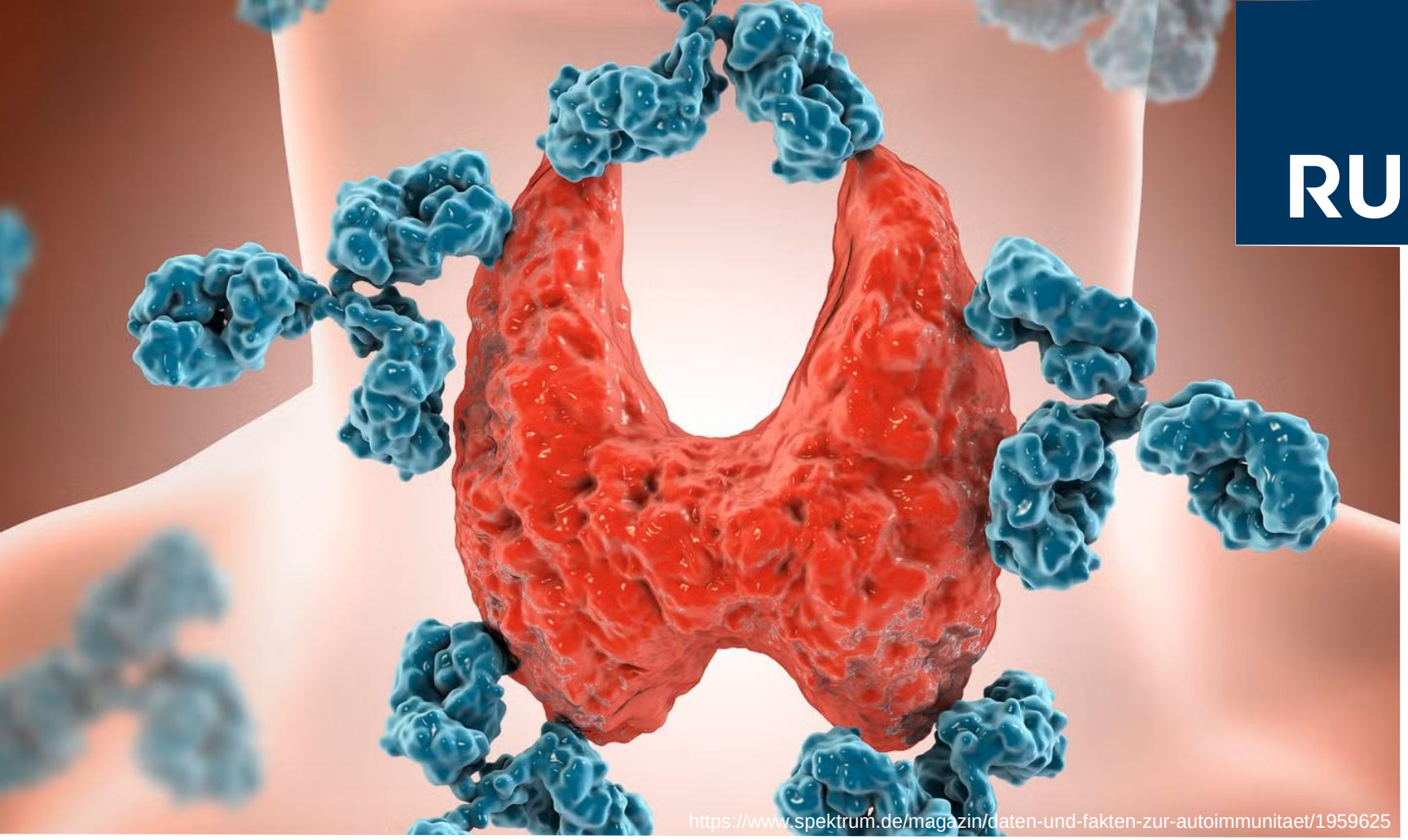

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AUTOIMMUNITY

Molecular Immunology I Louisa Clauß & Parisa Neisi Minaei I 25.06.2025

Overview

I. The making & breaking of self-tolerance

II. Autoimmune diseases & pathogenic mechanisms

III. The genetic & environmental basis

IV. Responses to alloantigens & transplant rejection

I. The making & breaking of self-tolerance

The immune system has strong effector mechanisms that eliminate pathogens

If misdirected, these same mechanisms can cause severe self-tissue damage

The concept of autoimmunity was introduced by Paul Ehrlich as *"horror autotoxicus"*

Autoimmune responses are:

Antigen-specific	Target self-antigens (autoantigens)	Generate autoreactive T cells and autoantibodies	Dysregulated self-reactivity leads to chronic autoimmune diseases	Autoimmune diseases vary in:	Severity	Target organs	Pathogenic mechanisms

Autoimmune Disease: Scope, Challenge, and Key Examples

Representative Autoimmune Diseases

- **Rheumatoid Arthritis**
- *Mechanism*: Autoreactive T cells + autoantibodies against joint antigens
- *Effect*: Chronic joint inflammation, cartilage & bone destruction
- **Systemic Lupus Erythematosus (SLE)**
- *Mechanism*: Autoantibodies + T cells against nuclear components
- *Effect*: Systemic inflammation – rash, nephritis, vasculitis
- **Multiple Sclerosis (MS)**
- *Mechanism*: Autoreactive T cells against CNS myelin
- *Effect*: Demyelination → motor dysfunction, ataxia
- **Type 1 Diabetes (IDDM)**
- *Mechanism*: $CD8^+$ T cells attack pancreatic β cells
- *Effect*: Insulin deficiency → hyperglycemia

Scope & Immune Discrimination

- Affects **~5%** of individuals in Western countries
- **Incidence rising**, especially in developed regions
- Individual diseases are **relatively rare** → Reflects **effective self-tolerance mechanisms**
- Immune system must distinguish **self from nonself** — a complex task:
- **B cells** recognize 3D shapes → shared between pathogens & self
- **T cells** recognize peptides → mimicry by pathogens
- No unique “self” tag → recognition is **context-dependent**

Mechanisms of Self-Tolerance (Central + Peripheral)

Central Tolerance (Thymus, Bone Marrow)

- **Clonal deletion** of strongly self-reactive T/B cells
- **Receptor editing** in B cells to reduce self-reactivity
- **Antigen segregation**: some self-antigens hidden in immune-privileged sites

Peripheral Tolerance

- **Anergy**: weak TCR signal without co-stimulation → functional inactivation
- **Regulatory T cells (Tregs)**: suppressive cytokines (e.g., IL-10, TGF-β) inhibit response
- **Functional deviation**: naive T cells become Tregs instead of effectors
- **Activation-induced cell death (AICD)**: overstimulated cells undergo apoptosis

Contextual Mechanisms

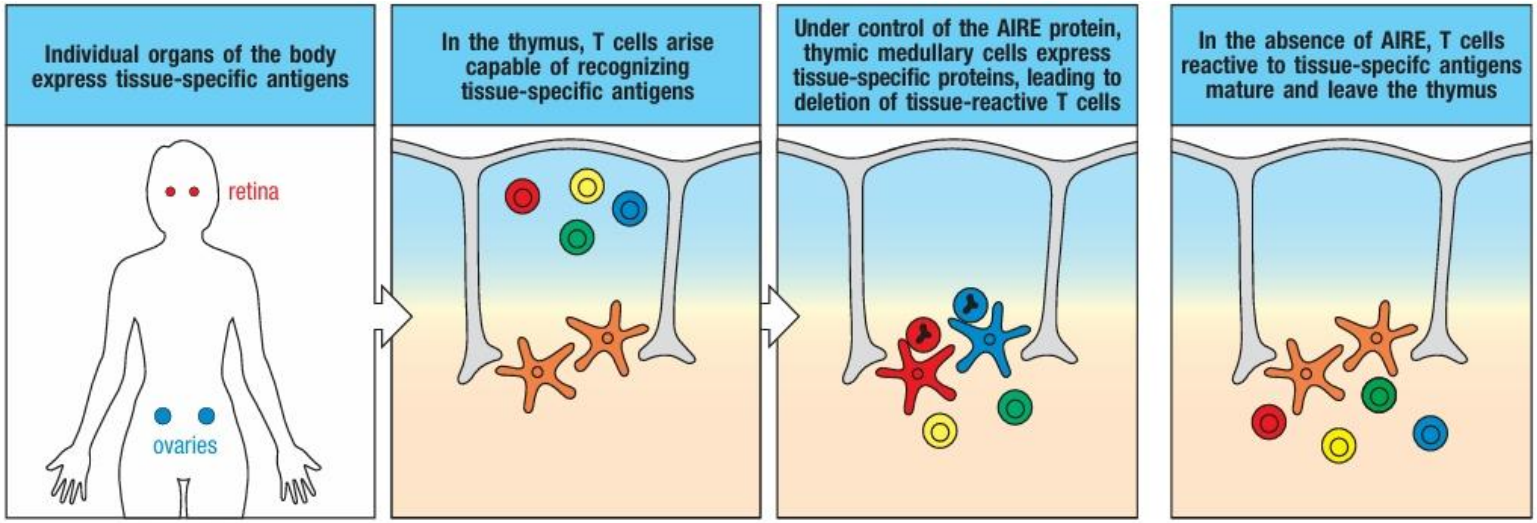
- **Apoptotic cell clearance**: silent removal prevents inflammation
- **Absence of danger signals** (no DAMPs/MAMPs): keeps APCs tolerogenic
- **Tolerance to microbiota**: maintained by Tregs unless epithelial damage occurs

Central Tolerance & AIRE

- First checkpoint in self-tolerance
- Clonal deletion of self-reactive lymphocytes
- Site: Thymus (T cells), Bone marrow (B cells)
- Prevents early-onset, lethal autoimmunity
- Peripheral tolerance ≠ sufficient backup

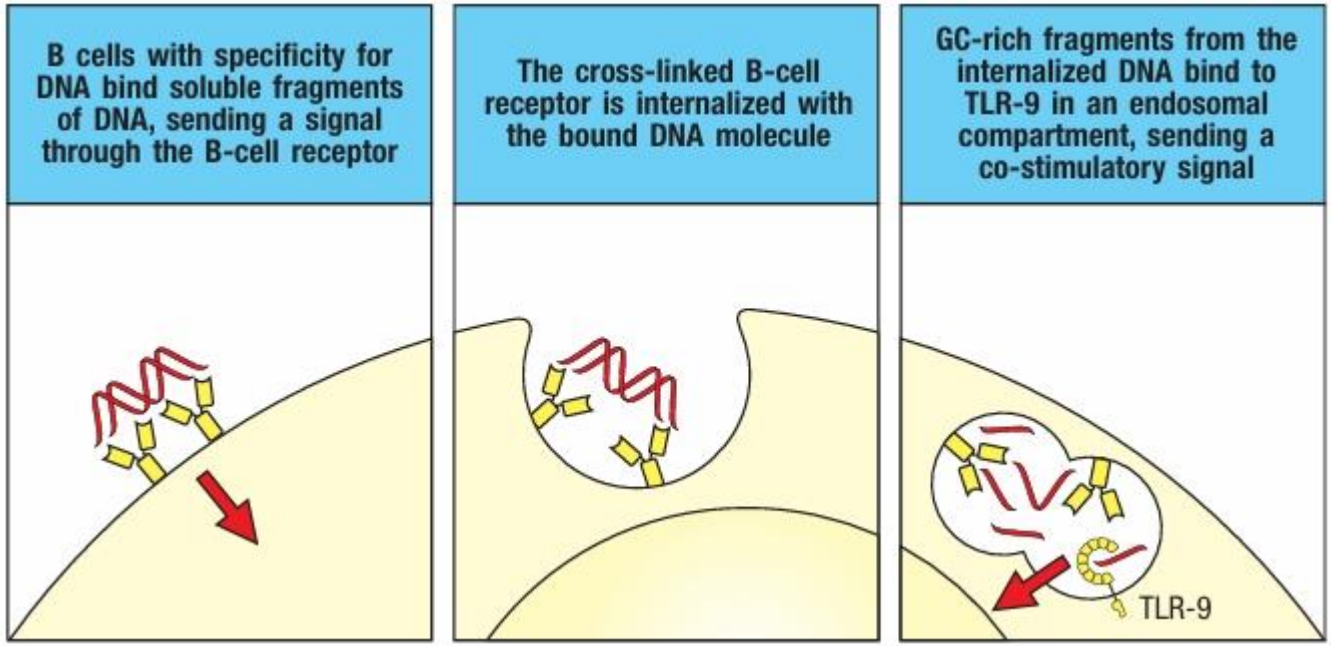
- Tissue-specific antigens (e.g., insulin) expressed in thymus
- Mediated by **AIRE** (Autoimmune Regulator)
- Controls ectopic gene expression in thymic medulla
- Deletes tissue-reactive T cells

- **AIRE mutation → APS-1 / APECED**
- Autoimmunity against endocrine tissues
- Fungal infections (e.g., candidiasis)
- Gradual disease onset → role for additional tolerance layers



Activation of Ignorant Self-Reactive Lymphocytes

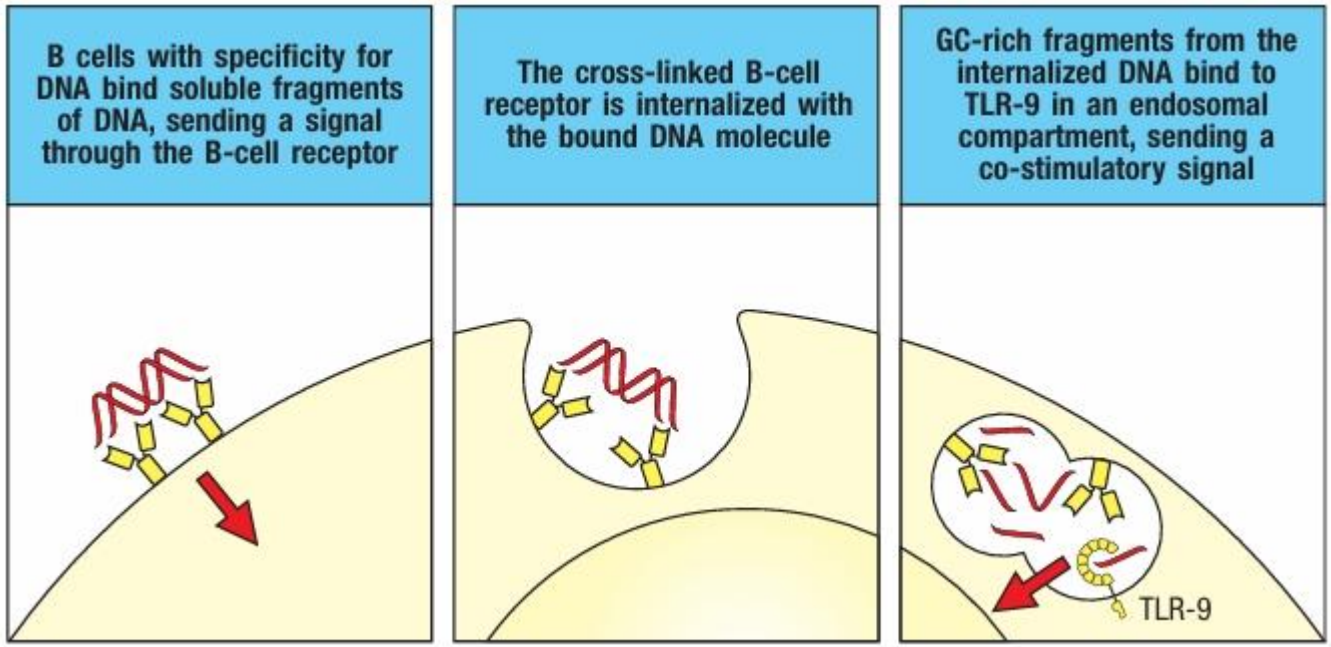
Activation of Ignorant Self-Reactive Lymphocytes
- **Ignorant lymphocytes**:
- Self-reactive cells with **low affinity** for self-antigen
- Circulate without responding under normal conditions



- **Activation triggers**:
- **Infection** → activated dendritic cells present self-antigen + co-stimulation
- **Toll-like receptor (TLR) signaling**:
- Example: TLR-9 recognizes **CpG DNA** (common in bacteria & apoptotic cells)
- Chromatin-reactive **B cells internalize DNA** → activate via TLR-9
- **Result**:
- Production of **autoantibodies against DNA/chromatin**
- Seen in **Systemic Lupus Erythematosus (SLE)**

Activation of Ignorant Self-Reactive Lymphocytes

- **Release of hidden antigens**:
- Normally sequestered antigens exposed during **tissue damage**
- Example: **cardiac antigens** released after myocardial infarction
- May cause **transient or chronic** autoimmunity



- **Changes in antigen form**:
- Monomeric **IgG** (non-immunogenic) → **immune complexes** (immunogenic)
- Activates B cells → **rheumatoid factor** (anti-IgG antibodies)
- **Somatic hypermutation in germinal centers**:
- Some B cells gain **self-reactivity** after mutation
- Controlled by deletion of hypermutated self-reactive B cells via **apoptosis**

Immune Privilege & Its Breakdown in Autoimmunity

Immunologically Privileged Sites & Autoimmunity

Sites: Brain, eye (anterior chamber), testes, placenta

Grafts placed here often **do not trigger immune rejection**

Mechanisms of Immune Privilege

Limited lymphatic drainage → reduced immune surveillance

Physical barriers (e.g., **blood-brain barrier**) exclude naive lymphocytes

Local production of **TGF-β** → promotes **Treg differentiation** over effector T cells

Fas ligand expression → induces apoptosis of infiltrating T cells

Paradox

Antigens leave privileged sites and **interact with T cells** → often induce **tolerance**, not inflammation

However, if **autoreactive lymphocytes are activated elsewhere**, these antigens become **targets for attack**

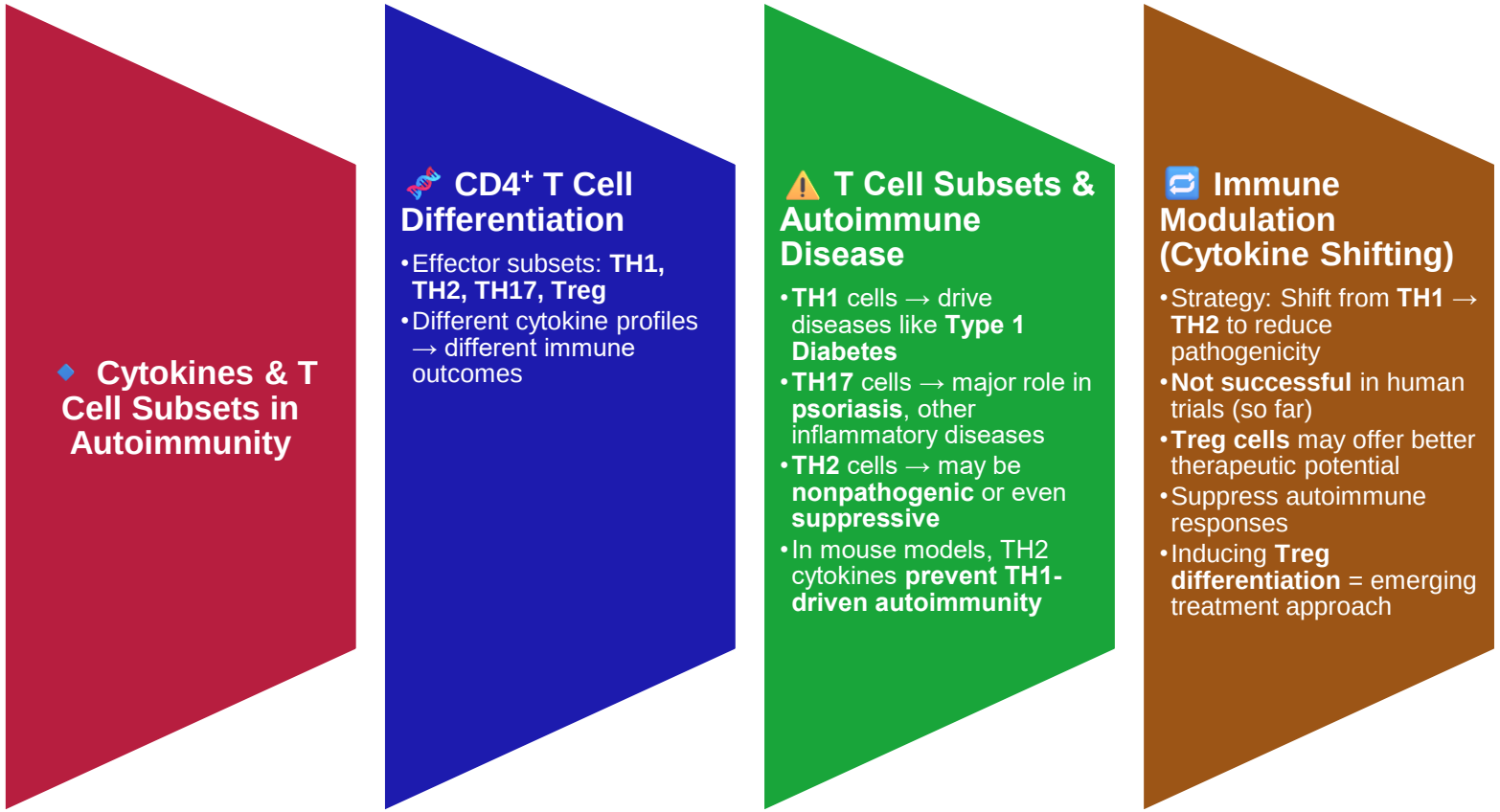
Examples

Multiple Sclerosis (target: **myelin basic protein** in CNS)

Sympathetic ophthalmia: trauma to one eye triggers autoimmunity affecting **both eyes**

Activated effector T cells can **enter these sites during infection** or inflammation

T Cell Subsets & Cytokine Balance in Autoimmune Pathogenesis



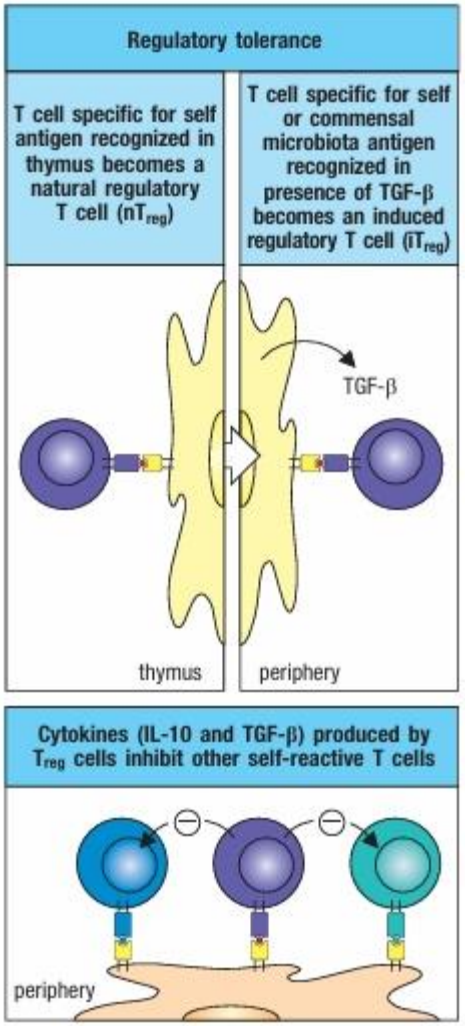
Regulatory T Cells & Autoimmune Control

Mechanisms of Treg-Mediated Tolerance
- **Extrinsic regulation**: Tregs suppress effector T & B cells
- **Intrinsic regulation**: programmed limits on lymphocyte activation/survival

Types of Treg Cells
- **Natural Tregs (nTregs)**
- Develop in **thymus**
- Recognize **self antigens**
- Express **FoxP3**
- **Induced Tregs (iTregs)**
- Develop in **periphery**
- Activated in presence of **TGF-β**, without pro-inflammatory cytokines
- Important in **oral tolerance**, gut immunity

Key Features
- Suppress autoreactive cells via **IL-10**, **TGF-β**
- Can inhibit T cells with **different antigen specificities** (same tissue/APC)
- **FoxP3 mutations** → severe autoimmunity (e.g., IPEX, APS-2)

Additional Regulatory Mechanisms
- **FoxP3⁻ IL-10⁺ Tregs** in intestine → suppress IBD
- **Regulatory B cells** → suppress arthritis, EAE
- **Apoptosis pathways** (Fas/Bcl-2) → eliminate autoreactive clones



Summay

🔹 Balancing Self-Tolerance and Immune Competence

- **Self-reactive lymphocytes** exist naturally in the immune repertoire
- **Autoimmunity** occurs when these cells are **persistently activated by autoantigens**

🛡️ Mechanisms of Tolerance

- **Central tolerance** (thymus, bone marrow):
- Clonal deletion of strongly self-reactive cells
- Generation of **FoxP3⁺ natural Tregs (nTregs)** from self-reactive CD4 T cells
- **Peripheral tolerance**:
- **Anergy**, **deletion**, and **iTreg induction** for antigens not seen centrally
- **iTregs** develop in periphery under **TGF-β** influence

⚖️ Balancing Immunity

- **Weakly self-reactive cells** are retained to preserve **immune repertoire**
  → Not deleted centrally
- Controlled **only when activated** in periphery
- Suppressed by **Treg cells** (autoregulative but nonpathogenic)
- Tregs suppress nearby autoreactive cells in **shared tissue environments**

🧬 Intrinsic Control

- Immune responses are **self-limiting**
- Activated lymphocytes → **apoptosis-prone**
- Sensitive to **Fas-mediated death signals**

II. Autoimmune diseases & pathogenic mechanisms

Autoimmune Diseases & Pathogenic Mechanisms

Overview

- Autoimmune diseases = **loss of self-tolerance** → tissue damage
- Immune mechanisms **resemble anti-pathogen responses**

Pathogenic Mechanisms

- **Autoantibodies**:
  - Activate **complement**
  - Engage **Fc receptors** → inflammation (e.g., **SLE**)
- **Cytotoxic T cells**:
  - Kill self cells like **virus-infected cells**
  - Example: **β cell destruction** in Type 1 Diabetes
- **Receptor-targeting antibodies**:
  - Modify receptor function without killing cells
  - Example: **Myasthenia gravis**
  - **Chronicity of Autoimmunity**
- Self antigens are **not cleared** like pathogens
- Immune responses become **chronic and self-sustaining**

Classification of Autoimmune Diseases

Organ-Specific Autoimmunity
- Targets antigens restricted to one tissue
- Examples:
- *Type 1 Diabetes*: pancreatic β cells
- *Multiple Sclerosis*: CNS myelin
- *Graves' Disease*: TSH receptor
- *Crohn's Disease*: microbiota antigens in the gut

Systemic Autoimmunity
- Targets **ubiquitous nuclear antigens** (e.g., chromatin, ribonucleoproteins)
- Example: *Systemic Lupus Erythematosus (SLE)*
- Leads to **multi-organ chronic inflammation**

Effector Mechanisms
- **T cells**: initiate, sustain inflammation; kill target cells
- **B cells**: present antigen, produce autoantibodies, support T cells
- **Autoantibodies**:
- Trigger inflammation
- Disrupt receptors (agonists or antagonists)
- Cross placenta → neonatal disease

Pathogenesis Insights
- Diseases often involve **multiple overlapping mechanisms**
- Immune response mimics that against pathogens: **innate + adaptive** arms
- **IBD** is a borderline case: not classic "self" target, but still immune-driven

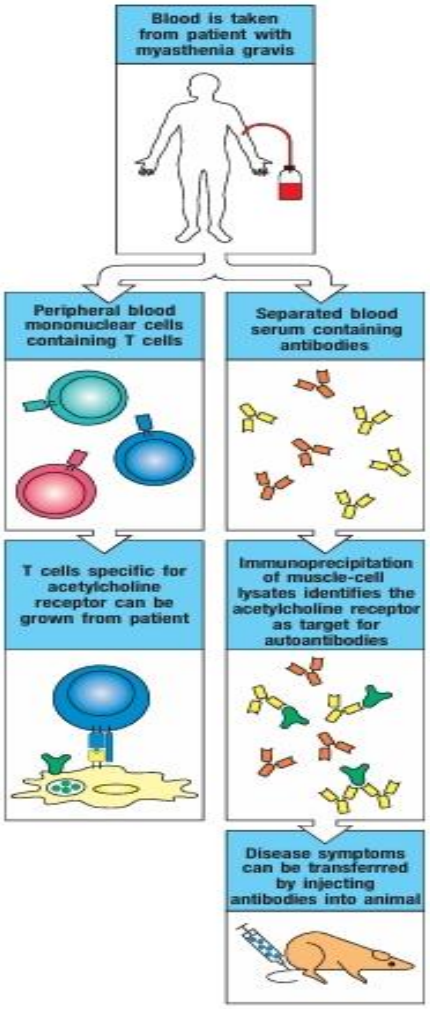
Immune Effectors in Autoimmune Diseases

Effector Mechanisms

- **Autoantibodies**:
- Bind to target receptors → block function
- *e.g.,* **Myasthenia Gravis** → anti-AChR → muscle weakness
- Form **immune complexes** → activate **complement** and **Fc receptors**
- Leads to **inflammation** and tissue damage
- **Effector T Cells**:
- Recognize **self peptides or microbiota-derived peptides** on MHC
- Cause damage by:
- **Recruiting innate myeloid cells** → local inflammation
- **Direct cytotoxicity** to tissue cells
- Seen in: **Type 1 Diabetes**, **Multiple Sclerosis**, **Psoriasis**, **IBD**

Experimental Evidence

- **Myasthenia Gravis**:
- **Patient serum** transfers disease to animals → confirms role of autoantibodies
- **EAE (MS model)**:
- **T cells** from diseased animals transfer symptoms to healthy animals
- Confirms **pathogenic role of autoreactive T cells**



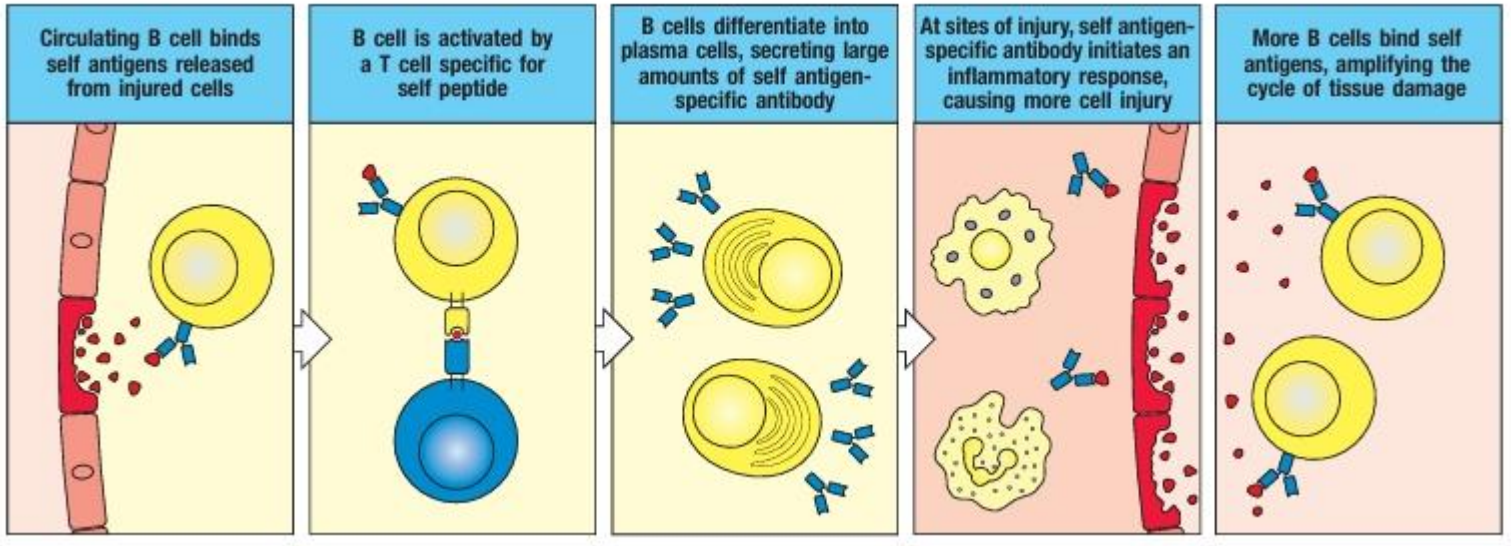
Chronic Autoimmune Disease & Positive Feedback

Why Autoimmune Responses Persist

- **Self-antigens not cleared** → chronic stimulation
- **Autoantigens released from tissue damage** → amplify immune response
- Inflammation attracts innate cells → **macrophages, neutrophils**

Positive Feedback Cycle

1. Cell damage releases autoantigens
2. B cells bind autoantigen → activate with help from T cells
3. Autoantibodies produced → more damage → more antigen release
4. Cycle perpetuates inflammation and tissue injury

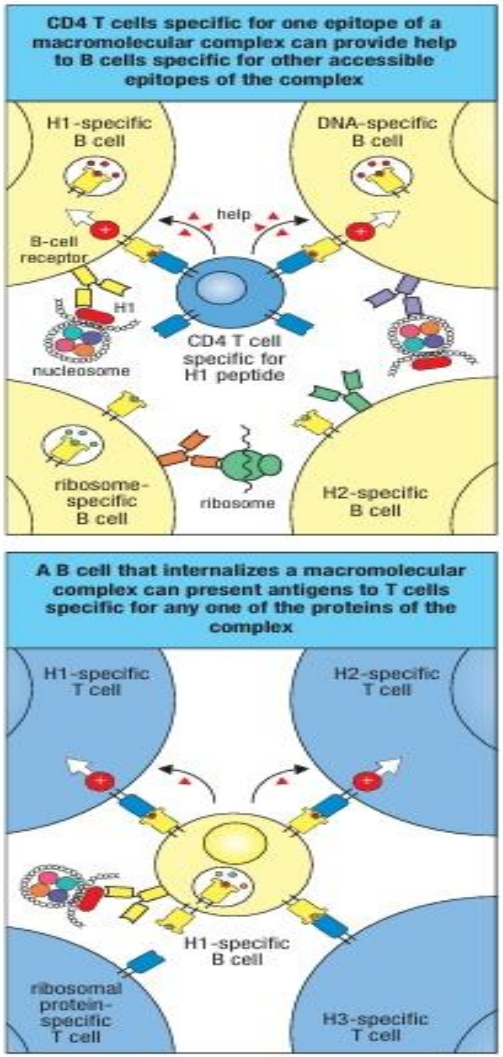


Epitope Spreading in Autoimmunity

What is Epitope Spreading?
- Autoimmune response **broadens** over time:
- More **epitopes** on the same antigen targeted
- Or spread to **entirely new autoantigens**

How it Happens
- B cell internalizes complex antigen (e.g., nucleosome)
- Presents various peptides to CD4 T cells
- **T cells help activate B cells** with other specificities
- New autoantibodies generated → more damage

Clinical Examples
- **SLE**: anti-DNA + anti-histone antibodies
- **Pemphigus vulgaris**:
- Initial: anti-Dsg-3 (mucosa only)
- Later: anti-Dsg-1 (epidermis) → skin blisters



Chronic Autoimmune Inflammation

- **Self-antigens persist** (e.g., chromatin, insulin) → no clearance → ongoing immune response
- **Tissue damage** releases new antigens → **positive feedback loop**
- **Epitope spreading** amplifies disease (e.g., SLE, pemphigus)

Most Autoimmune Diseases Are Mixed

- **T cells**: essential for both cytotoxicity and B cell help
- **B cells**: present antigen + secrete autoantibodies
- **Innate cells**: amplify inflammation, tissue injury
- Modern view: autoimmunity = **coordinated, multi-effector immune response**

Mechanism	Example Disease	Autoantigen	Consequence
Antibody against cell surface/matrix antigens (Type II Hypersensitivity)	**Pemphigus vulgaris**	Epidermal cadherins (Dsg-1, Dsg-3)	Blistering of skin due to loss of keratinocyte adhesion
Immune-complex mediated disease (Type III Hypersensitivity)	**Rheumatoid arthritis**	Rheumatoid factor (IgG) complexes	Joint inflammation and destruction
T-cell-mediated disease (Type IV Hypersensitivity)	**Type 1 Diabetes**	Pancreatic β-cell antigens	β-cell destruction → insulin deficiency
TH17-driven (Type 3 immunity)	**Crohn's disease**	Commensal microbiota antigens	Chronic inflammation and scarring of intestinal tissue

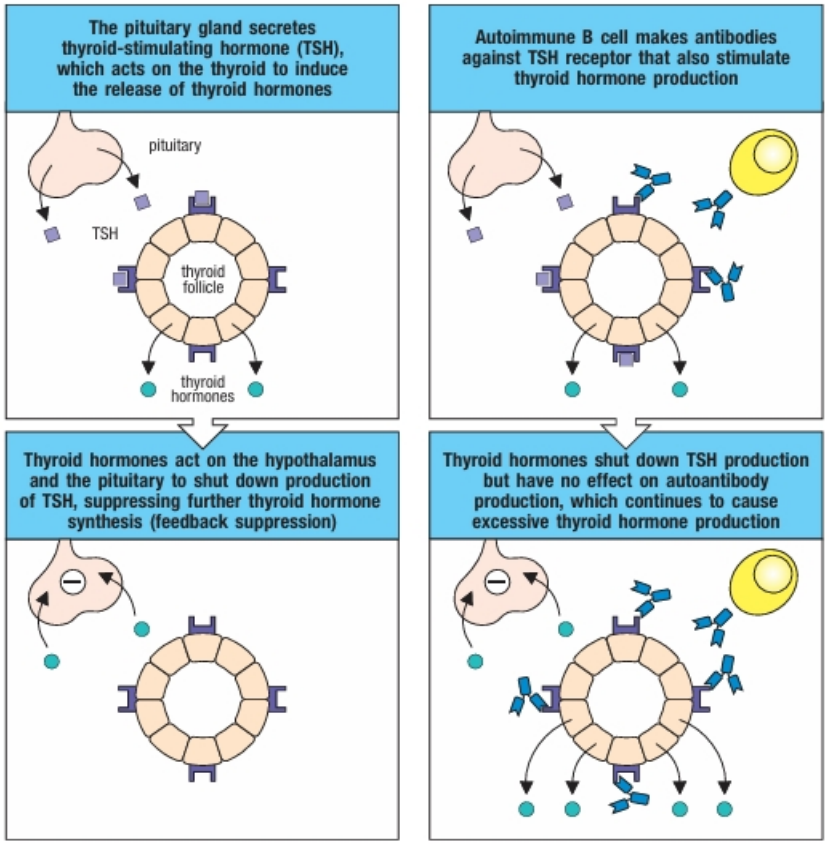
Inflammatory and Functional Effects of Autoantibodies

Sublytic Complement Activation (Inflammatory Trigger)

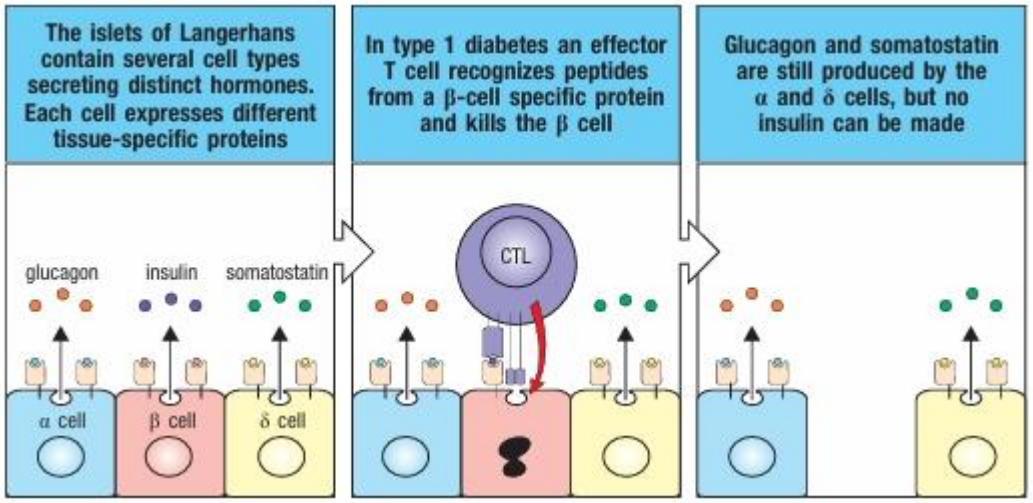
- Autoantibodies bind tissue cells → activate **complement** without full lysis
- **Sublytic MAC** triggers:
- **Cytokine release**
- **Respiratory burst**
- Production of **pro-inflammatory lipids** (prostaglandins, leukotrienes)
- **C5a** and leukotriene B4 recruit innate immune cells
- **Fc and C3 binding** activates leukocytes → amplifies **tissue damage**
- Seen in **Hashimoto's thyroiditis** (long-lasting antibody-driven inflammation)

Autoantibodies That Alter Receptor Function

- **Graves' disease**:
- Autoantibodies **stimulate** the TSH receptor
- Override negative feedback → **hyperthyroidism**
- **Myasthenia gravis**:
- Autoantibodies **block** acetylcholine receptors
- Receptor **internalization & degradation → muscle weakness**



T Cell–Mediated Autoimmune Diseases (Type I Diabetes)

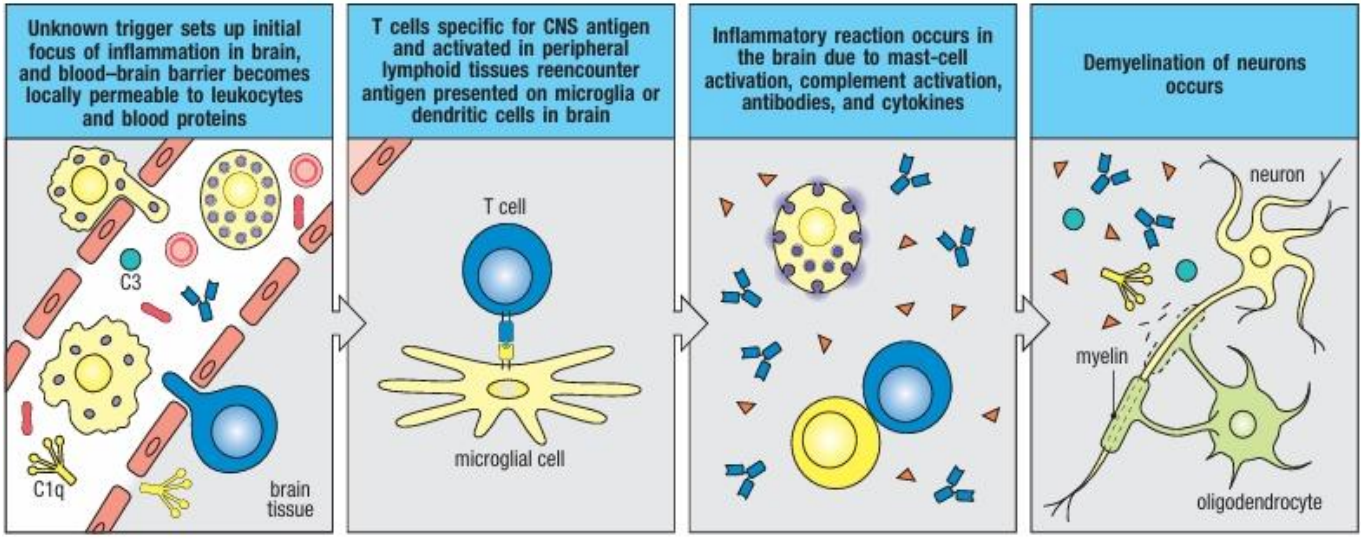


- **Key T Cells**: $CD8^+$ cytotoxic T cells
- **Target**: Insulin-producing β cells in pancreatic islets
- **Mechanism**:
- Direct killing of β cells
- No damage to α or δ cells
- **Features**:
- Highly selective
- Confirmed by β cell loss in identical twin pancreas transplants
- Suppressible by cyclosporin A

T Cell–Mediated Autoimmune Diseases (MS)

- **Key T Cells**: TH1 and TH17 $CD4^+$ T cells
- **Target**: Myelin antigens (MBP, PLP, MOG)
- **Mechanism**:
- Infiltration across blood–brain barrier
- Cytokine production (IL-17, IFN-γ, GM-CSF)
- Activation of macrophages, microglia → demyelination

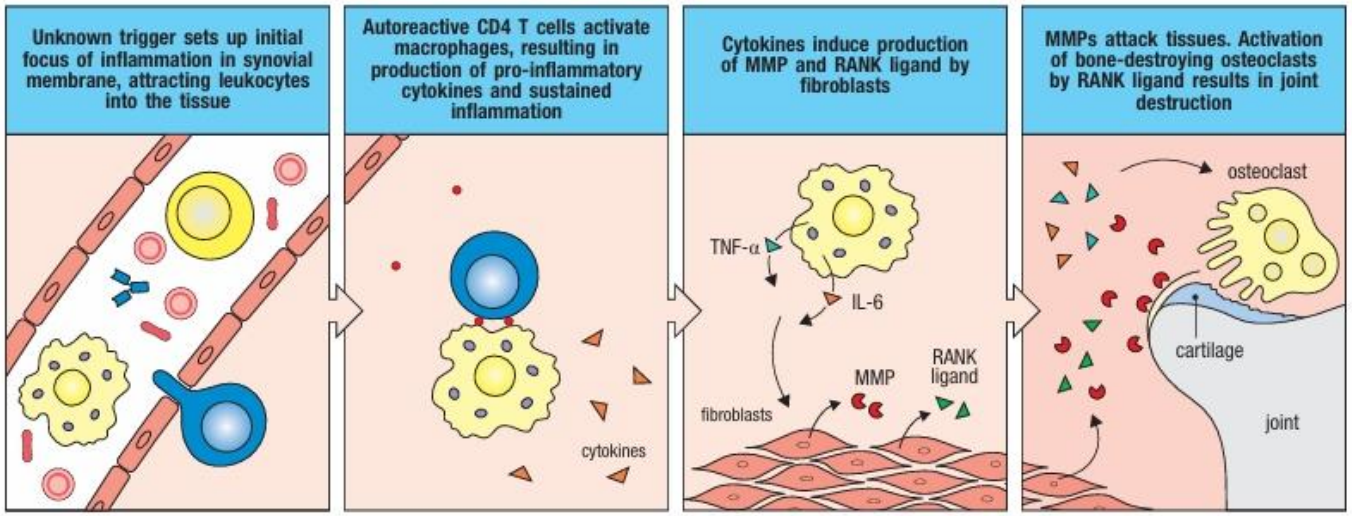
- **Features**:
- Relapsing–remitting course → secondary progressive
- Blood–brain barrier breakdown critical in disease initiation



T Cell–Mediated Autoimmune Diseases (Rheumatoid Arthritis)

- **Key T Cells**: TH17 cells (plus macrophages, fibroblasts)
- **Target**: Citrullinated joint proteins (ACPAs)
- **Mechanism**:
- Cytokine storm (IL-17, TNF-α, IL-6)
- Fibroblast activation → MMPs → cartilage damage
- RANKL → osteoclast differentiation → bone erosion

- **Features**:
- Autoantibodies aid diagnosis (ACPAs)
- Smoking + HLA-DR = key risk combo
- Both B and T cells required in early disease



T Cell–Mediated Autoimmune Diseases (Summary)

Disease	Key T Cells	Target/Antigen	Mechanism & Effect	Notable Features
Type 1 Diabetes	$CD8^+$ cytotoxic T cells	β-cell proteins (e.g., insulin)	Direct killing of pancreatic β cells	Selective islet destruction; prevented by T-cell immunosuppression
Multiple Sclerosis	TH1 & TH17 $CD4^+$ T cells	Myelin (MBP, PLP, MOG)	Demyelination via cytokines + microglial/macrophage activation	Relapsing–remitting or progressive CNS disease
Rheumatoid Arthritis	TH17 $CD4^+$ T cells + macrophages	Citrullinated joint proteins (ACPAs)	IL-17, TNF-α induce inflammation; MMPs & RANKL → cartilage and bone destruction	Smoking + HLA-DR = strong gene–environment link

Shared T Cell Features

- T cells **activate B cells** → autoantibody production
- Infiltrate tissues and sustain **chronic inflammation**
- Drive **relapse–remission cycles** and **progressive damage**

Summary

Two Major Categories of autoimmune diseases

- **Organ-Specific Autoimmunity**
- Targets antigens restricted to one tissue
- Examples:
- *Type 1 Diabetes*: pancreatic β cells
- *Multiple Sclerosis*: CNS myelin
- *Graves' Disease*: TSH receptor
- *Crohn's Disease*: microbiota antigens in the gut
- **Systemic Autoimmunity**
- Targets **ubiquitous nuclear antigens** (e.g., chromatin, ribonucleoproteins)
- Example: *Systemic Lupus Erythematosus (SLE)*
- Leads to **multi-organ chronic inflammation**

Effector Mechanisms

- **T cells**: initiate, sustain inflammation; kill target cells
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- Disrupt receptors (agonists or antagonists)
- Cross placenta → neonatal disease

Pathogenesis Insights

- Diseases often involve **multiple overlapping mechanisms**
- Immune response mimics that against pathogens: **innate + adaptive** arms
- **IBD** is a borderline case: not classic "self" target, but still immune-driven

III. The genetic & environmental basis

Genetical basis of autoimmunity

- Autoimmune diseases are a result of **genetic & environmental factors**
  - ➢ Together they overcome **tolerance mechanisms**
- Some individuals/families are genetically predisposed
  - ➢ Not all develop autoimmunity at all or at the same time
    - → Influence of environmental factors, e.g. intestinal microbiota
- Many autoimmune diseases are more common in females – reasons still unclear
- Most notably pathways are involved in **T cell activation & function** and **development & function of $T_H17/1$**
- Majority of risk alleles (>80%) aren't contained in exons
  - ➢ May lay in **critical gene-regulatory elements**
- Many genes/mutations affect one or more tolerance mechanism:
  - ➢ **Autoantigen** availability & clearance
  - ➢ **Apopotosis** – especially of self-reactive lymphocytes
  - ➢ Expression or signalling of **cytokines & co-stimulatory molecules**
  - ➢ **T_{reg} cell** development & function

Genetical basis of autoimmunity

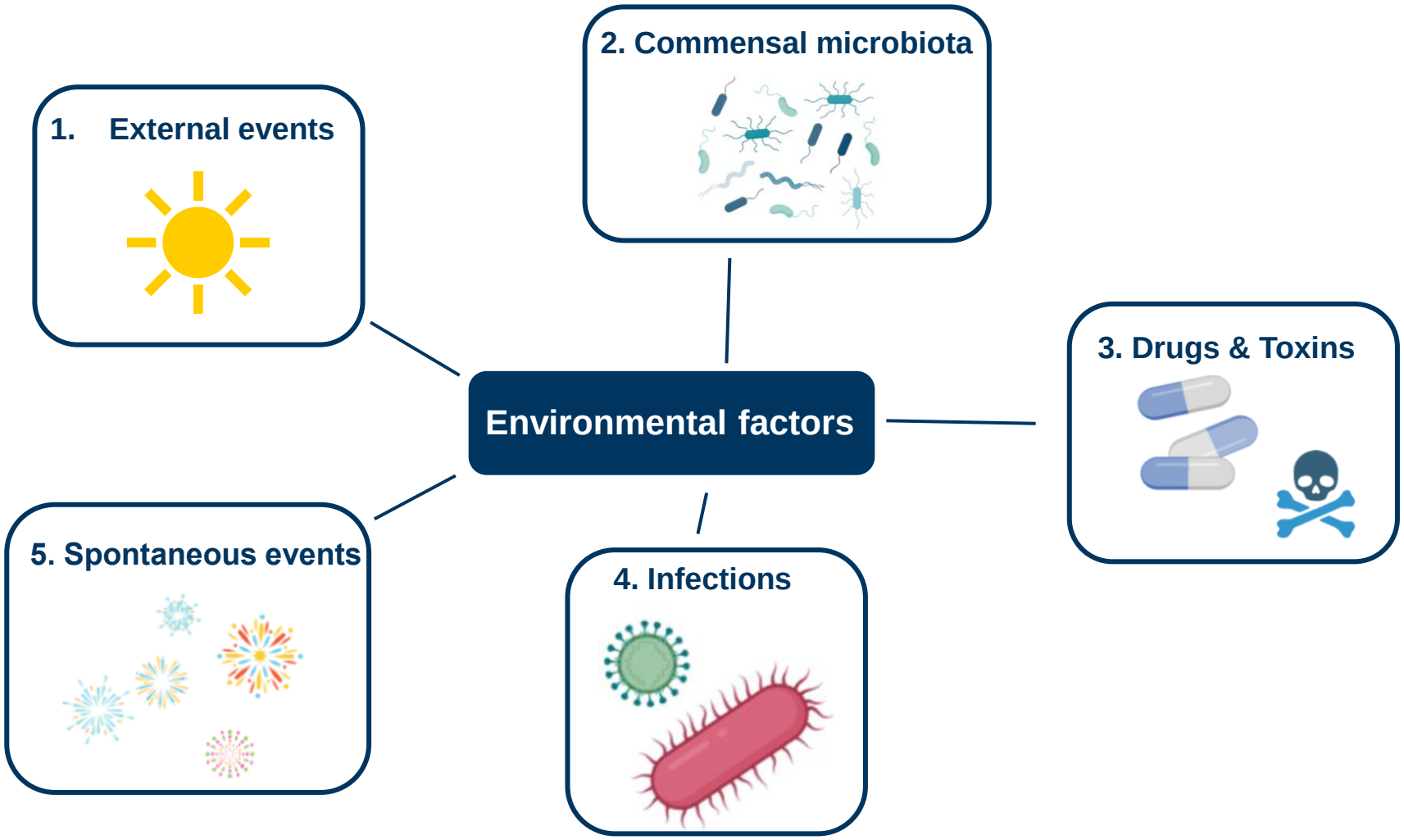
- **Monogenic diseases:**
  - Predisposition mostly due to combined effects of multiple genes
  - Some monogenic diseases → alleles usually recessive or X-linked
  - Monogenic diseases are rare but great of interest → identify pathways that normally prevent autoimmunity

Gene	Human disease	Mechanism of autoimmunity
AIRE	APECED (APS-1)	Decreased expression of self antigens in the thymus, resulting in defective negative selection of self-reactive T cells
FOXP3	IPEX	Decreased function of CD4 CD25 T_{reg} cells
FAS	ALPS	Failure of apoptotic death of self-reactive B & T cells

- **MHC genes** have an important role
  - **MHC genotype** most consistently associated with susceptibility – particularly MHC class II alleles
  - Differences in the ability to present autoantigenic peptides to autoreactive T cells
  - MHC alleles shape the T-cell receptor repertoire, e.g. weak binding of autoantigenic peptides leads to less effective thymic negative selection

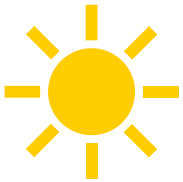
- Genetic variants impairing to innate immune response can predispose chronic inflammation

Environmental triggers of autoimmunity

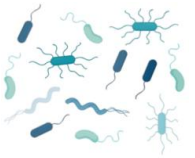


Environmental triggers of autoimmunity

1. **External factors:**
   - **Heterogenous geographic distribution** of autoimmune diseases
     - ➢ Numerous nongenetic factors: socioeconomic status & diet
   - Higher incidence in more developed countries – reasons unknown

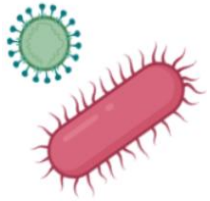


2. **Diversity of the commensal microbiota:**
   - Having a role in contributing to autoimmune disease – including extraintestinal disease
   - Reflecting importance of interplay of the microbiome with the immune system



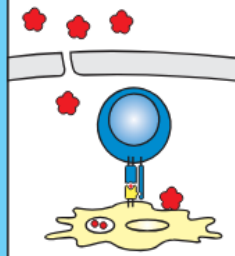
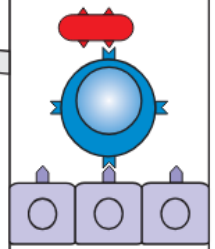
3. **Drugs & toxins:**
   - Drugs are the clearest evidence of external causative agents in human autoimmunity
   - Toxins can cause autoimmunity
   - Some drugs may react chemically with self-proteins and form derivates
     - ➢ Recognition as foreign → immune response to original self-protein

Environmental triggers of autoimmunity



4. Infections

- Infectious agents could break self-tolerance in different ways
- Providing an environment that promote lymphocyte activation
  - ➢ Release of inflammatory mediators can affect bystander cells
  - ➢ Tissue destruction increases availability of self-antigens
  - ➢ Pro-inflammatory cytokines impair the suppressive activity of T_{reg} cells
  - ➡ Activation of self-reactive lymphocytes
- Expression of antigens that resemble host molecules – **molecular mimicry**
  - ➢ Antibodies against pathogen epitope may cross-react with self-molecule
    → Structure must be similar enough but not necessarily identical
  - ➢ Resembled peptide may activate autoreactive T cells

Mechanism	Disruption of cell or tissue barrier	Molecular mimicry
Effect	Release of sequestered self antigen; activation of nontolerized cells	Production of cross-reactive antibodies or T cells
Example	Sympathetic ophthalmia	Rheumatic fever Reactive arthritis Lyme arthritis
		

5. Random events:

- No understandable pattern of events – random events may be required
- Rare events could be more frequent in susceptible individuals or more difficult to control
- May explain why many diseases occur in early adulthood or later

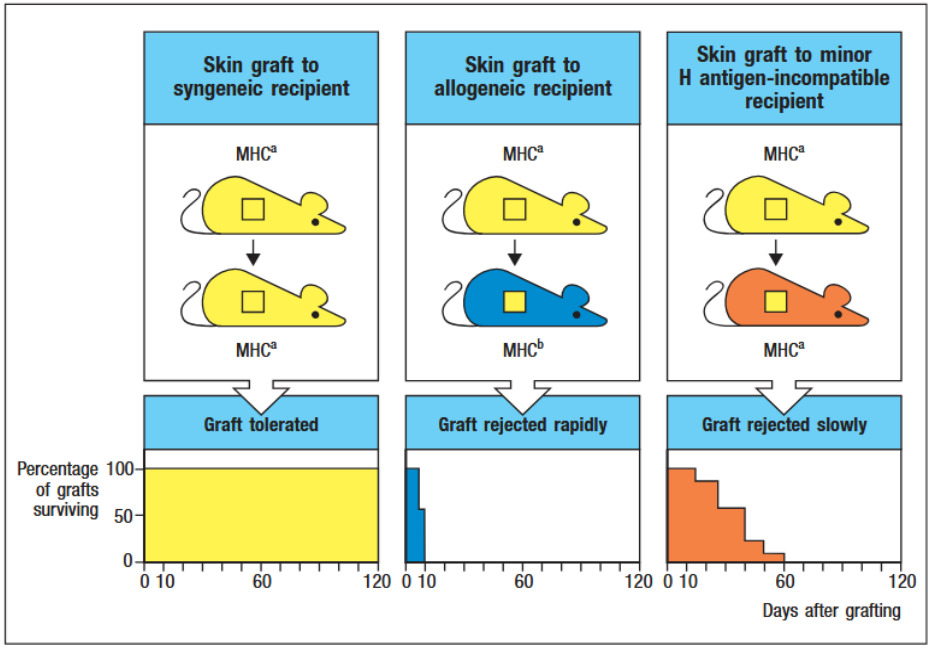
Summary

- **Autoimmune diseases** arise from a combination of **genetic predisposition** and **environmental triggers**
- **Genetic risk factors** include:
  - Specific **MHC alleles**
  - Mutations/polymorphisms in genes affecting **tolerance, signalling, cytokines**
- Some autoimmune diseases are caused by **monogenic defects** → offering insight into key mechanism
- **Innate immune pathways** also contribute to disease susceptibility and inflammation
- **Environmental factors** (e.g., infections, drugs, toxins) influence disease onset and progression
- **Infections** may promote autoimmunity via **inflammation, molecular mimicry**, and **bystander activation**
- Likely, **no single cause** is responsible — rather, a **multifactorial and sometimes random** interplay of genetic and external influences

IV. Responses to alloantigens & transplant rejection

Basics of transplant rejection

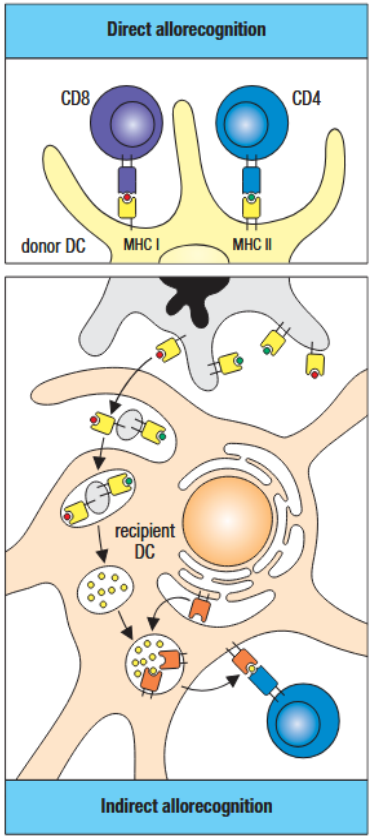
- Transplantation of tissues is an important medical therapy
- 100 % success between different sites on same animal (**autograft**) or genetically identical animals (**syngeneic graft**)
- Between allogeneic individuals (**allograft**): graft gets rejected 10-13 days after grafting → **acute rejection**
- **Main reason:** alloreactive response of T cells directed at allogeneic MHC molecules
- Even perfect HLA locus match doesn't prevent rejection
  - ➢ MHC molecules present peptides from proteins that can be recognized as foreign
    → **minor histocompatibility antigens**
- All recipients need immunosuppressive drugs chronically

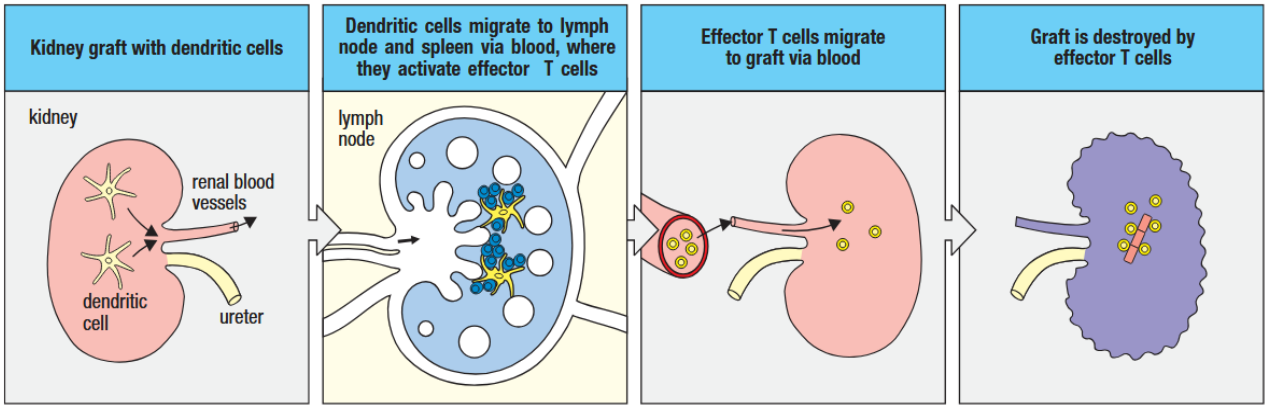


Ways of alloantigen presentation

- **Direct allorecognition:**
  - Organ grafts carry antigen-presenting cells = passenger leukocytes
  - Migrate via blood to secondary lymphoid tissues
  - Activate alloreactive effector T cells
  - T cells circulate to graft and attack directly

- **Indirect allorecognition:**
  - Uptake of allogeneic proteins by recipient's antigen-presenting cells
  - Presentation to T cells by self MHC molecules
  - Presentation of foreign MHC molecules or minor histocompatibility antigens

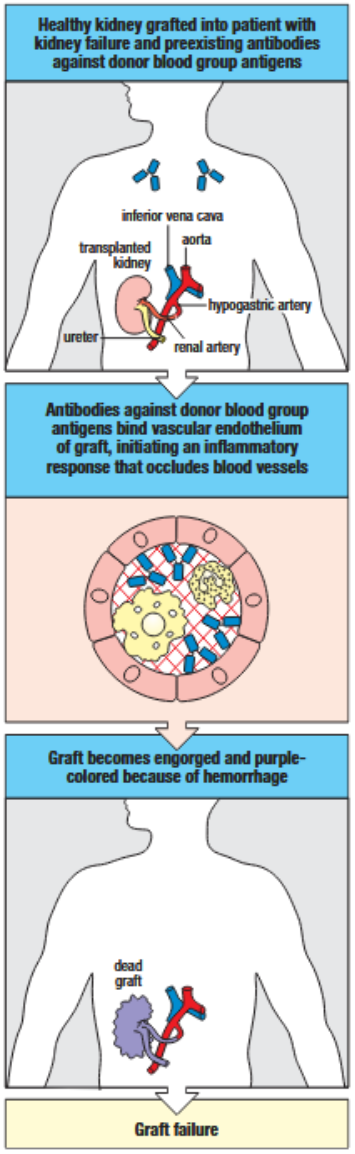




Different types of allograft rejection

- **Hyperacute graft rejection:**
  - Caused by preexisting alloantibodies against blood group antigens & polymorphic MHC antigens
  - React with antigens on the vascular endothelial cells of the graft → initiate the complement & blood clotting cascade
  - Blocked or thrombosed vessels cause rapid destruction within minutes
  - Can be avoided by ABO- as well as cross-matching (determination of antibodies against white blood cells of donor)

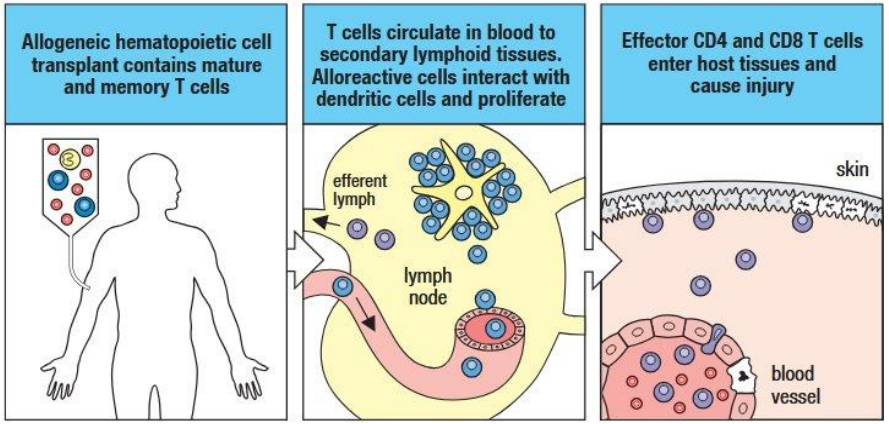
- **Chronic rejection:**
  - Late failure of transplanted organs
  - Caused by specific immune alloreactivity, nonimmune injury, or both
  - Major component for vascularized grafts: chronic allograft vasculopathy → concentric arteriosclerosis of graft blood vessels results in hypoperfusion of the graft
  - Other causes: viral infections, recurrence of the original disease



T_{reg} cells & Graft-vs-Host disease (GvHD)

- **T_{regs} suppress alloreactive T cells** → help maintain **transplant tolerance**
- **Suppress activation, cytokine release**, and **effector function**
- **Therapeutic potential**: T_{reg} expansion or transfer may reduce need for immunosuppressants and provide a possible therapy for GvHD
- **Main challenge:** maintaining T_{reg} stability under inflammatory conditions

- **GvHD:** Opposite of graft rejection → Mature donor T cells attack recipients tissue
- Occurs mainly in **hematopoietic stem cell** (HSC) transplants
- Aggressive if MHC class I or II antigens mismatch → **HLA matching** more important



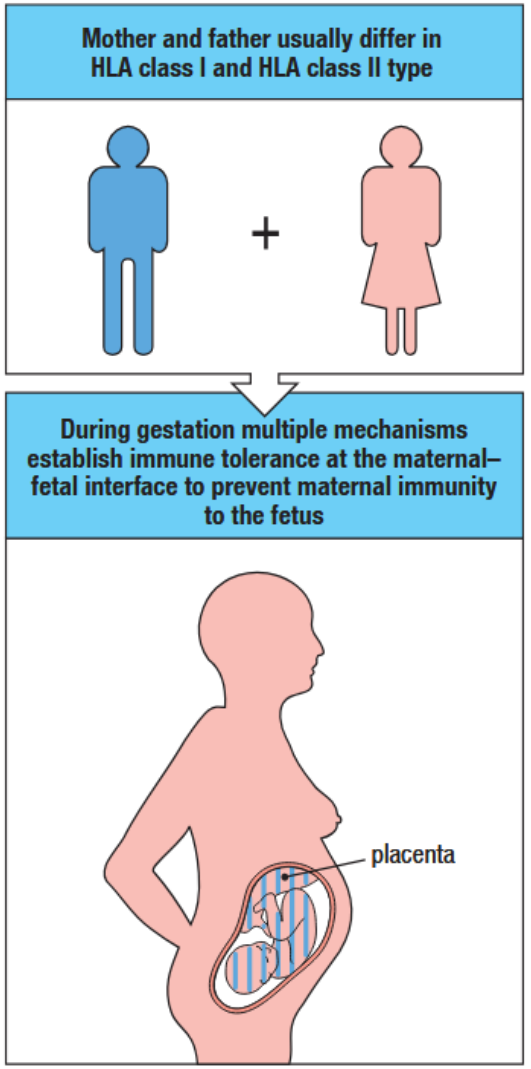
- Can have beneficial effects: **graft-versus-leukemia effect**
  - ➢ Donor T cells recognize minor histocompatibility antigens of leukemic cells → kill them

The fetus as a tolerated allograft

- **Immunological paradox:**
  - Fetus expresses paternal antigens, yet is not rejected by the maternal immune system

- **Mechanisms of tolerance:**
  - Placenta acts as a physical and immunological barrier.
  - Trophoblast cells (fetal-derived) do not express classical MHC class I or II molecules → reducing visibility to maternal T cells
  - Secretion of immunosuppressive cytokines such as IL-10 and TGF-β at the maternal-fetal interface
  - Increase in maternal regulatory T cells (Tregs) during pregnancy → promoting systemic and local immune tolerance

- **Significance:**
  - This natural model of tolerance helps researchers understand mechanisms that could support transplant tolerance



Summary

- **Graft rejection** is a **T cell-mediated immune response** to **alloantigens**, especially foreign **MHC molecules**
- **Direct and indirect antigen presentation** pathways activate host T cells against the graft:
  - **Direct**: Donor APCs present their own MHC
  - **Indirect**: Host APCs present processed donor antigens
- **Antibodies** also contribute to rejection:
  - Can cause **hyperacute rejection** (via preexisting anti-donor antibodies)
  - Contribute to **chronic rejection** through vascular damage
- **Graft-versus-host disease (GvHD)** occurs when **donor immune cells attack recipient tissues** — a risk in **bone marrow transplants**
- **Immunosuppression** and **HLA matching** are key to improving graft survival
- **Regulatory T cells (Tregs)** can suppress alloimmune responses and are potential tools for **inducing transplant tolerance**
- **Maternal immune system tolerates the semi-allogeneic fetus** → offering a natural model of immune regulation during allogeneic interactions

Thank you for your attention!

Any Questions?