

# Autoimmune disease

Course	 <a href="#">Immunology</a>
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Autoimmunity is the immune response mounted against a **self (auto-) antigen**

- the result of loss of **self-tolerance** leading to cellular and/or antibody responses to body components.
- May or may not cause **autoimmune diseases**
  - affect up to 5% of the population.

## Autoimmune diseases

The autoimmune diseases with the highest prevalence, and the antigens targeted by the autoantibodies in these diseases.

DISEASE	PREVALENCE (%)	CHARACTERISTIC AUTOANTIBODIES
Graves' disease	1.12	TSH receptor (stimulatory)
Rheumatoid arthritis	0.92	Citrullinated proteins, IgG Fc
Hashimoto's disease	0.55	Thyroid peroxidase, thyroglobulin
Sjögren's syndrome	0.37	SS-A, SS-B
Pernicious anemia	0.15	Intrinsic factor
Multiple sclerosis	0.14	Myelin basic protein
Ankylosing spondylitis	0.13	Multiple connective tissue & skeletal proteins
Type I diabetes	0.12	Glutamic acid decarboxylase 65, insulin, IA-2
SLE	0.08	dsDNA, Sm, U1RNP, SS-A, SS-B, histones

**Autoimmunity can be organ-specific or systemic**

Organ-specific autoimmune diseases	Systemic autoimmune diseases
Type I diabetes mellitus	Rheumatoid arthritis
Goodpasture's syndrome	Scleroderma
Multiple sclerosis	Systemic lupus erythematosus
Graves' disease Hashimoto's thyroiditis Autoimmune pernicious anemia Autoimmune Addison's disease Vitiligo Myasthenia gravis	Primary Sjögren's syndrome Polymyositis

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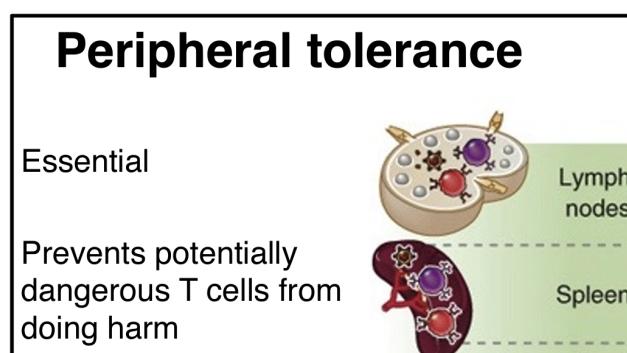
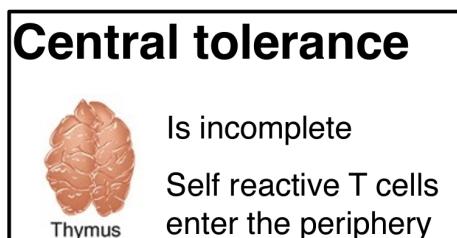
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Figure 13-1 Immunobiology, 6/e. (© Garland Science 2005)

Autoimmune diseases affect a range of organs, but traditionally they are classified as either organ- or non-organ specific, according to whether the autoimmune response affects one principle target organ (or tissue) or several.

The affected organ/tissue is determined by the location of the autoantigen.

The mechanisms for tissue damage are to some extent different for the two major kinds of autoimmune diseases, organ-specific disease being mediated primarily through type II, type IV or type V hypersensitivities whereas non-organ specific tend to be more type III-mediated.



Treg are key components of peripheral tolerance

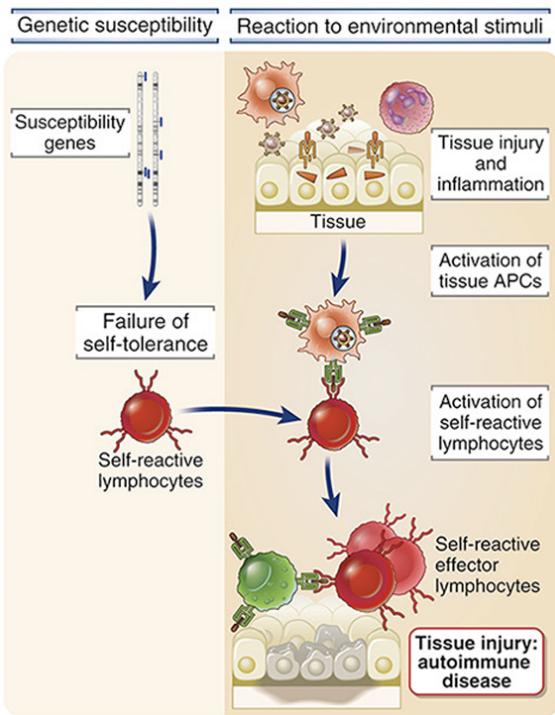
- Evidence: Treg deficient mice
  - Lymphadenopathy
    - Enlarged LN due to lots of T cell activation

- Splenomegaly
  - Spleen enlargement
- Lymphocytic tissue infiltration
  - T cells into tissue and cause damage
- Die around 4 wk of age
- KO of Foxp3 and CTLA4 have similar phenotype
- Treg deficient humans
  - **IPEX**: Immune dysregulation polyendocrinopathy enteropathy X-linked syndrome (mutations in Foxp3 gene)
  - Also known as XLAAD
  - **Inflammatory bowel disease (IBD)**
  - Aggressive autoimmunity and early death
  - Onset within first months of life (can be a few days post birth)
  - >80% IPEX patients have Type 1 diabetes (also **IBD**, allergy)



Regulatory T cells are essential to prevent autoimmune disease

## Aetiology of autoimmune diseases



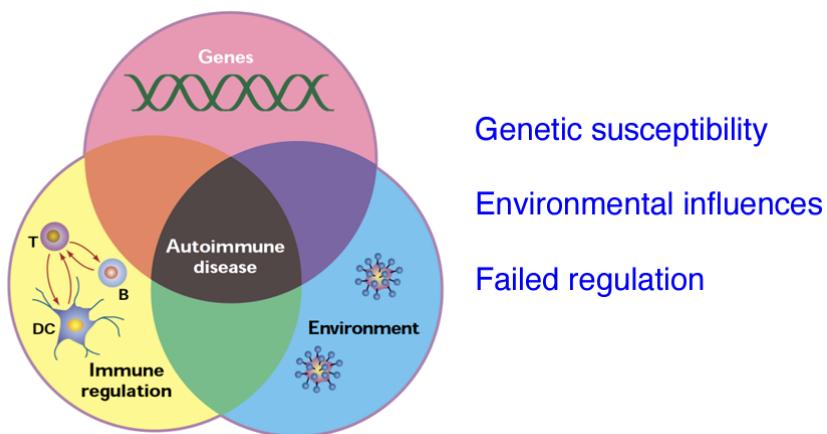
Postulated mechanisms of autoimmunity of an organ-specific T cell-mediated autoimmune disease.

- Various genetic loci may confer susceptibility to autoimmunity, in part by influencing the maintenance of self-tolerance.
- Environmental triggers, such as infections and other inflammatory stimuli, promote the influx of lymphocytes into tissues and the activation of self-reactive T cells, resulting in tissue injury.

Although the aetiology of autoimmune diseases is not entirely clear, there are some clues as to the 'predisposing factors'.

- In spontaneous animal models of SLE and type I diabetes mellitus the animals are genetically programmed to develop autoimmunity, and there is a higher 'risk factor' associated with certain **HLA class I and II** alleles in man.
- Other genes are also involved, i.e. autoimmune diseases are mostly **polygenic**.

Both **genes** and **environment** contribute to the development of autoimmune diseases.



- A failure in immune regulation is evidenced by autoimmune patients having altered number of Tregs or other functionality

## Genetic susceptibility

Largest contribution to genetic susceptibility is the MHC (HLA) genes

Many immune diseases are linked to particular MHC alleles

Disease	MHC allele	Relative risk
Ankylosing spondylitis	HLA-B27 (MHC I)	90
Rheumatoid arthritis	HLA-DRB1*01/*04/*10	4-12
Type 1 diabetes mellitus	HLA-DRB1*0301/*0401	35
Pemphigus vulgaris	HLA-DR4 (MHC II)	14

- MHC (HLA) controls what the T cells can “see”
  - Depending on the HLA gene of individual - different peptides are presented
    - Note that HLA is highly polymorphic in the population
  - Different MHC stimulate TCR in slightly different way
- Relative risk: Risk of developing the disease if having the corresponding allele

Polymorphisms (variants) in genes can contribute to complex disease

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Genes that may contribute to genetically complex autoimmune diseases		
Gene(s)	Disease association	Mechanism
<i>PTPN22</i>	RA, several others	Abnormal tyrosine phosphatase regulation of T cell selection and activation?
<i>NOD2</i>	Crohn's disease	Defective resistance or abnormal responses to intestinal microbes?
<i>IL23R</i>	IBD, PS, AS	Component of IL-23 receptor; role in generation and maintenance of Th17 cells
<i>CTLA4</i>	T1D, RA	Impaired inhibitory checkpoint and regulatory T cell function
<i>CD25</i> (IL-2R $\alpha$ )	MS, type 1 diabetes, others	Abnormalities in effector and/or regulatory T cells?
<i>C2, C4</i> (Complement proteins)	SLE	Defects in clearance of immune complexes or in B cell tolerance?
<i>FCGR2B</i> (Fc $\gamma$ RIIB)	SLE	Defective feedback inhibition of B cells

- Variants may be just slightly different and increase susceptibility to certain diseases, in this case autoimmune disease
  - One variant might be small risk factor, but multiple variants may build into a significant one, increasing the likelihood of autoimmune disease
  - E.g. Variants in CD25 and CTLA4 which are important in Tregs function, some decrease in CTLA4 expression or functionality, thus more likely to develop autoimmune disease
- Variants can also be in non-coding regions
  - E.g. determining the amount of gene expressed, i.e. promoter region
- Some genes confers susceptibility to multiple disease
  - Underlies overlapping mechanism of immune regulation for all autoimmune disease, e.g. T cell activation etc.

Autoimmune diseases frequently run in families but there is low concordance rates between twins

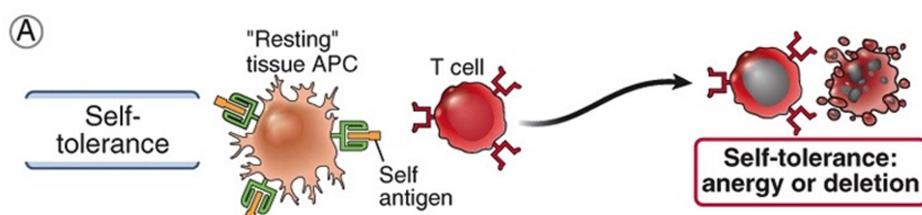
- Concordance rates in identical twins are typically <50%, indicating that **environmental factors** also contribute.

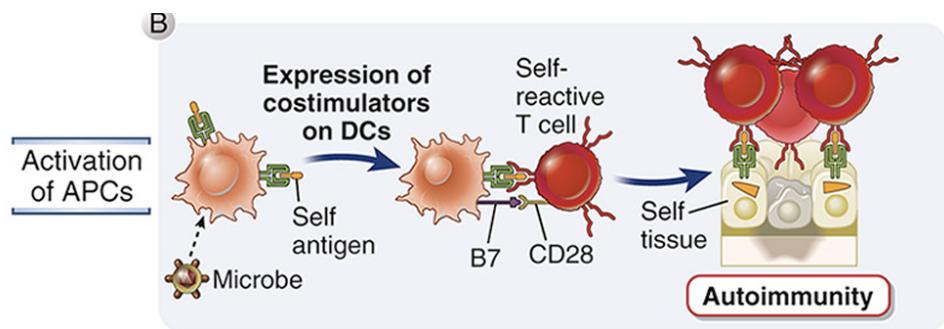
## Environmental influences

- Infection, Sunlight (sun exposure can exacerbate SLE), Diet, Microbiome, Obesity, Stress, Drugs
  - Different microbiota because of autoimmunity or because of different microbiota difference in autoimmunity
  - Inflammation: obesity, stress

Mechanisms by which microorganisms could give rise to autoimmunity include:

### Microbes activate APC presenting self-antigens



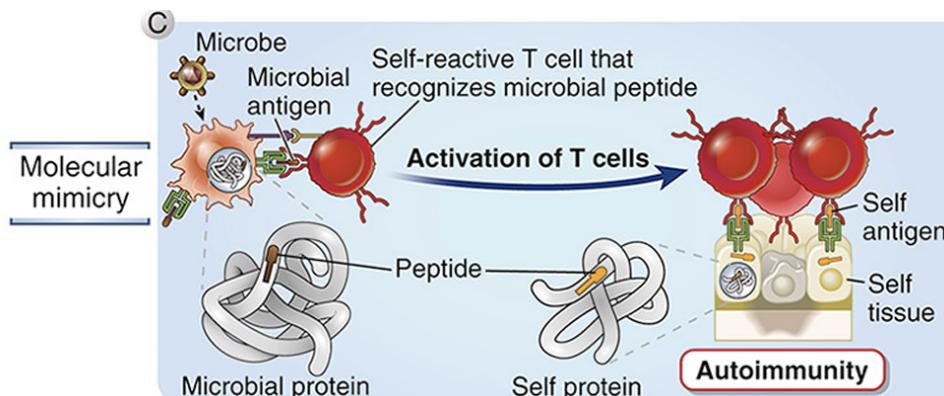


**FIGURE 15.14C Role of infections in the development of autoimmunity.** A, Normally, encounter of a mature self-reactive T cell with a self antigen presented by a costimulator-deficient resting tissue APC results in peripheral tolerance by anergy. (Other possible mechanisms of self-tolerance are not shown.) B, Microbes may activate the APCs to express costimulators, and when these APCs present self antigens, the self-reactive T cells are activated rather than rendered tolerant. C, Some microbial antigens may cross-react with self antigens (molecular mimicry). Therefore, immune responses initiated by the microbes may activate T cells specific for self antigens.

B: APCs with self peptides are activated due to infections or other inflammatory events

- Activated APCs present B7 (co-stimulatory ligands)
- Self-reactive T cells may then be activated and damage own cell

### Molecular mimicry



- **Cross-reactive antigens**
  - Occurs when an antibody raised against one specific antigen has a competing high affinity toward a different antigen, therefore the antibody is able to recognize a protein which is different to the one it was raised against
  - TCR has cross-reactivity to bind peptides that are very similar in the MHC although slightly less strong binding

- Some microorganisms, by displaying similar antigens to those present in the host, could provide a mechanism whereby T cells recognising foreign antigens on a microbe could provide help for any self-reactive B cells which have not been eliminated in the bone-marrow.
- This help could then result in autoantibody production.

### **Aberrant expression of MHC class II molecules**

- Cytokines (e.g. interferons induced by viruses) can lead to aberrant expression of MHC class II molecules on cells such as the beta-cells in the pancreatic islets (normally expressed only on professional antigen-presenting cells).
- The class II molecules could then associate with self antigens not normally presented to T helper cells.

### **Polyclonal activation**

- Anergic B cells often demonstrate the ability to recognise self-antigens (e.g. DNA) in normal individuals but not produce antibodies to these antigens.
- Non-specific polyclonal activation of B cells can induce antibodies against many different antigens including autoantigens.
- Perhaps some viral, bacterial, and protozoal infections act in this way, e.g. EBV.

Additional factors that are responsible for breakdown in self-tolerance leading to chronic autoimmune disease include genetics, gender and defective regulatory T cells.

### **Impact of gender**

Many autoimmune diseases are more common in women than men

- May be due to the difference between the setup of the immune system - women have to carry children thus tolerate the child's immune system

Regulatory mechanisms (e.g. regulatory T cells) normally act to prevent the development of autoimmune diseases.

## **Mechanism of autoimmunity**

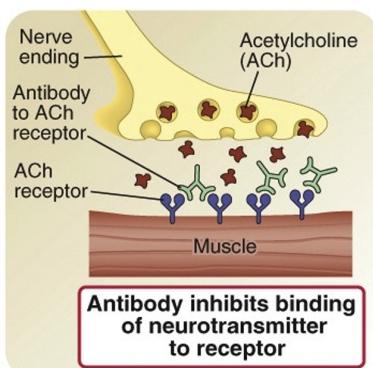
- Autoantibodies
- T cell mediated

- In autoimmune disease, both factors are usually associated
  - Determined by which one is the key driver of the disease

## Autoantibodies

**MOA: block receptors**

### Myasthenia gravis

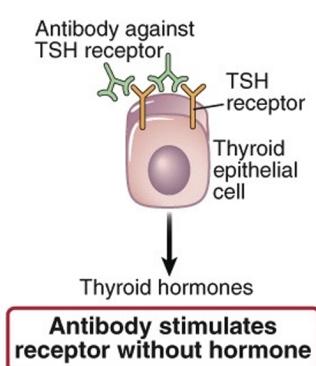


Autoantibodies act as **antagonists**

- Autoantibodies to **acetylcholine receptors** block transmission of nerve impulses at motor end plate junctions.
- Occasionally, transient “autoimmune” disease is found in newborn babies of mothers with myasthenia gravis, due to IgG autoantibody transfer across the placenta.

**MOA: Stimulating a receptor**

### Graves Disease - autoantibodies act as agonists

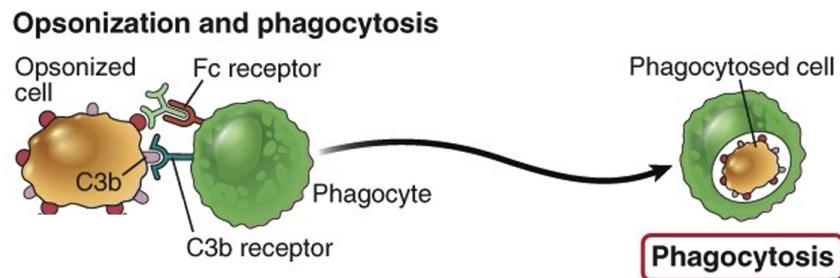


- Autoantibodies bind to the thyroid-stimulating hormone (**TSH**) **receptor** (type V hypersensitivity).
- Causing excessive thyroid hormone release

### Hashimoto's disease

- A classical example of an organ-specific disorder
- Thyroid-specific autoantibodies against thyroid peroxidise and **thyroglobulin** are also produced.
- **Thyroid** undergoes destructive infiltration by lymphocytes.

**MOA:** The antibodies act as opsonins, facilitating destruction of the cell coated by autoantibody



- Self-reactive antibodies bind to own cell and opsonise the cell
- Fc region of the antibody binds to the Fc receptors of the phagocyte and causes phagocytosis of the opsonised cell

### **Autoimmune cytopenias**

- Autoimmune thrombocytopenia (platelets)
- Autoimmune haemolytic anemia (erythrocytes)
- Autoimmune neutropenia (neutrophils)

### **Rheumatoid arthritis**

- A systemic autoimmune disease
- Rheumatoid factor (autoantibodies to the **Fc** part of the **IgG** molecule, i.e. anti-antibodies) is deposited in the joints leading to a chronic inflammatory response which results in destruction of the joint tissue.

### **Characteristic autoantibodies in major autoimmune diseases**

Disease	Prevalence (%)	Characteristic autoantibodies
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## T cell-mediated autoimmune destruction

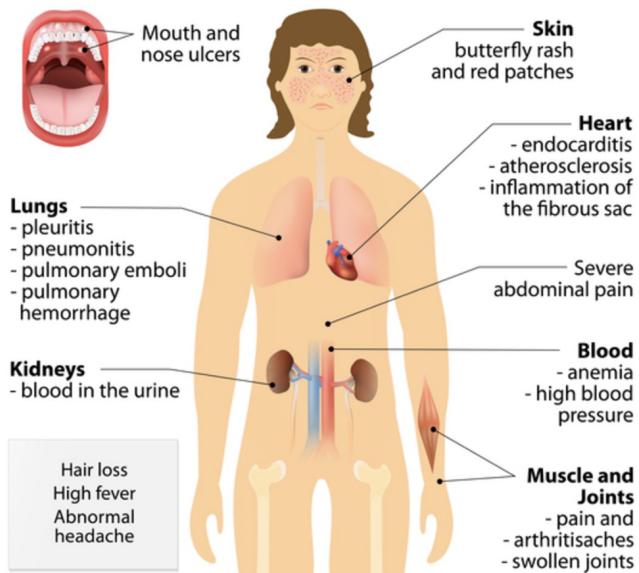
### Multiple sclerosis

- T cell driven attack of CNS
  - Normally CNS is protected from immune cells thus no infiltration
  - In disease: CD4 T cells infiltrate CNS, activate macrophages, B cells, etc.
    - CD4 T cells recognise proteins and activate other cells via cytokine production, causing inflammation
- Demyelination in brain and spinal cord
- Slower nerve conduction, axonal nerve conduction, axonal injury, neurological dysfunction

### Type I diabetes

- Organ specific
- Type IV hypersensitivity is thought to play an important role in tissue damage of the **beta-cells** in the **islets of Langerhans**.
- T cell driven attack of the insulin-producing pancreatic beta cells
- Thus not enough insulin production

### Systemic lupus erythematosus (SLE)



- A multifactorial systemic autoimmune disease
- Autoantibodies against nuclear components
  - Double stranded **DNA** (dsDNA) are prominent
- Immune complex deposition (skin, kidney, joints, vessels)
  - E.g. glomerular damage is a feature
  - Ag-Ab complex deposit where the blood flow is slow
  - Causing appearance of skin rash

- Defective clearance of dead cells e.g. due to complement defects
  - If not cleared effectively - activation of self-reactive cells or tissue damage
  - Variations/mutations in complement molecules at high risk of SLE

Here, the autoantigens are not limited to specific organs but are common to many or all cells.

Unlike an organ-specific disease, the major mechanism for tissue damage is **type III hypersensitivity**: immune complexes of autoantigen and autoantibody deposited from the circulation can cause disease in many sites, such as the skin and vascular system and especially the kidneys.

## Treatment

Most therapy is directed to alleviating chronic inflammation.

- **Anti-inflammatory drugs** are commonly used (e.g. corticosteroids).
- **Immunosuppressive drugs** are used in **serious cases** of both organ and non-organ specific disease, but these can lead to infections.

- **Blocking** the action of the cytokine **TNF** with monoclonal antibody (Infliximab) or with a soluble version of the TNF receptor (Etanercept) is beneficial in some patients with rheumatoid arthritis, as is **depletion of B-cells** with monoclonal antibody (Rituximab).
- Removal of antibodies by plasmapheresis has been successful in treating some organ-specific diseases.
- In autoimmune diseases where there is destruction of an endocrine gland (e.g. type I diabetes, Hashimoto's thyroiditis) **hormone replacement** therapy is used.

## Summary

- Autoimmune disease results from a breakdown of self tolerance
- Tregs protect against autoimmune disease
- Genetic & environmental factors
- Major genetic contributor = MHC genes
- Most autoimmune diseases are polygenic and complex
  - Variations in many different genes increase or decrease susceptibility
  - Damage self-tissue cause loss of function