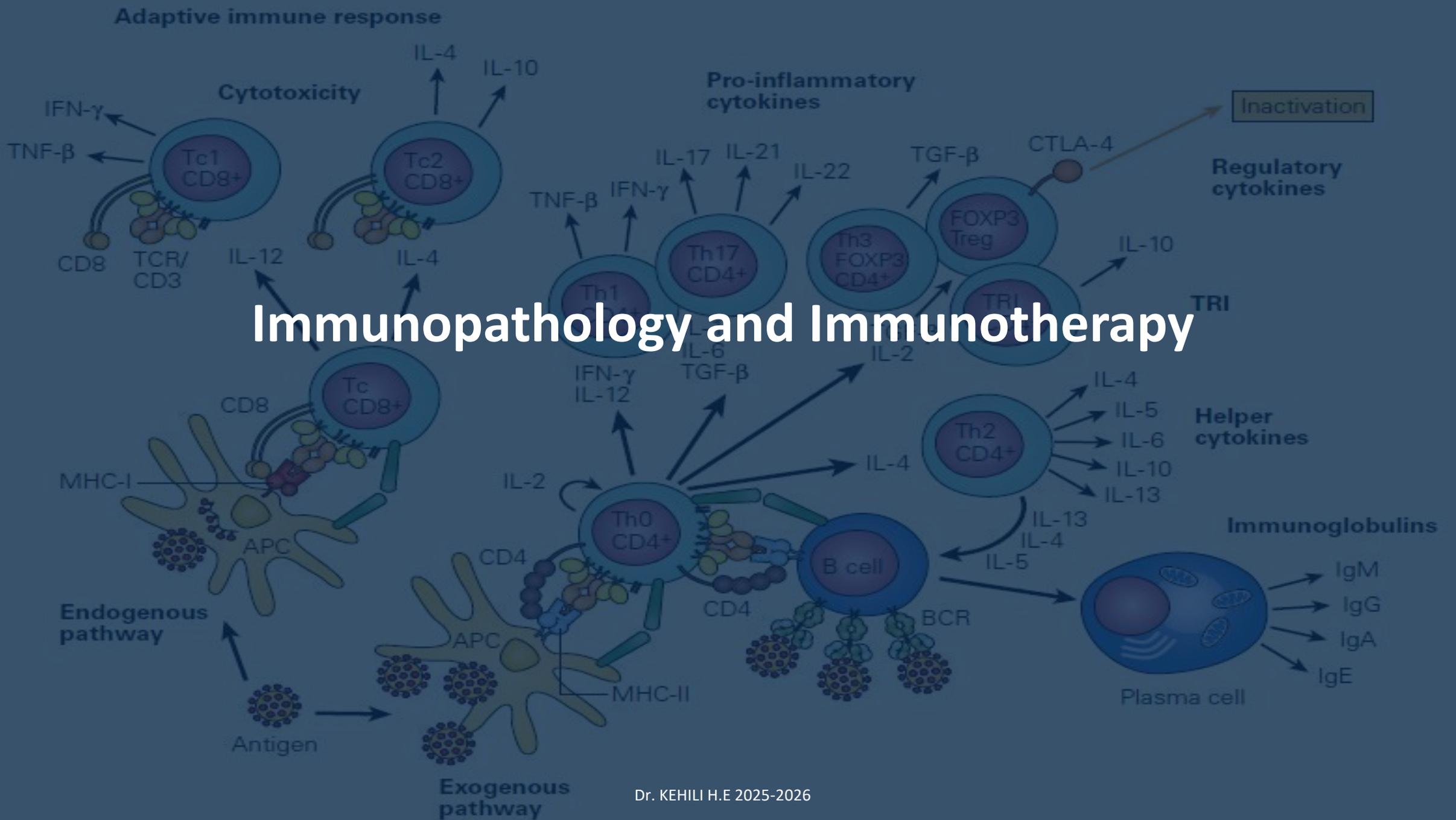


Immunopathology and Immunotherapy



Introduction

🛡️ The Immune System

Complex network of **cells, tissues, and molecules** evolved to protect against pathogens

↔️ Dual Nature

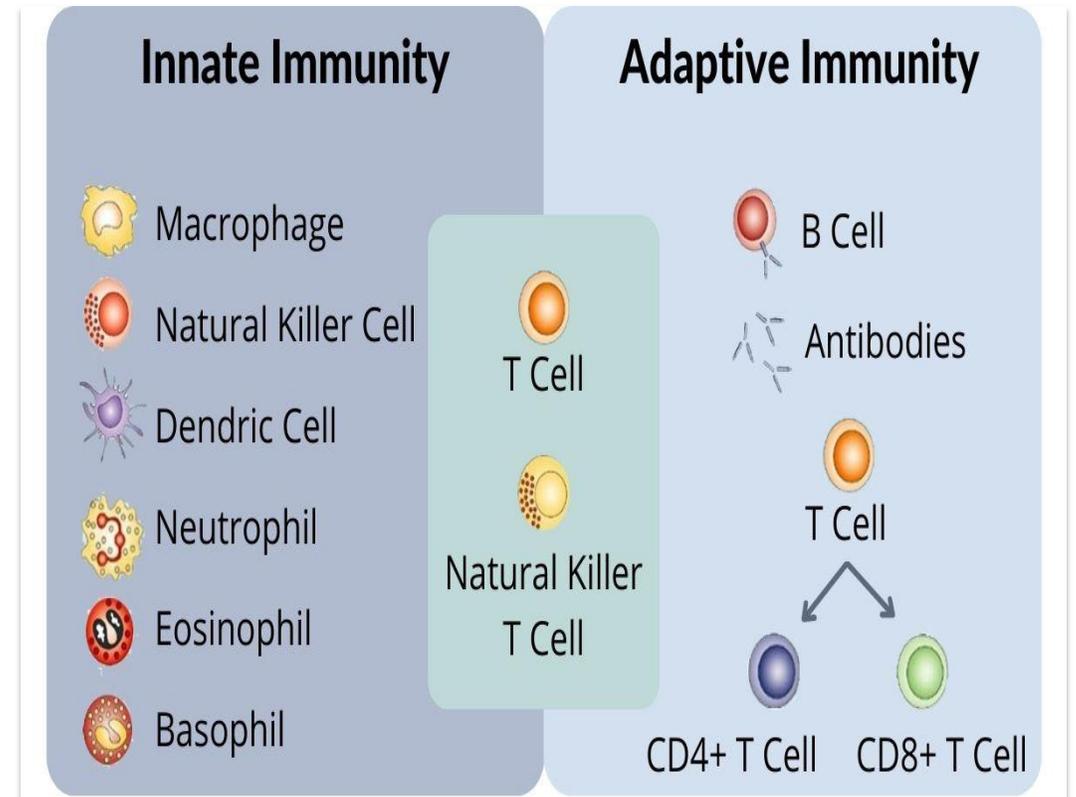
Protective: Defense against infections

Pathogenic: When regulation fails, immune system attacks host

🔗 Key Fields

Immunopathology: Study of immune-mediated diseases

Immunotherapy: Harnessing immune mechanisms for treatment



Autoimmune Diseases - Definition and Mechanisms

Definition

Breakdown in **self-tolerance** - the normal state of non-responsiveness to self-antigens

Key mechanisms leading to a loss of tolerance include:

👁️ Release of Sequestered Antigens

Hidden tissues (eye, testes) exposed due to trauma

↔️ Molecular Mimicry

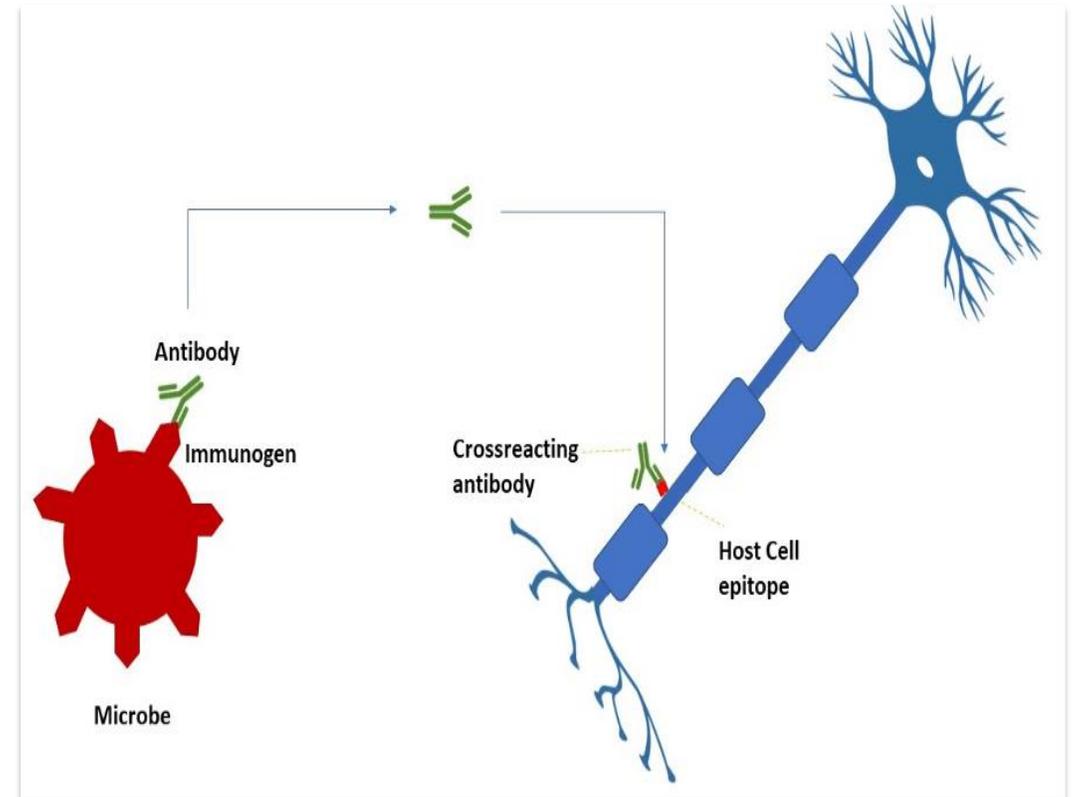
Pathogen antigen resembles self-antigen

📍 Epitope Spreading

Initial immune response releases new self-antigens

🔥 Bystander Activation

Inflammatory response activates autoreactive T cells



Autoimmune Diseases - Organ-specific

Definition

Immune response directed against **single organ or tissue type**



Type 1 Diabetes Mellitus

T-cell-mediated destruction of **insulin-producing beta cells** in pancreas



Multiple Sclerosis (MS)

T-cell and antibody attack on **myelin sheath** of neurons in CNS



Graves' Disease

Antibodies (TSI) mimic **Thyroid-Stimulating Hormone**, causing hyperthyroidism

Key Features

- Targeted to specific organs/tissues
- Often mediated by T cells or autoantibodies
- Can lead to organ dysfunction or failure

Prevalence

- Affects ~5% of population
- Higher incidence in females
- Often develops in young adulthood

Autoimmune Diseases - Systemic

Definition

Immune response targets antigens found in **multiple tissues throughout the body**

Systemic Lupus Erythematosus (SLE)

Autoantibodies against **nuclear components** (anti-dsDNA), forming immune complexes that deposit in kidneys, skin, and joints

Rheumatoid Arthritis (RA)

Targets **synovial joints**, involves autoantibodies like Rheumatoid Factor (RF) and anti-CCP

Sjögren's Syndrome

Lymphocytic infiltration of **exocrine glands** (salivary and lacrimal), causing dry mouth and dry eyes

Key Features

- Multi-organ involvement
- Presence of autoantibodies
- Immune complex deposition

Clinical Impact

- Fluctuating disease course
- Systemic symptoms common
- Often requires lifelong management

Hypersensitivity - Overview and Type I

i Definition

Exaggerated, damaging immune response to **harmless antigen** or self-antigen

▲ Gell and Coombs Classification

Type I: Immediate, IgE-mediated

Type II: Cytotoxic, IgG/IgM-mediated

Type III: Immune complex-mediated

Type IV: Delayed, T-cell mediated

+ Type I Hypersensitivity

↻ Mechanism

IgE-mediated, mast cell degranulation, release of histamine and other mediators

⊗ Examples

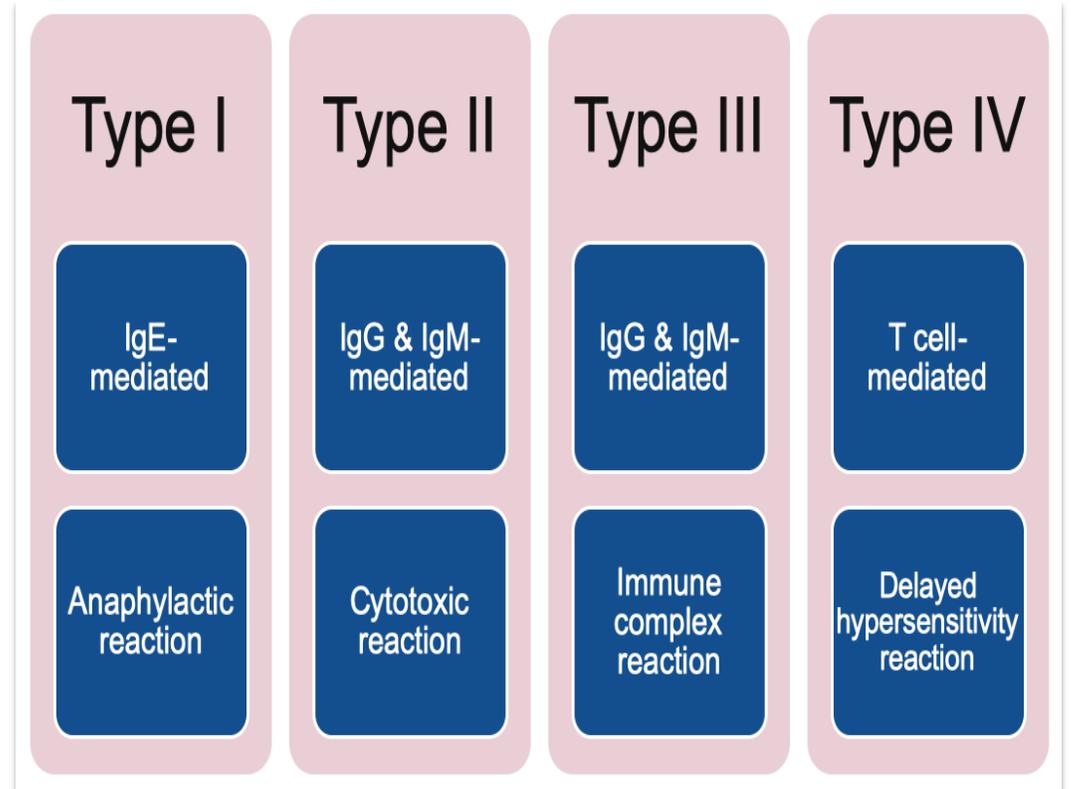
Allergic rhinitis, asthma, food allergies, anaphylaxis

🕒 Time Course

Minutes

+ Treatment

Antihistamines, corticosteroids, epinephrine for anaphylaxis



Hypersensitivity - Type II and Type III

Type II Hypersensitivity (Cytotoxic)



Mechanism

IgG/IgM antibodies bind to cell surface antigens, leading to cell destruction via:

Complement activation

ADCC

Opsonization



Time Course

Minutes to hours



Examples

Autoimmune hemolytic anemia

Goodpasture's syndrome

Hemolytic disease of newborn

Type III Hypersensitivity (Immune Complex)



Mechanism

Soluble antigen-antibody complexes (IgG/IgM) deposit in tissues, triggering:

Classical complement pathway

Inflammatory response

Tissue damage



Time Course

Hours to days



Examples

Serum sickness

Systemic Lupus Erythematosus

Arthus reaction

Hypersensitivity - Type IV

🕒 Type IV Hypersensitivity (Delayed-Type)



Mechanism

T-cell mediated, not antibody-mediated

👤 CD4+ Th1 Cells

Release IFN- γ , activate macrophages

🛡️ CD8+ CTLs

Directly kill target cells



Time Course

24-72 hours after antigen exposure



Examples

🦠 Tuberculin skin test

🍃 Contact dermatitis

🩺 Type 1 diabetes

! Key Features

- Cell-mediated immunity
- Delayed onset (24-72 hours)
- No antibodies involved

🔬 Clinical Significance

- Basis for skin testing
- Target for immunosuppressants
- Involved in organ rejection

Drug Hypersensitivity

Definition

Immune-mediated responses to pharmaceutical agents (ADRs)

Mechanisms



Hapten Hypothesis

Small drug molecules (haptens) bind to carrier proteins, forming immunogenic complexes



p-i Concept

Drugs bind non-covalently to TCR or MHC, stimulating T-cell response

Classification (Types I-IV)

Type I

IgE-mediated: Penicillin allergy causing anaphylaxis

Type II

Cytotoxic: Drug-induced hemolytic anemia (methyldopa)

Type III

Immune complex: Serum sickness-like reaction (cefaclor)

Type IV

T-cell mediated: Maculopapular rash, SJS, TEN

Key Point: Drug hypersensitivity can manifest as any of the four types of hypersensitivity reactions, with varying severity and clinical presentations.

Immune Deficiencies - Primary Immunodeficiencies

Definition

Genetic defects affecting immune cell development or function



B-cell (Humoral) Deficiencies

X-linked Agammaglobulinemia

BTK gene mutation prevents B-cell maturation

Clinical Features

Low immunoglobulins, recurrent bacterial infections



T-cell (Cell-mediated) Deficiencies

DiGeorge Syndrome

Developmental defect of 3rd/4th pharyngeal pouches

Clinical Features

Thymic aplasia, profound T-cell deficiency

Key Features

- ✓ Often inherited (X-linked or autosomal)
- ✓ Present in early childhood
- ✓ May require specialized treatment

Clinical Impact

- ✓ Recurrent infections
- ✓ Failure to thrive
- ✓ May require bone marrow transplant



Combined Immunodeficiencies

SCID

IL-2R γ chain deficiency

Clinical Features

Near-complete absence of adaptive immunity

Immune Deficiencies - Secondary Immunodeficiencies

Definition

Acquired defects in individuals with previously normal immune systems

HIV/AIDS

Mechanism

HIV infects and destroys **CD4+ T helper cells**, progressively dismantling adaptive immune response

Consequences

Leads to opportunistic infections and cancers characteristic of AIDS

Other Causes



Chemotherapy



Radiation Therapy



Malnutrition



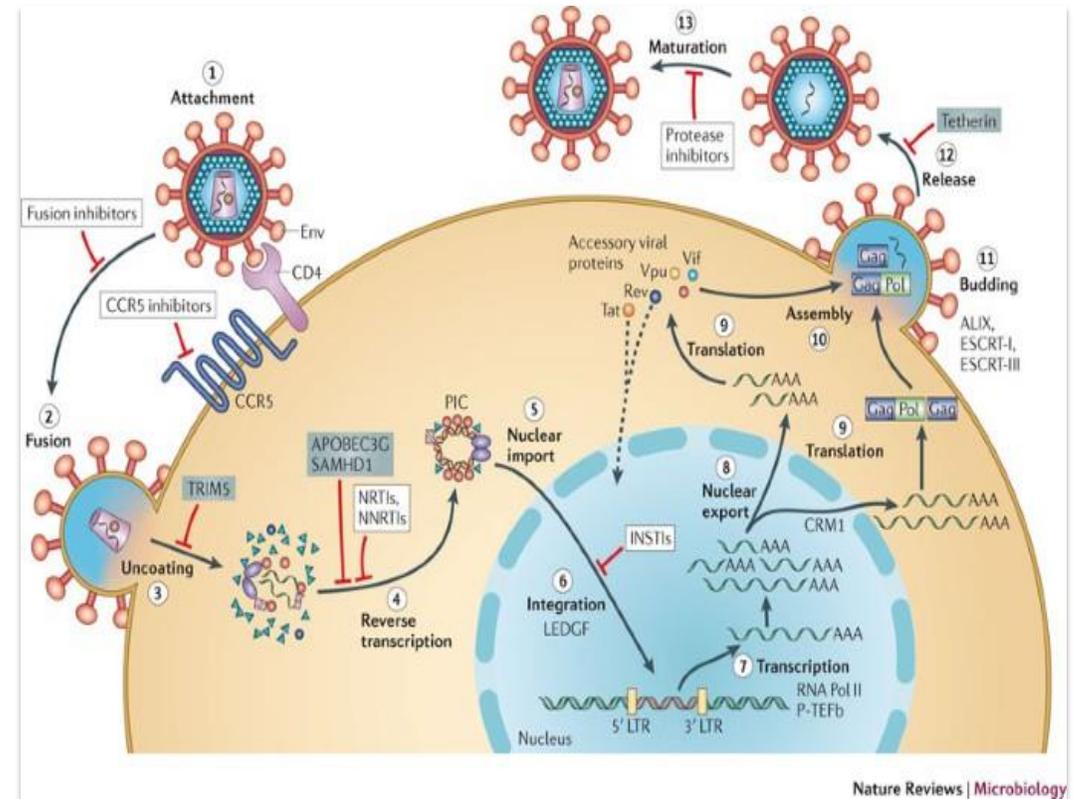
Advanced Age



Diabetes



Chronic Diseases



Nature Reviews | Microbiology

Immunotherapy - Cancer Immunotherapy (Checkpoint Inhibitors)

Definition

Modulating the immune system to achieve therapeutic goals

Immune Checkpoint Inhibitors



Mechanism

Block inhibitory pathways to **"release the brakes"** on T cells



Ipilimumab

Anti-CTLA-4



Pembrolizumab

Anti-PD-1



Nivolumab

Anti-PD-1

Key Checkpoint Pathways

CTLA-4

- ✓ Early T-cell activation
- ✓ Priming phase
- ✓ Lymph nodes

PD-1/PD-L1

- ✓ Effector phase
- ✓ Peripheral tissues
- ✓ Tumor microenvironment

! Clinical Impact

- ✓ Revolutionized cancer treatment
- ✓ Durable responses in some patients
- ✓ Immune-related adverse events

Immunotherapy - Cancer Immunotherapy (CAR-T Cell Therapy)

🔬 Definition

Living drug that enhances immune system's ability to recognize and destroy cancer cells

🔄 Mechanism

Patient's T cells are genetically engineered to express a **synthetic receptor (CAR)** that recognizes specific cancer antigens, allowing them to target and destroy cancer cells with high specificity

📈 Process

1

T Cell Collection

Patient's T cells are harvested from blood

2

Genetic Modification

Viral vector introduces CAR gene into T cells

3

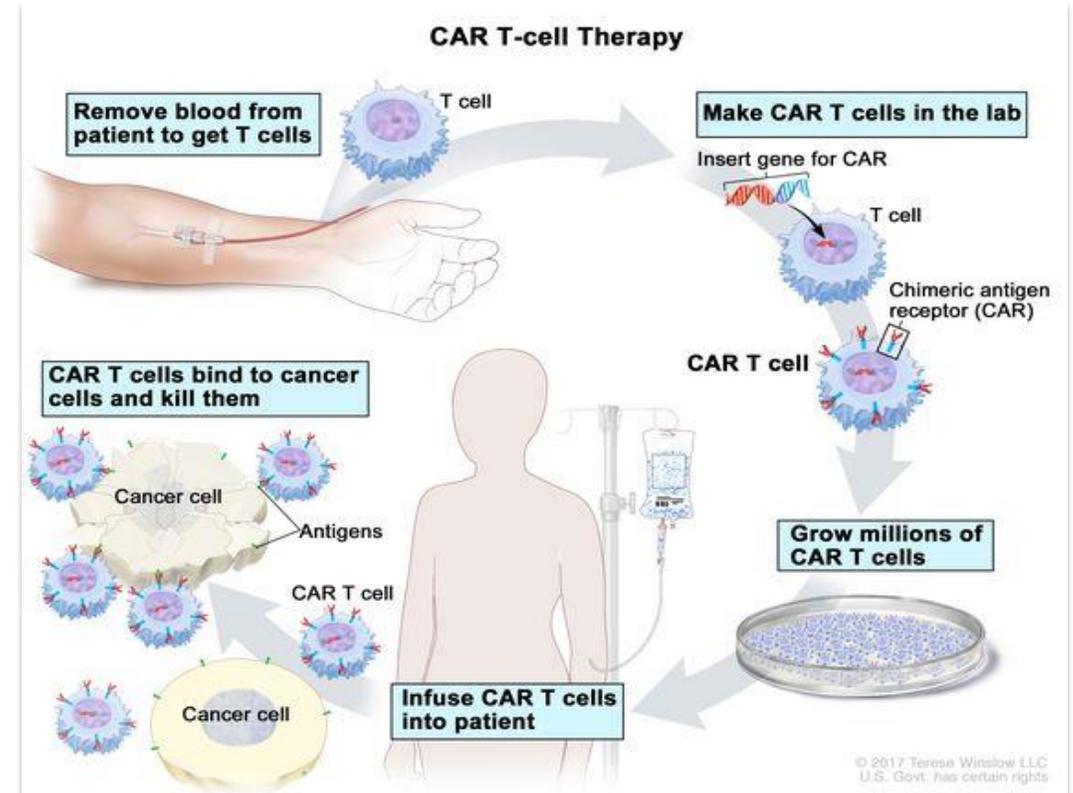
Expansion

Engineered CAR-T cells are multiplied in lab

4

Infusion

CAR-T cells are infused back into patient



Immunotherapy - AIDS and Allergy Immunotherapy

AIDS Immunotherapy

Antiretroviral Therapy (ART)

Combination of drugs targeting different stages of HIV life cycle:

- Reverse transcriptase inhibitors
- Protease inhibitors
- Integrase inhibitors

Experimental Approaches

- **Therapeutic vaccines** to boost anti-HIV immunity
- **"Kick and kill"** strategies to expose hidden virus
- **Gene editing** (CCR5 disruption) to create HIV-resistant cells

Allergy Immunotherapy

Mechanism

Administration of gradually increasing allergen doses shifts immune response:

- From **Th2/IgE-mediated** profile
- To **Treg/Th1** response
- Increases production of **blocking IgG4** antibodies
- Reduces activity of mast cells and eosinophils



SCIT

Subcutaneous Immunotherapy
Allergen injections under the skin



SLIT

Sublingual Immunotherapy
Allergen tablets or drops under the tongue