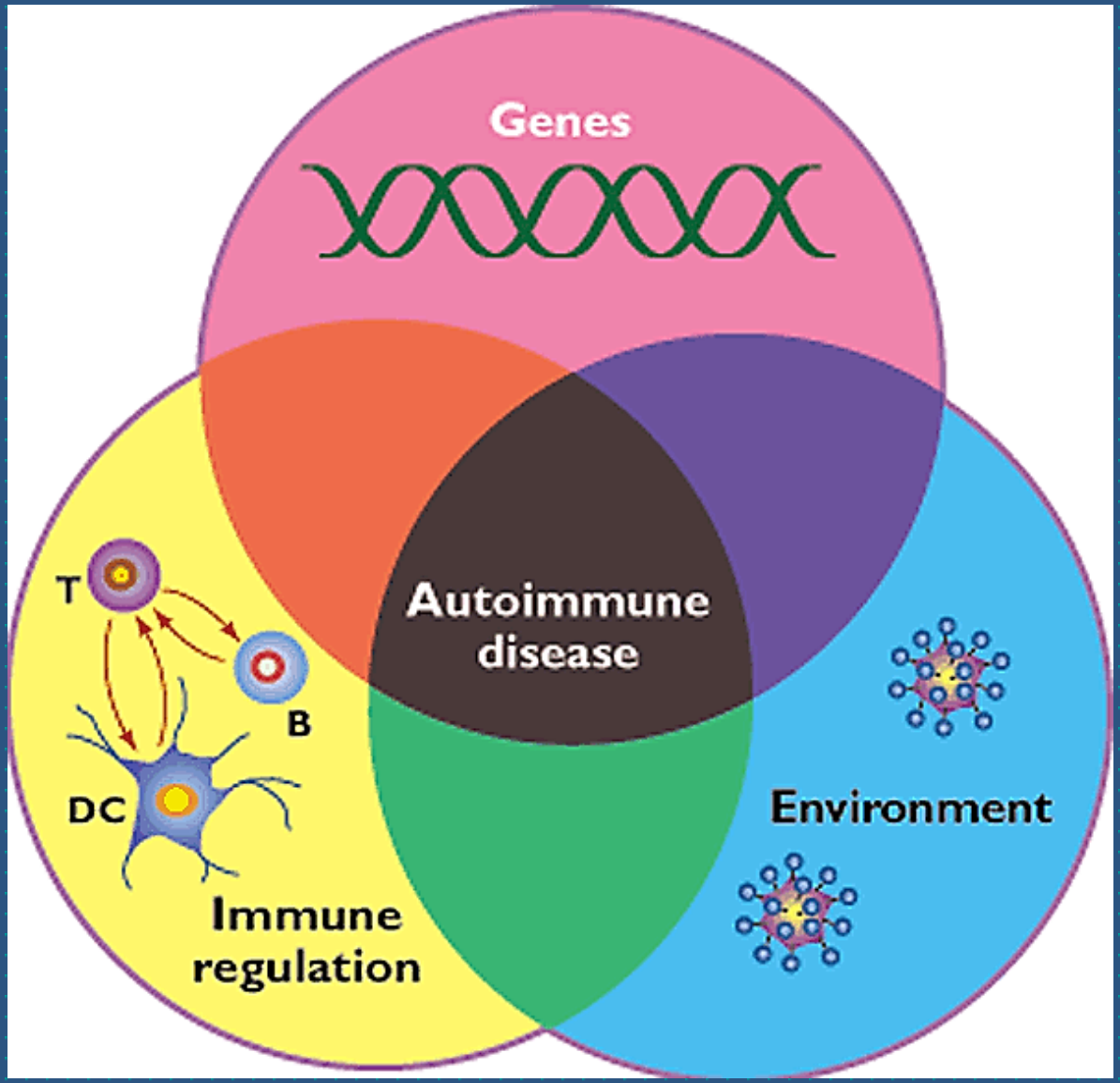
Immunopatology

- As a branch of Immunology, **immunopathology** concerns disorders caused by alterations of the immune response

- 3 main categories of alterations:

  - excessive response ⟹ hypersensitivity reactions
  - inappropriate response ⟹ autoimmune diseases
  - defective response ⟹ immunodeficiencies

Factors involved in the aetiopathogenesis of autoimmune diseases

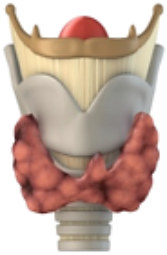


Autoimmunity

- Immune reactions to self antigens (i.e., autoimmunity) are the underlying cause of numerous human diseases
- Autoimmune diseases are estimated to affect **2% to 5%** of the population in developed countries, and appear to be **increasing in incidence**
- The **evidence** that some human diseases are indeed the result of autoimmune reactions is **more persuasive for some than for others** in which the role of autoimmunity is **suspected** but **not proved**

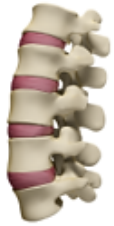
AUTOIMMUNE DISEASES

Brain
Multiple Sclerosis
Guillain-Barre Syndrome
Autism



Thyroid
Thyroiditis
Hashimoto's Disease
Graves' Disease

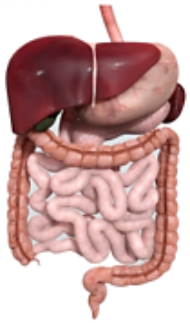
Blood
Leukemia
Lupus Erythematosus
Hemolytic Dysglycemia



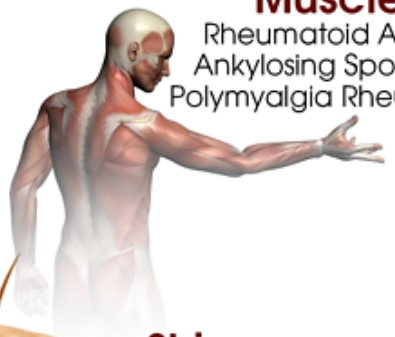
Bones
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica

Over 100
Different Types of AutoImmune Disorders

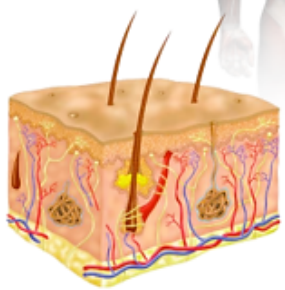
GI Tract
Celiac's Disease
Crohn's Disease
Ulcerative Colitis
Diabetes Type I



Muscles
Rheumatoid Arthritis
Ankylosing Spondylitis
Polymyalgia Rheumatica



Nerves
Peripheral Neuropathy
Diabetic Neuropathy



Skin
Psoriasis
Vitiligo
Eczema
Scleroderma

Lung
Fibromyalgia
Wegener's Granulomatosis

Evidence for the autoimmune nature of some human diseases

- In many autoimmune disorders, **multiple high-affinity autoantibodies** have been identified, and in some cases **these antibodies are known to cause pathologic abnormalities**

- Similarly, in some of these diseases, there is growing evidence for the **activation of pathogenic self-reactive T cells**

- **Experimental models** in rodents have proved very informative, providing circumstantial evidence in **support of an autoimmune etiology** of selected pathologies

Introducing autoimmunity

Physiological unresponsiveness to self-antigens based on

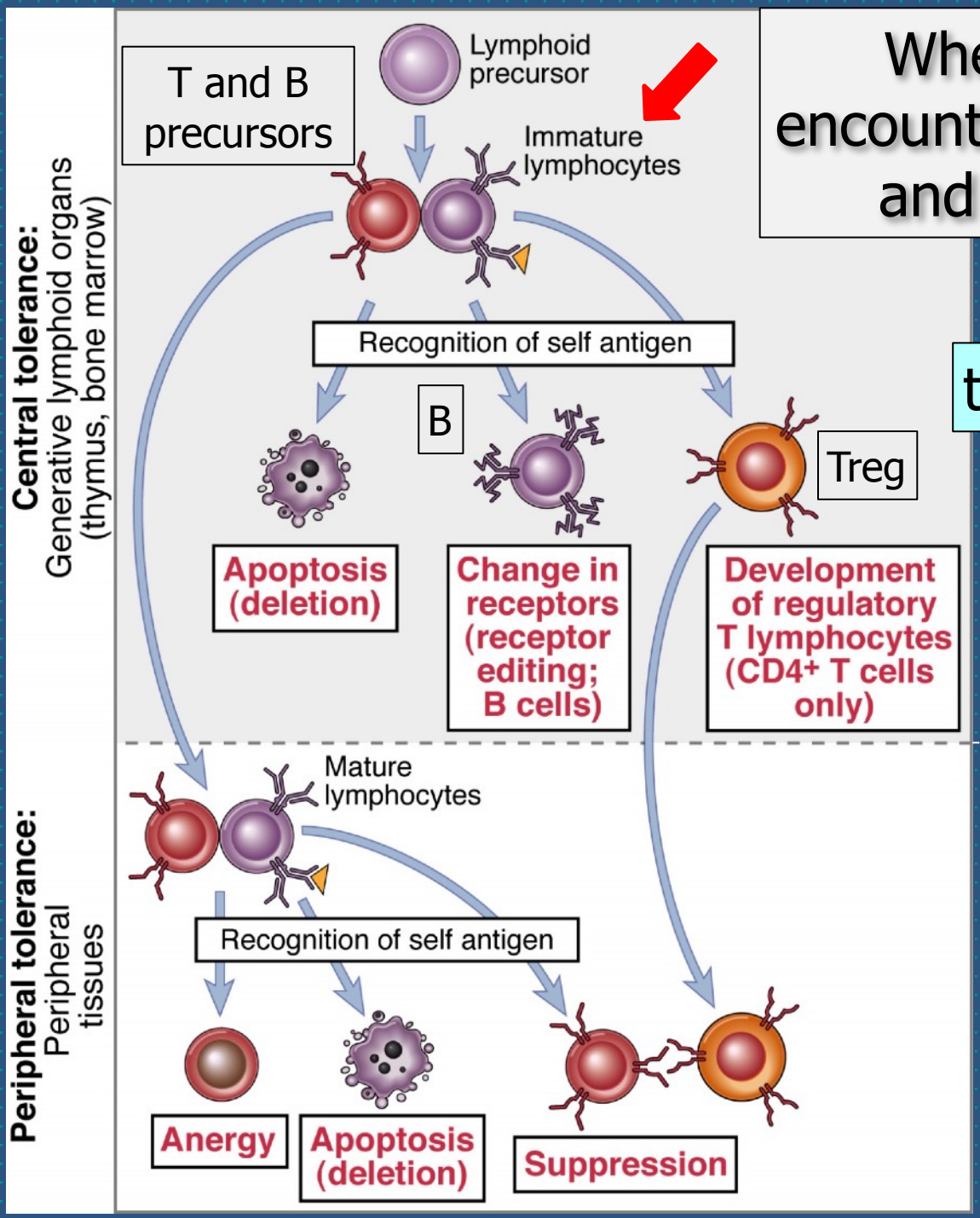
- Negative selection
- Immunological tolerance (central and peripheral)
- Role of regulatory T cells (Treg)

Immunological tolerance

- Billions of different antigen receptors are randomly generated in developing T and B lymphocytes
- It is not surprising that during this process, receptors that recognize **self antigens** are produced
- Since these antigens cannot all be concealed from the immune system, there must be means of eliminating or controlling self-reactive lymphocytes [**tolerance**]

The **breakdown of tolerance** is the basis of **autoimmunity**

Where can lymphocytes encounter self antigens? Central and peripheral tolerance



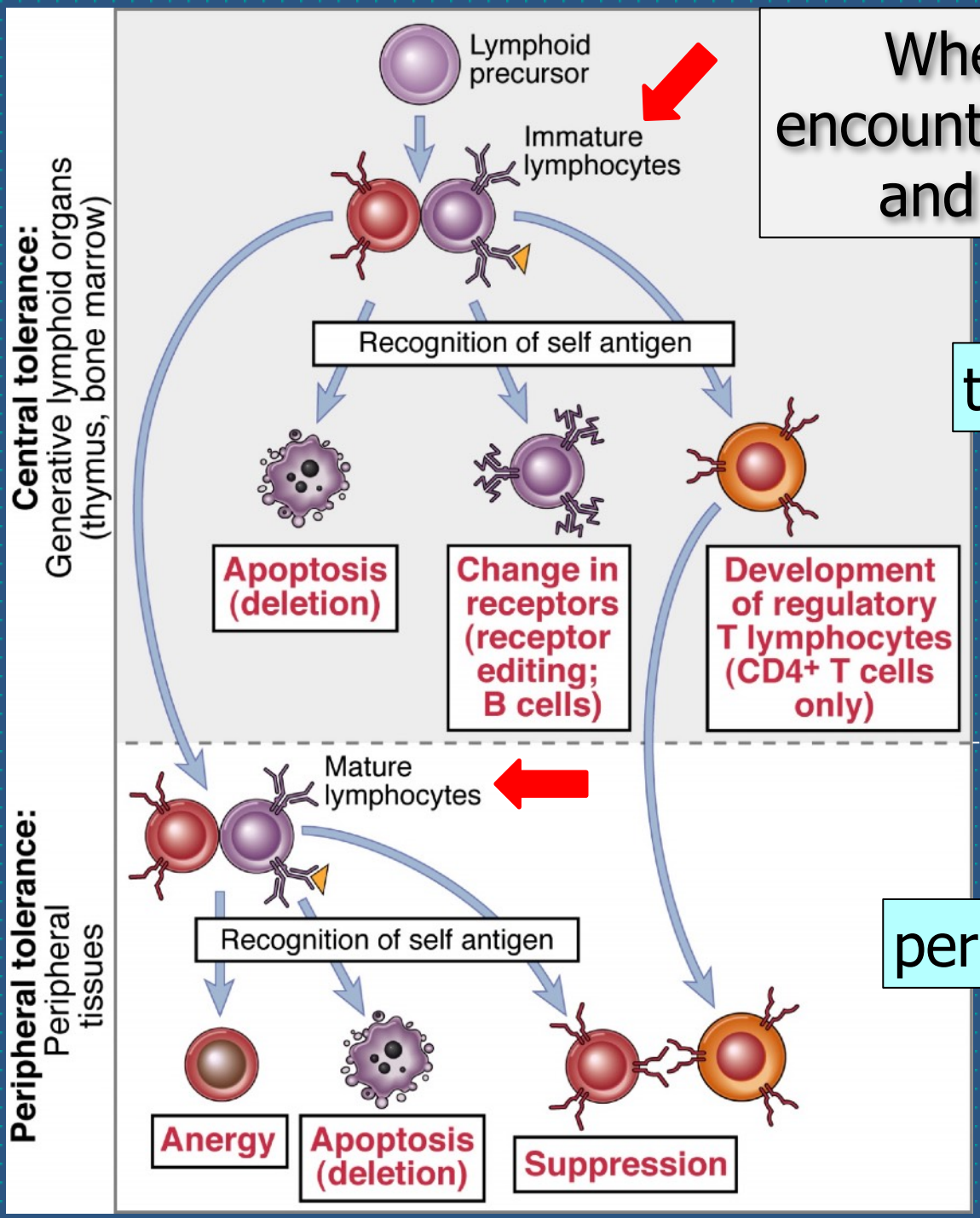
thymus, bone marrow

Central tolerance: thymus and bone marrow

The interaction of **lymphoid precursors** with **self antigens** in the **central lymphoid organs** may have three main outcomes:

1. some immature lymphos (both B and T) are **killed by apoptosis** (**negative selection**)
2. in the **bone marrow**, some self-reactive **B lymphos** switch to new antigen receptors that are not self-reactive (**receptor editing**)
3. in the **thymus**, some **T lymphos differentiate into regulatory T cells (Treg)**

Where can lymphocytes encounter self antigens? Central and peripheral tolerance



thymus, bone marrow

peripheral lymphoid tissues

Mechanisms of **peripheral** tolerance

- Self-reactive mature lymphos which gain access to peripheral tissues may undergo negative selection (**apoptosis**) or functional inhibition (**anergy**)

- **T cells** are made anergic **in the absence of costimulatory signals by APC**

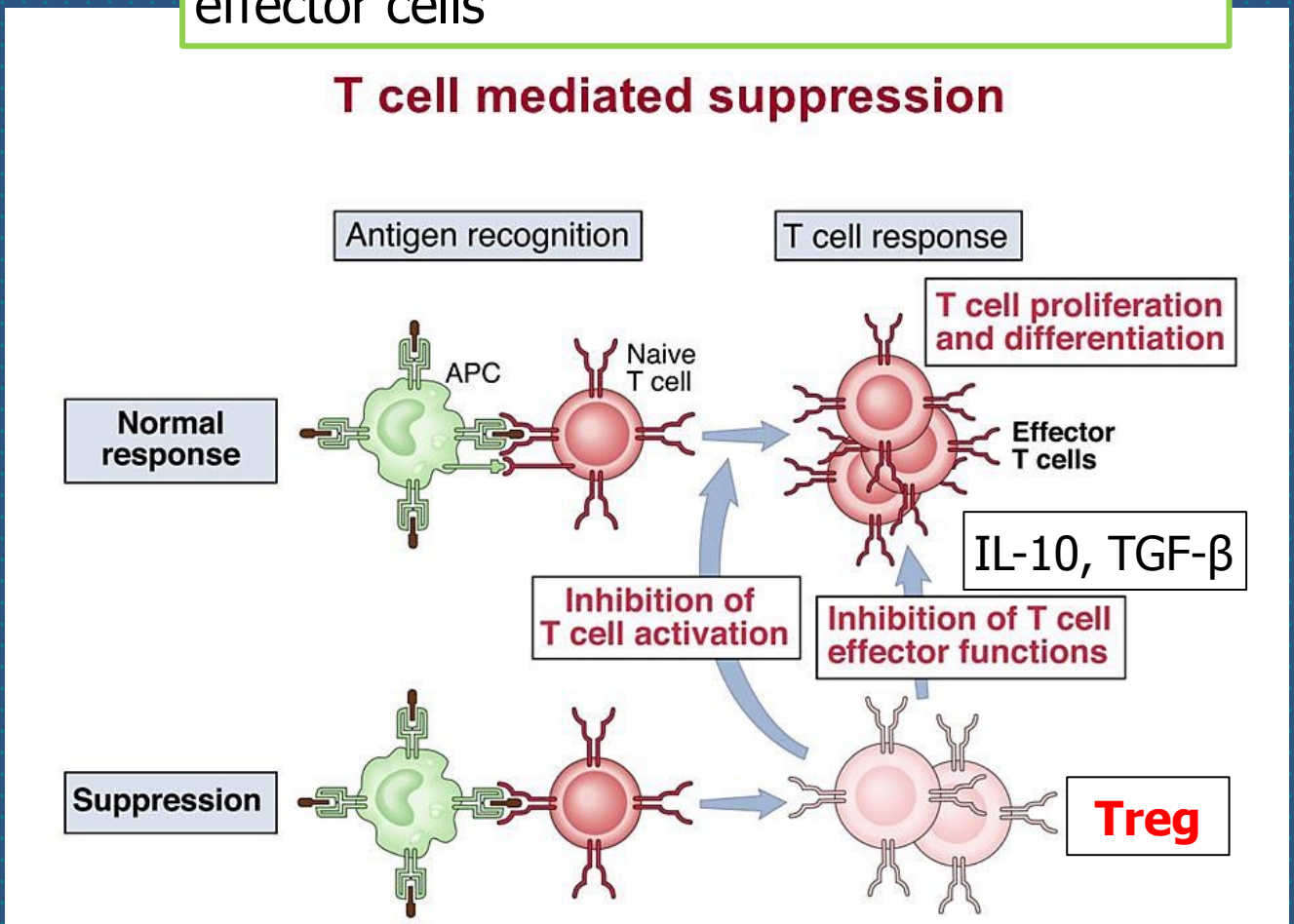
- **B cells** become anergic if they encounter antigen **in the absence of specific helper T cells**

Current investigations have not yet completely disclosed the **molecular mechanisms** underlying anergy

Peripheral tolerance of T lymphos: role of T regulatory cells (**Treg**)

- The responses of T lymphos to **self antigens** may be actively suppressed by **Treg**, a subtype of T cells (CD4+) generated in the **thymus** by self antigen recognition (high IL-2 receptor number; role for IL-2?)
- Main mechanisms **proposed** to explain **how** Treg control immune responses:
  - secretion of **immunosuppressive cytokines** (e.g., IL-10, TGF-β) which down-regulate T cell responses
  - **blocking of costimulatory signals by APC** leads to inhibition of T cell activation (direct contact ? undefined mechanism)

In a normal response, T cells recognize antigen, proliferate and differentiate into effector cells



Tregs generated by self antigen recognition **inhibit** the development or functions of effector T cells (negative control of **autoreactive T cells**)

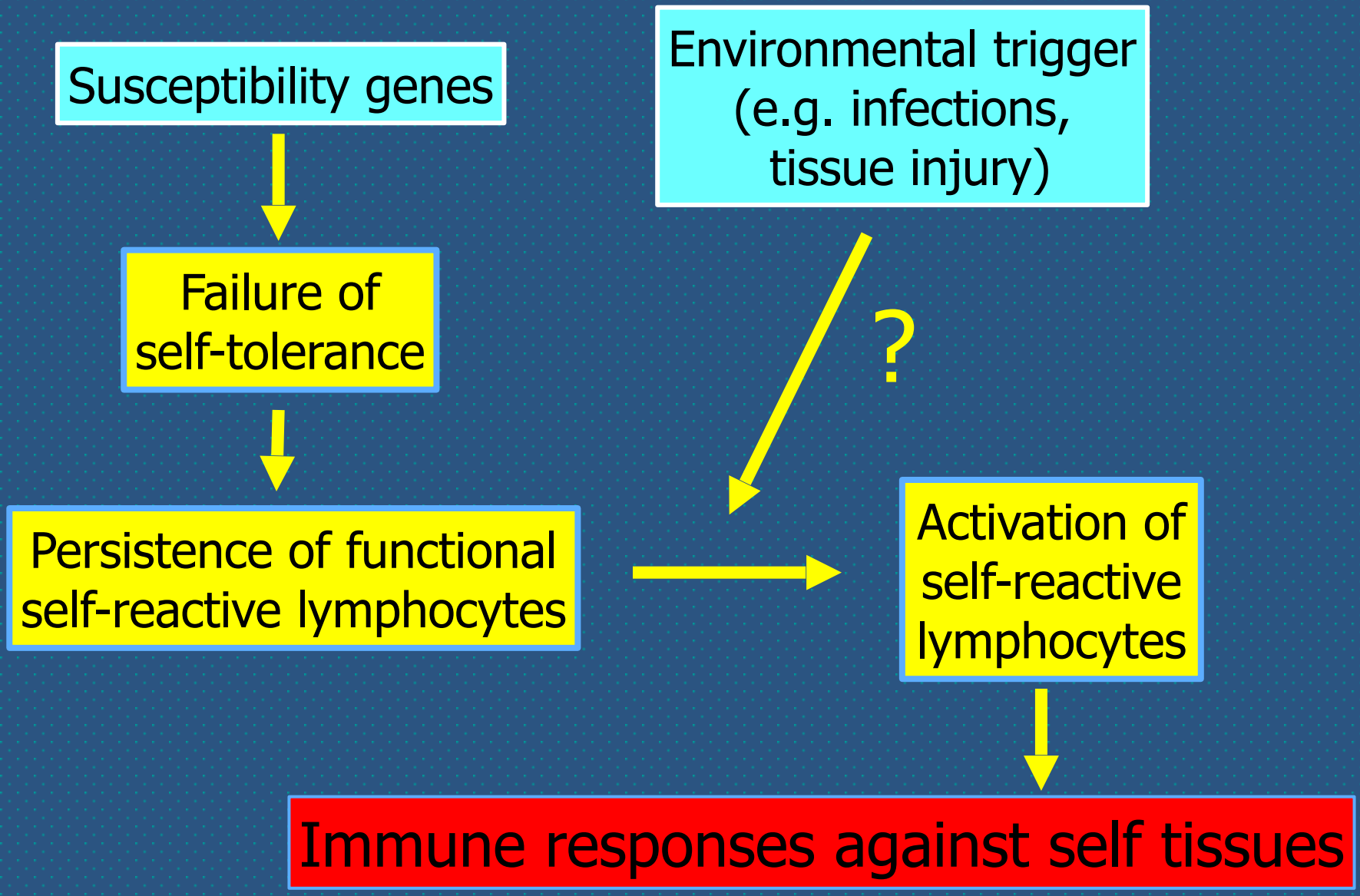
Postulated failures of Treg-mediated regulation of autoreactive T cells

- **Inadequate number** of Treg cells owing to their inadequate development, proliferation or survival
- **Defects in** Treg cell **function** (poor production of immune suppressive cytokines, e.g. IL-10, TGFβ)

intrinsic defects of Treg

- **Resistance of pathogenic effector T cells** to **suppression** by Treg cells: increased production of cytokines which impede Treg function, such as TNF-α, IL-4, IL-6

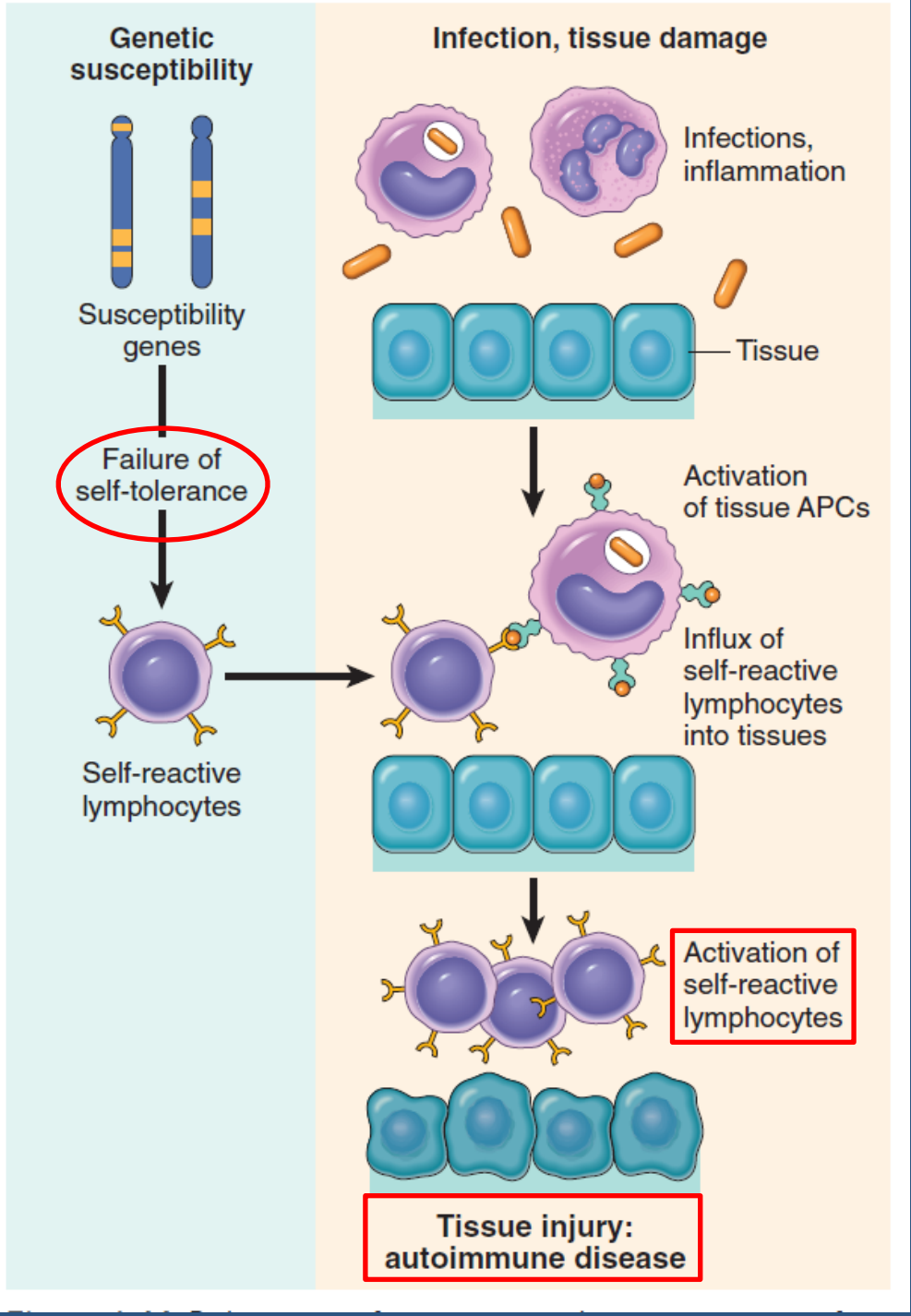
Essential steps in the pathogenesis of autoimmunity



Major factors involved in the pathogenesis of autoimmunity

Autoimmunity arises from: **(1)** the **inheritance of susceptibility genes**, that may interfere with selftolerance; **(2)** association with **environmental triggers** (infection, tissue injury, inflammation) that:

- alter the display of self antigens
- promote **entry of self-reactive lymphocyte into tissues**
- enhance their activation



Genetic susceptibility to autoimmunity (1)

- Most autoimmune diseases are **polygenic**; affected individuals inherit multiple **genetic polymorphisms** that **contribute** to disease susceptibility

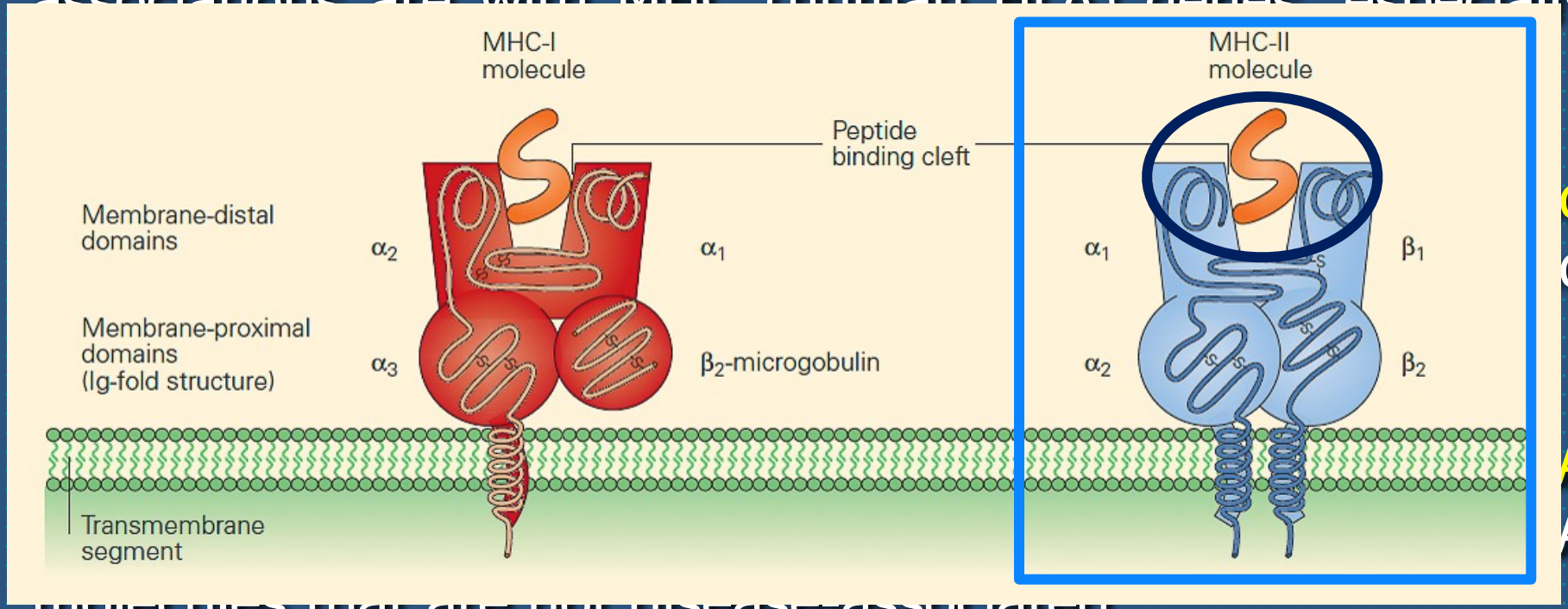
- The **products** of many of these polymorphic genes **influence** the development of **self-tolerance**:

  - some are believed to influence **negative selection** of self-reactive T cells (central tolerance)
  - others control T cell **anergy** to self antigens (peripheral tolerance)

The mechanistic links between susceptibility genes and failure of tolerance are not yet conclusively established

Genetic susceptibility to autoimmunity (2)

- Among the **genes linked to autoimmunity**, the strongest associations are with MHC (human HLA) genes, especially



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molecules that are not disease-associated

- Disease-associated HLA molecules favour the binding of particular **self-peptides** that will ultimately be recognized by **self-reactive T lymphos**

Role of infections in autoimmunity (1)

- Viral and bacterial infections may contribute to the development and exacerbation of autoimmunity
- Two main mechanisms:
  - **Microbes** may **activate the APC** to express **costimulatory molecules** for T lymphos; when these APC present self antigens, the **self-reactive T cells are activated**
  - Some **microbial antigens** may **cross-react with self antigens** (**molecular mimicry**); immune response initiated by the microbes may activate T cell specific for self antigens

Role of infections in autoimmunity (2)

- Example of **molecular mimicry**:
  - **Rheumatic fever**: after streptococcal infection, **anti-streptococcus antibodies** cross-react with **miocardial proteins**; onset of inflammatory response (**myocarditis**)
  - **Myocarditis** also takes place due to **homologies** between **myocardial** protein **antigens** and some antigens of Chlamydia and Trypanosoma cruzi
  - **Lyme artrhritis**: **homologies** between a surface molecule of Borrelia burgdorferi and a lymphocyte antigen (LFA-1, lymphocyte function antigen-1)

Other factors involved in the development of autoimmunity

- Anatomic alterations in tissues, possibly induced by inflammation, ischemic injury or trauma, may lead to **exposure of self antigens normally concealed from the immune system**
  - Intra-ocular antigens (post traumatic uveitis)
  - Sperm proteins (orchitis after vasectomy)
- Hormonal influences: many autoimmune diseases have a higher incidence in females than in males
  - Systemic lupus erythematosus affects women about 10 times as frequently as men

Organ-specific *vs* systemic autoimmune diseases

Organ-specific

- Autoimmune attack vs. self-antigens of a given organ
- It results in a damage of organ structure and function
- Treatment is focused on the replacement of organ function

Systemic

- Targets are widespread self-antigens
- Damage affects structures as blood vessels, cell nuclei, etc.
- Treatment is aimed to inhibit excessive activation of the immune system

Examples of **organ-specific** and **systemic** autoimmune diseases

Organ-specific

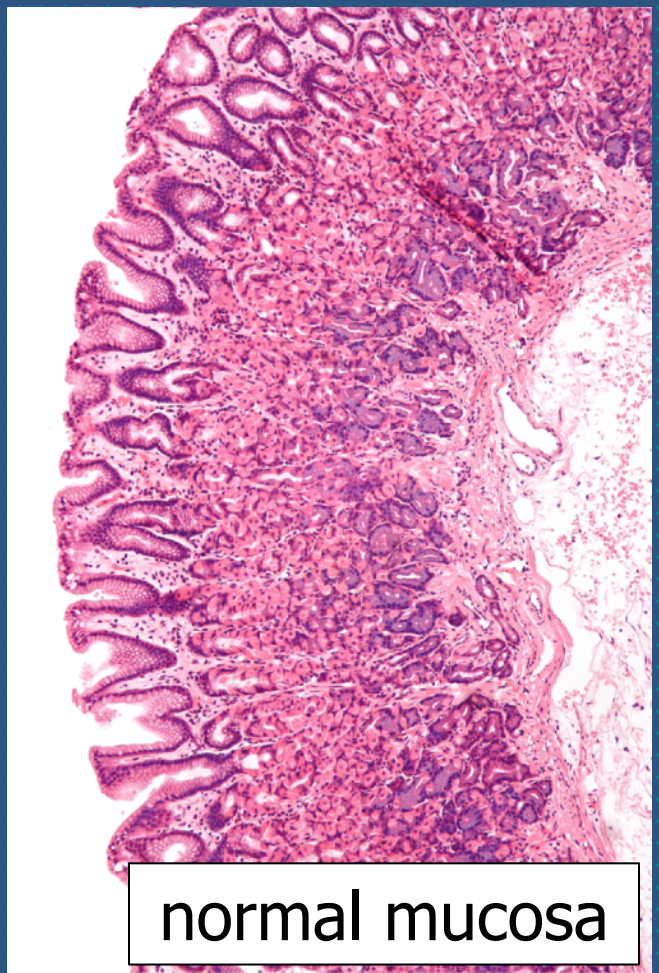
- Hashimoto thyroiditis (thyroid destruction)
- Grave's disease (hypertyroidism)
- Addison's disease (adrenal g. failure)
- Juvenile diabetes mellitus
- Multiple sclerosis
- Atrophic gastritis
- Myasthenia gravis

Systemic

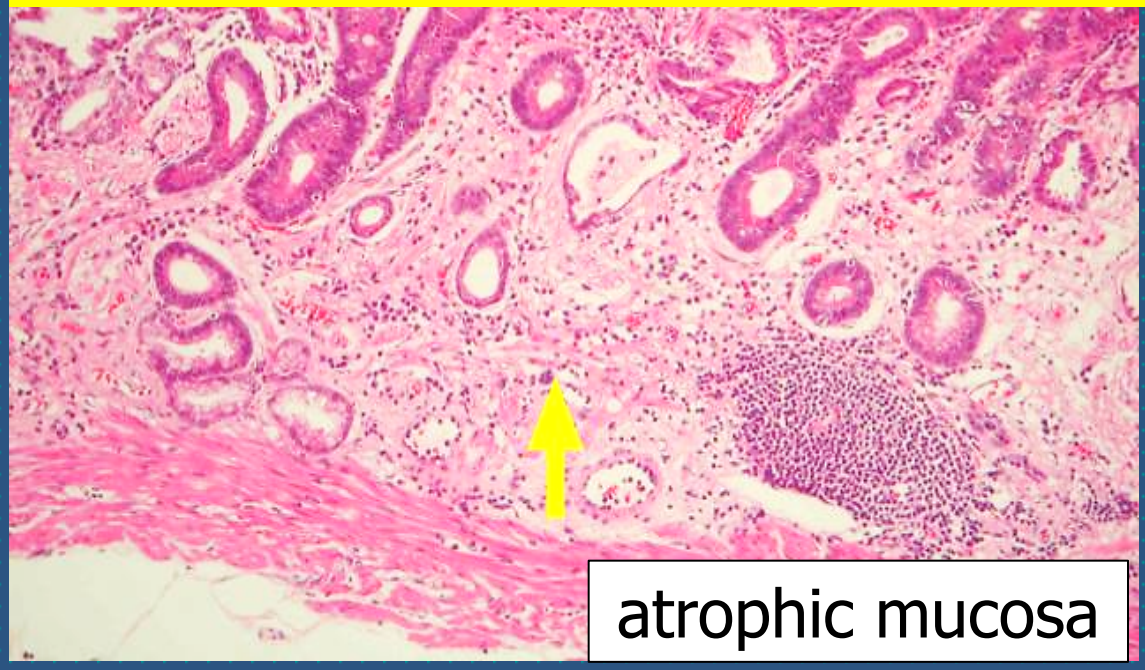
- Systemic lupus (SLE)
- Rheumatoid arthritis
- Scleroderma
- Dermatomyositis

Pernicious **anemia**

Atrophic gastritis in pernicious anemia: loss of stomach parietal cells is due to autoimmune reaction mediated by **auto-antibodies against parietal cells** and **intrinsic factor**



Intrinsic factor: glycoprotein secreted by gastric mucosa; favours absorption of **iron** and **vitamin B12** (**essential** cofactors for **erythropoiesis**)



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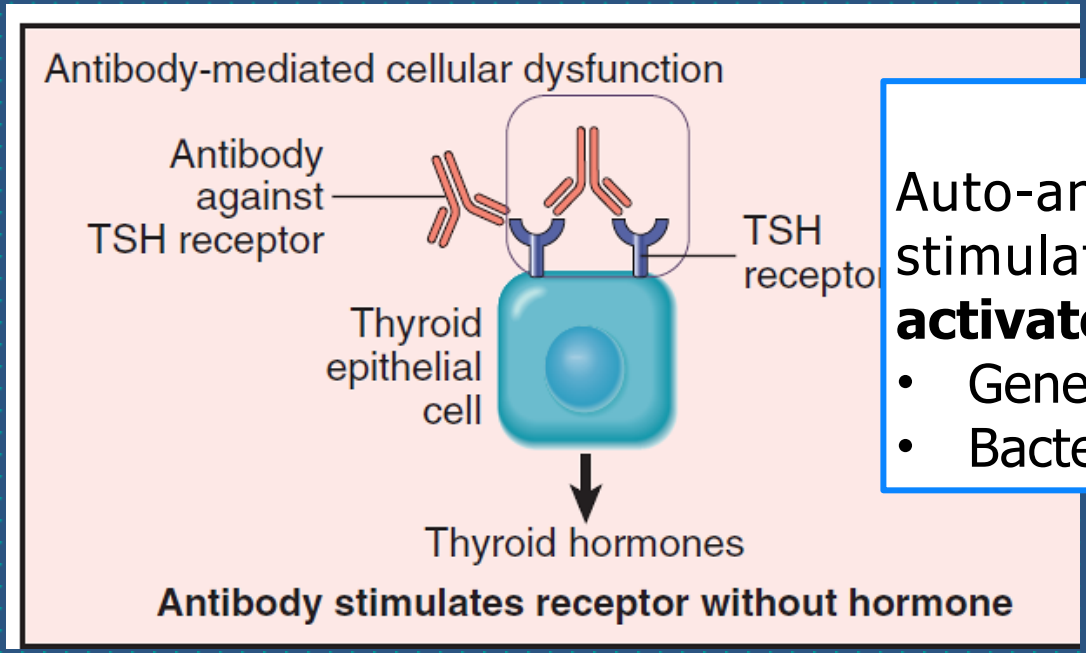
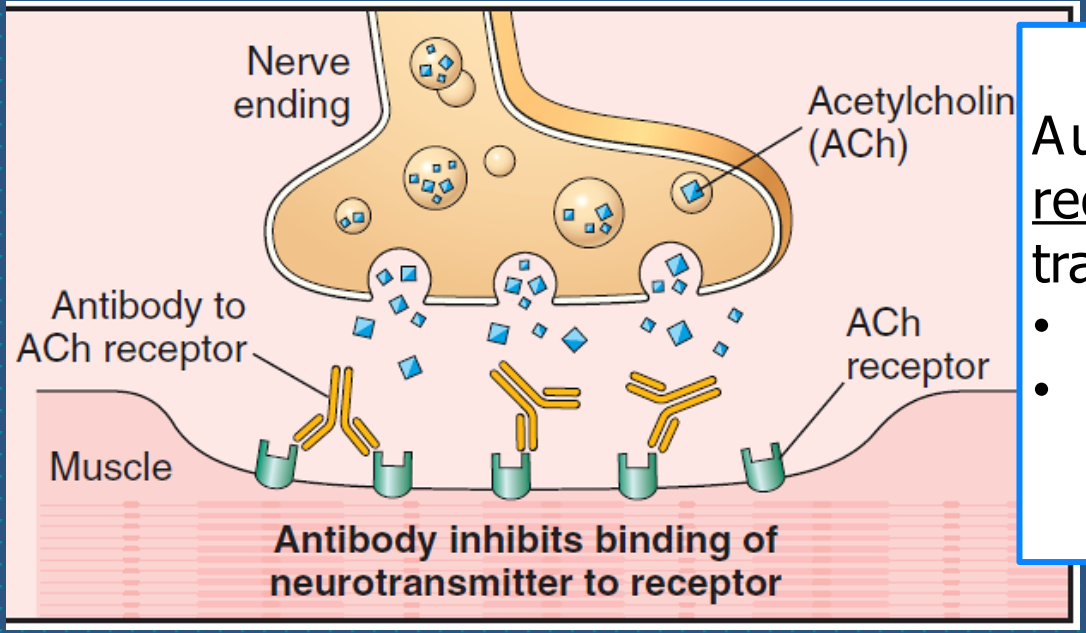
Antireceptor antibodies disturb the normal function of receptors



Graves disease

Auto-antibodies against the thyroid-stimulating hormone (TSH) receptor **activate** thyroid cells: **hyperthyroidism**

- Genetic susceptibility
- Bacterial and/or viral infections (?)



Myastenia gravis

Auto-antibodies against ACh receptor impair neuromuscular transmission: muscle **weakness**

- Genetic susceptibility
- **Treg dysfuntion** (low levels of transcription factor **FOXP3**, crucial for Treg function)