Tolerance and Autoimmunity

Objectives

- Define and discuss the general characteristics of tolerance
- Define the main factors that influence the development of tolerance
- Identify the main mechanisms of tolerance induction in B and T cells
- Identify the mechanisms involved in the development of autoimmunity
- Approach to treatment of autoimmune diseases

Immune tolerance, or immunological tolerance,

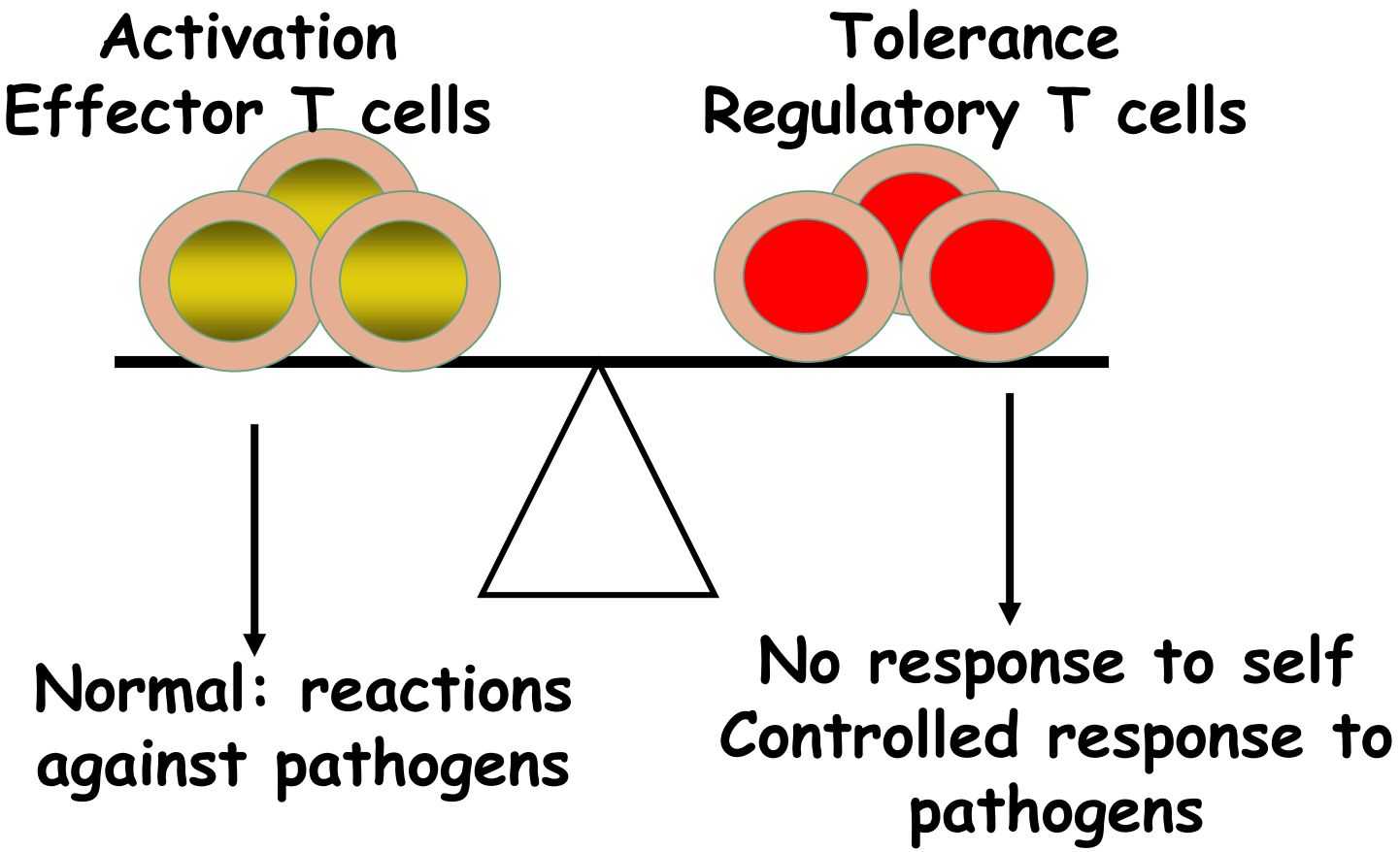
- The process by which immune cells are made unresponsive to self-antigens to prevent damage to healthy tissues.
- It prevents an immune response to antigens produced by the body itself
- Tolerance is built by the body's ability to determine self vs. non-self cells.

unresponsiveness to self antigens

When lymphocytes exposed to an antigen:

- The lymphocytes may be activated to proliferate and to differentiate into effector cells, leading to a productive immune response;
  - antigens that elicit such a response are said to be immunogenic
- The lymphocytes may be functionally inactivated or killed, resulting in tolerance;
  - antigens that induce tolerance are said to be tolerogenic.

Balancing lymphocyte activation and control

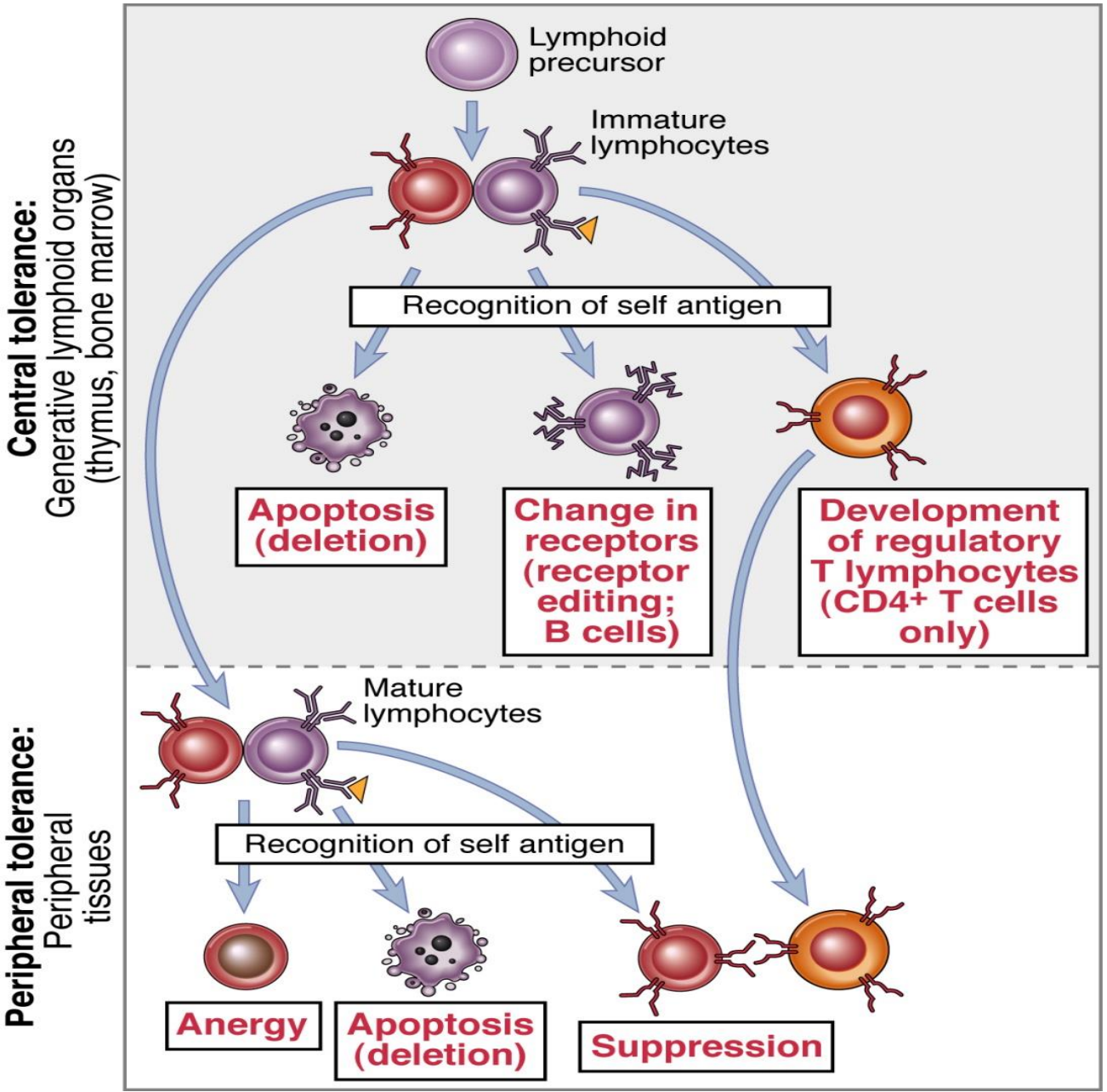


Immunological tolerance to different self antigens may be induced when developing lymphocytes encounter these antigens in the generative (central) lymphoid organs, called central tolerance,

or when mature lymphocytes encounter self antigens in peripheral tissues, called peripheral tolerance

- **Immunological tolerance**: specific unresponsiveness to an antigen that is induced by exposure of lymphocytes to that antigen (tolerogen vs immunogen)
- **Autoimmunity**: immune response against self (auto-) antigen, by implication pathologic
  - Disorders are often classified under "immune-mediated inflammatory diseases"

Central and peripheral tolerance



Mechanism of Central tolerance

- The principal fate of lymphocytes that recognize self antigens in the generative organs is death (deletion)
- Some B cells may change their specificity (called "receptor editing")
- Some CD4 T cells may differentiate into regulatory (suppressive) T lymphocytes

The principal mechanisms of central tolerance in T cells are

- **Cell death (negative selection)**
- **The generation of regulatory T cells**

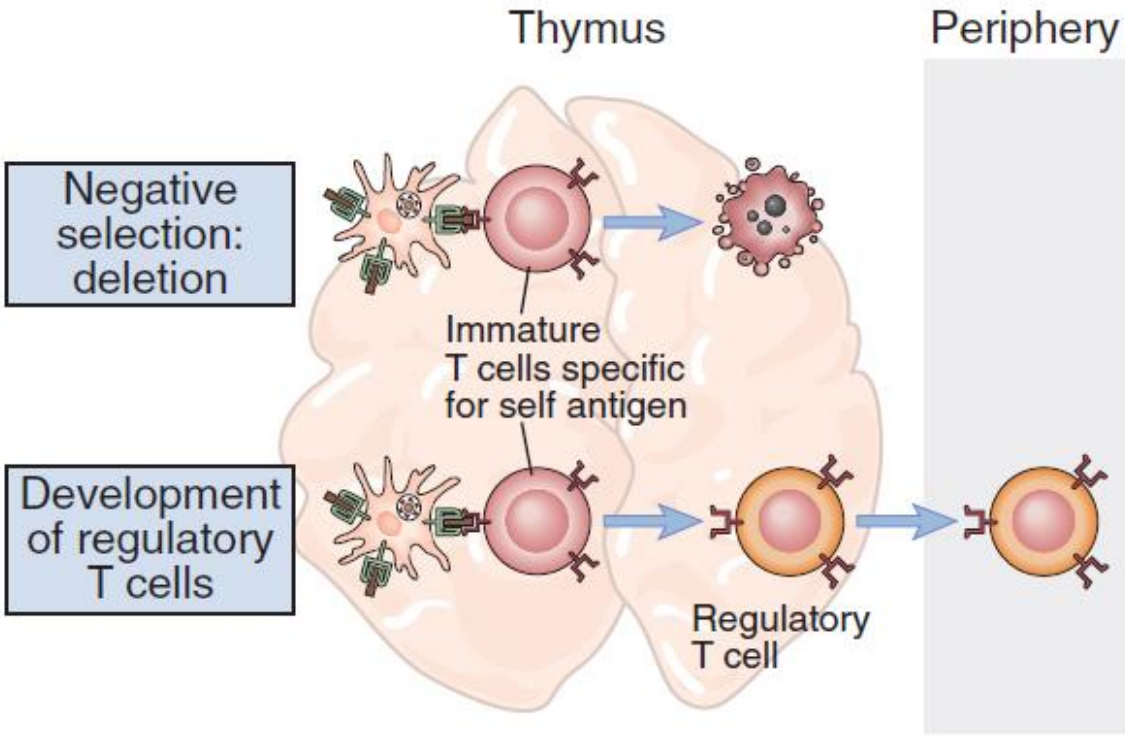
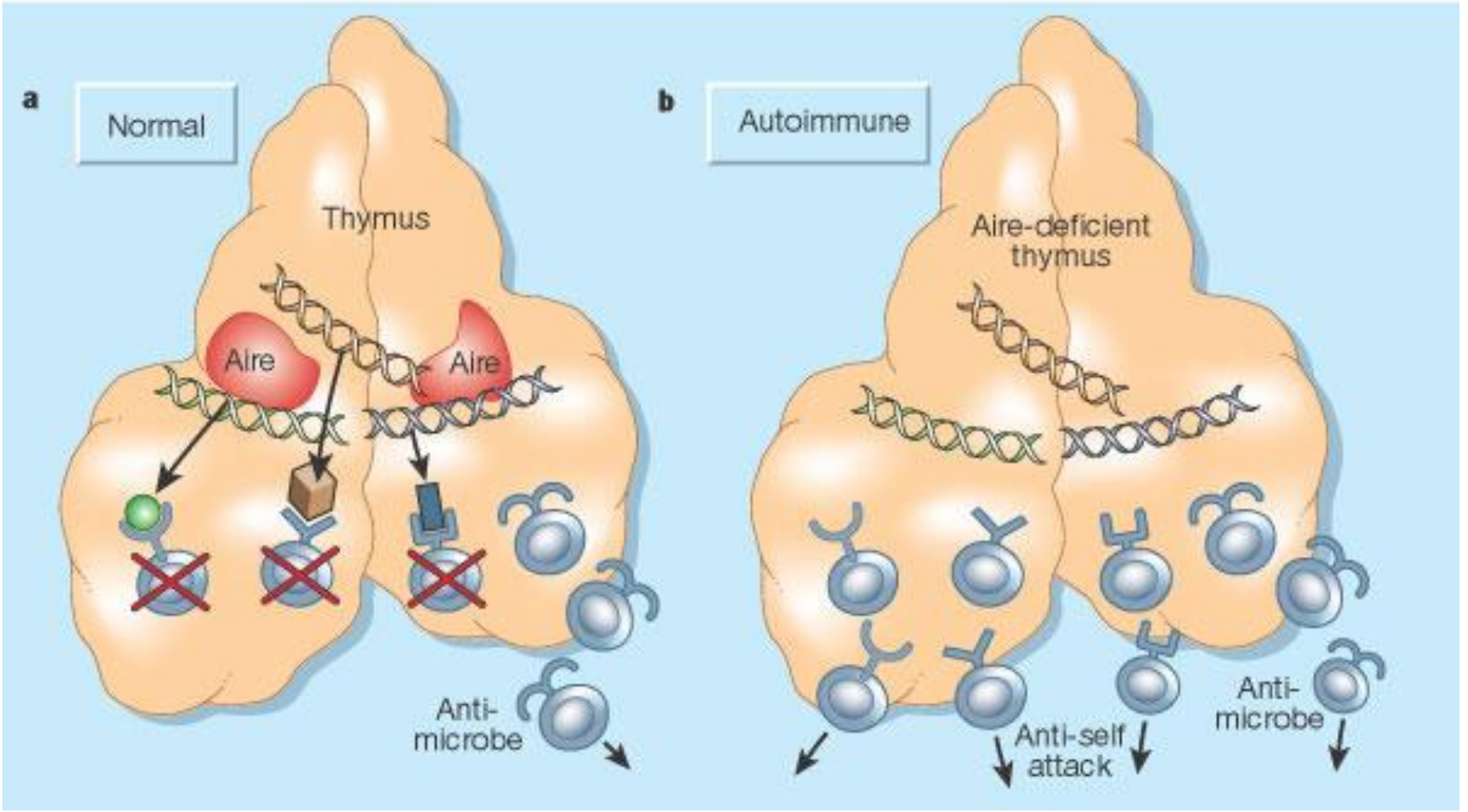


FIGURE 9-2 **Central T cell tolerance.** Strong recognition of self antigens by immature T cells in the thymus may lead to death of the cells (negative selection, or deletion). Self antigen recognition in the thymus also may lead to the development of regulatory T cells that enter peripheral tissues.

T cell Central tolerance : Cell death (negative selection)

- The **autoimmune regulator** (*AIRE*) is a protein that in humans is encoded by the *AIRE* gene. AIRE is a transcription factor expressed in the medulla (inner part) of the thymus and controls a mechanism that prevents the immune system from attacking the body.

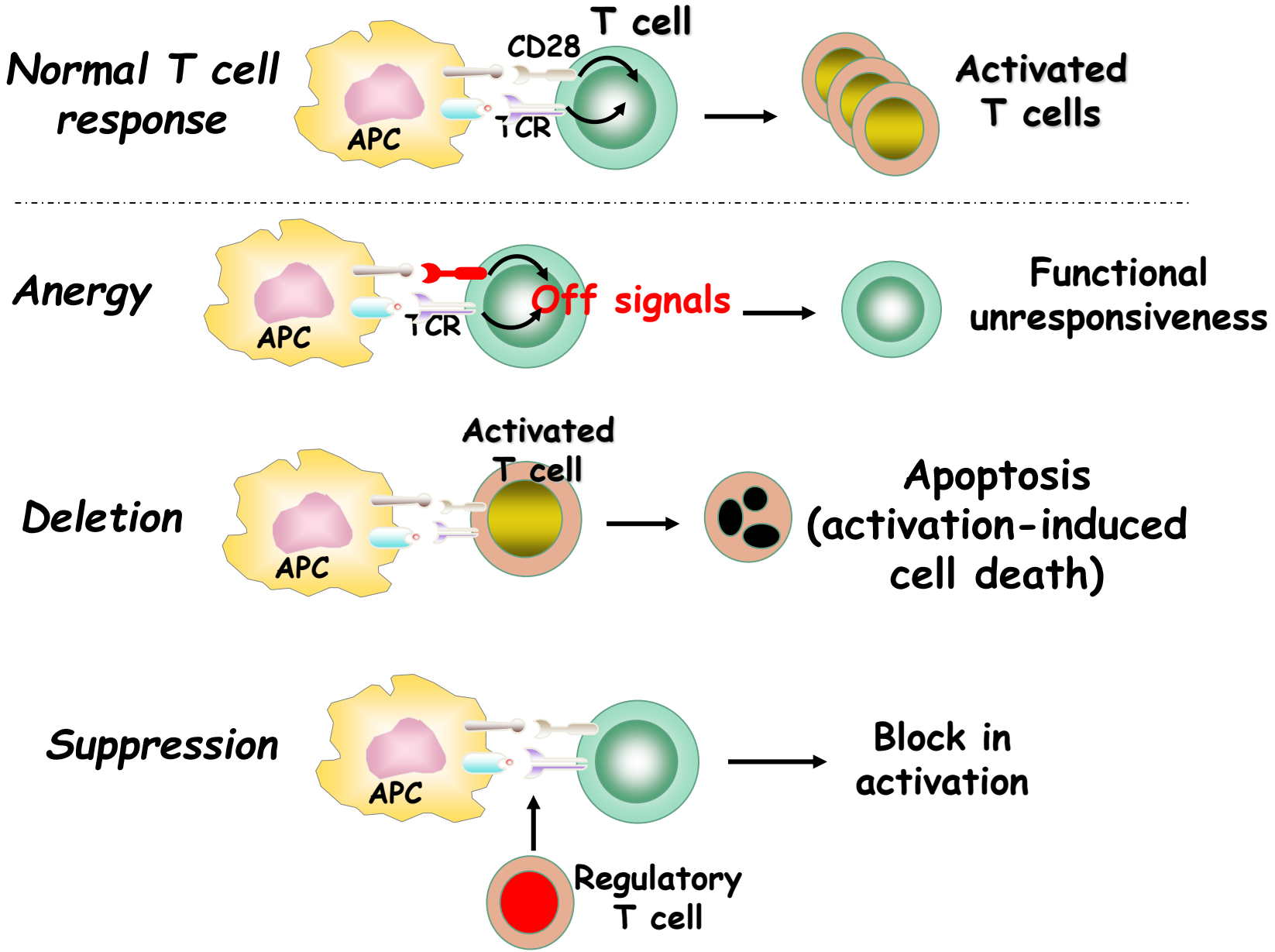
Autoimmune Regulator (AIRE)



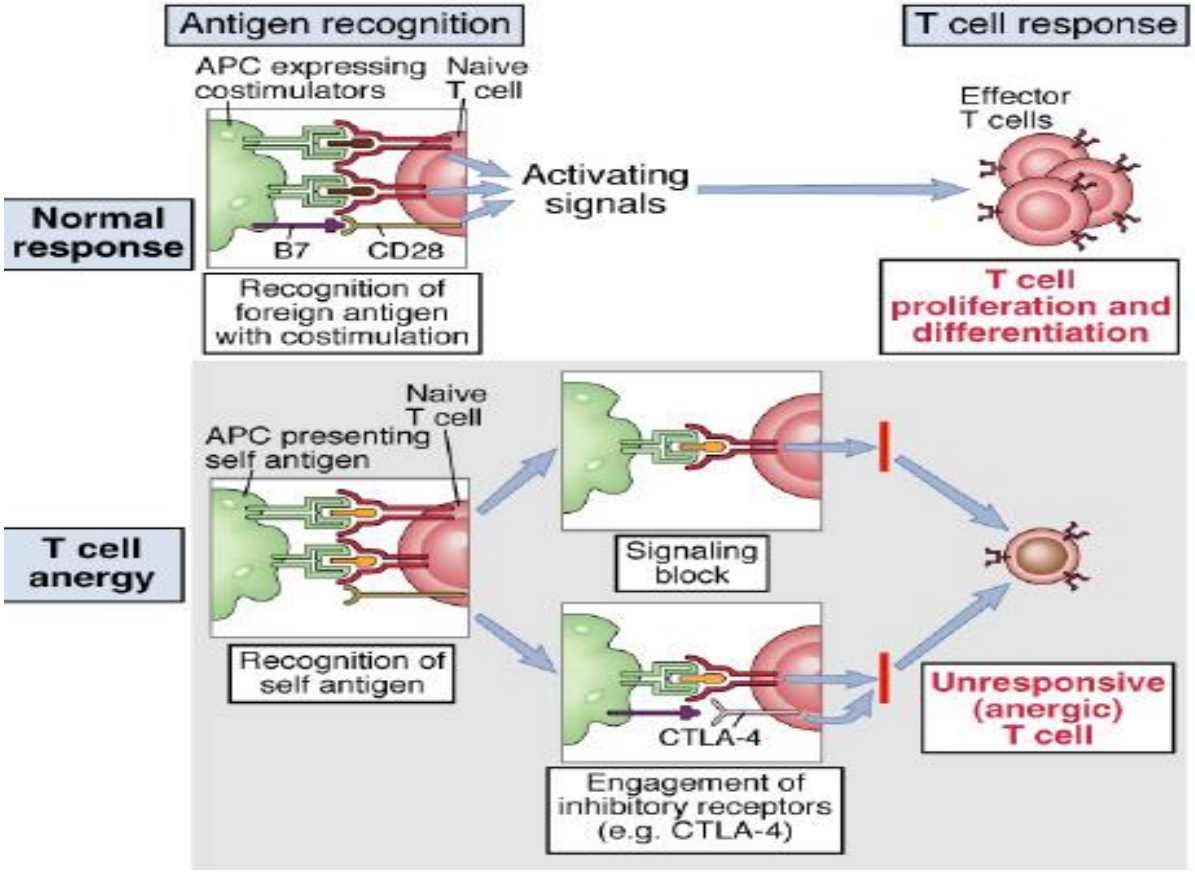
Thymic ("natural") regulatory T cells (Treg)

- Development requires recognition of self antigen during T cell maturation
- Reside in peripheral tissues to prevent harmful reactions against self

Peripheral tolerance of T cell

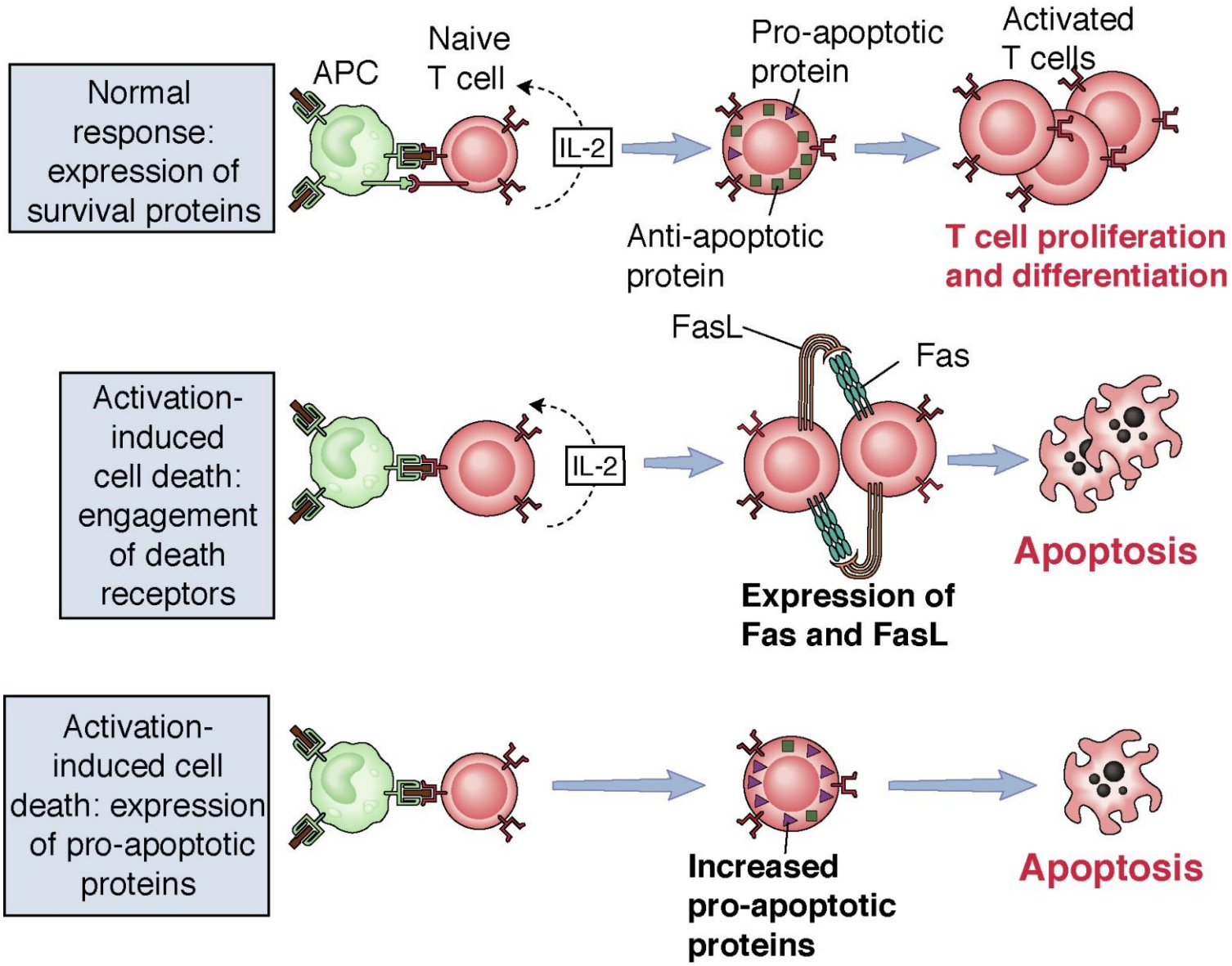


1. T cell anergy



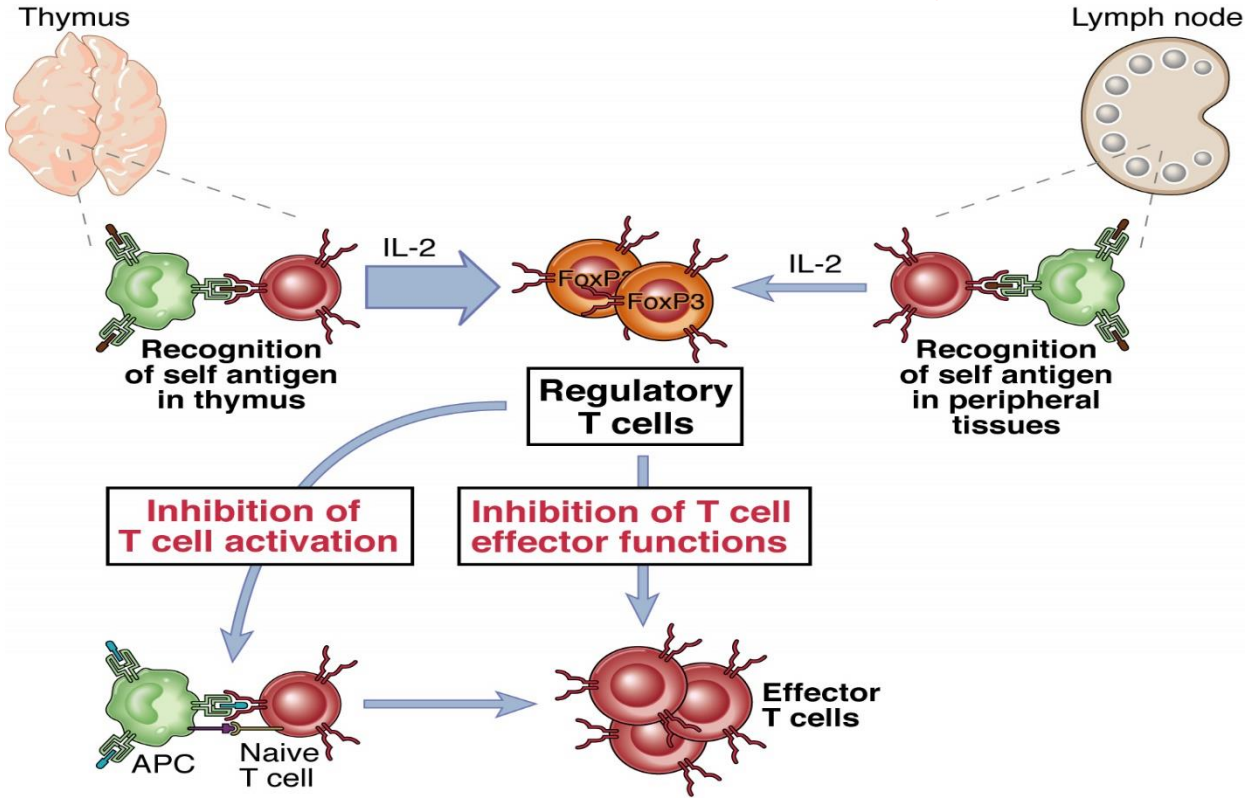
Anergy is the functional inactivation of T lymphocytes that occurs when these cells recognize antigens without adequate levels of the costimulators (second signals) that are needed for full T cell activation

2. Apoptosis "Activation-induced cell death"



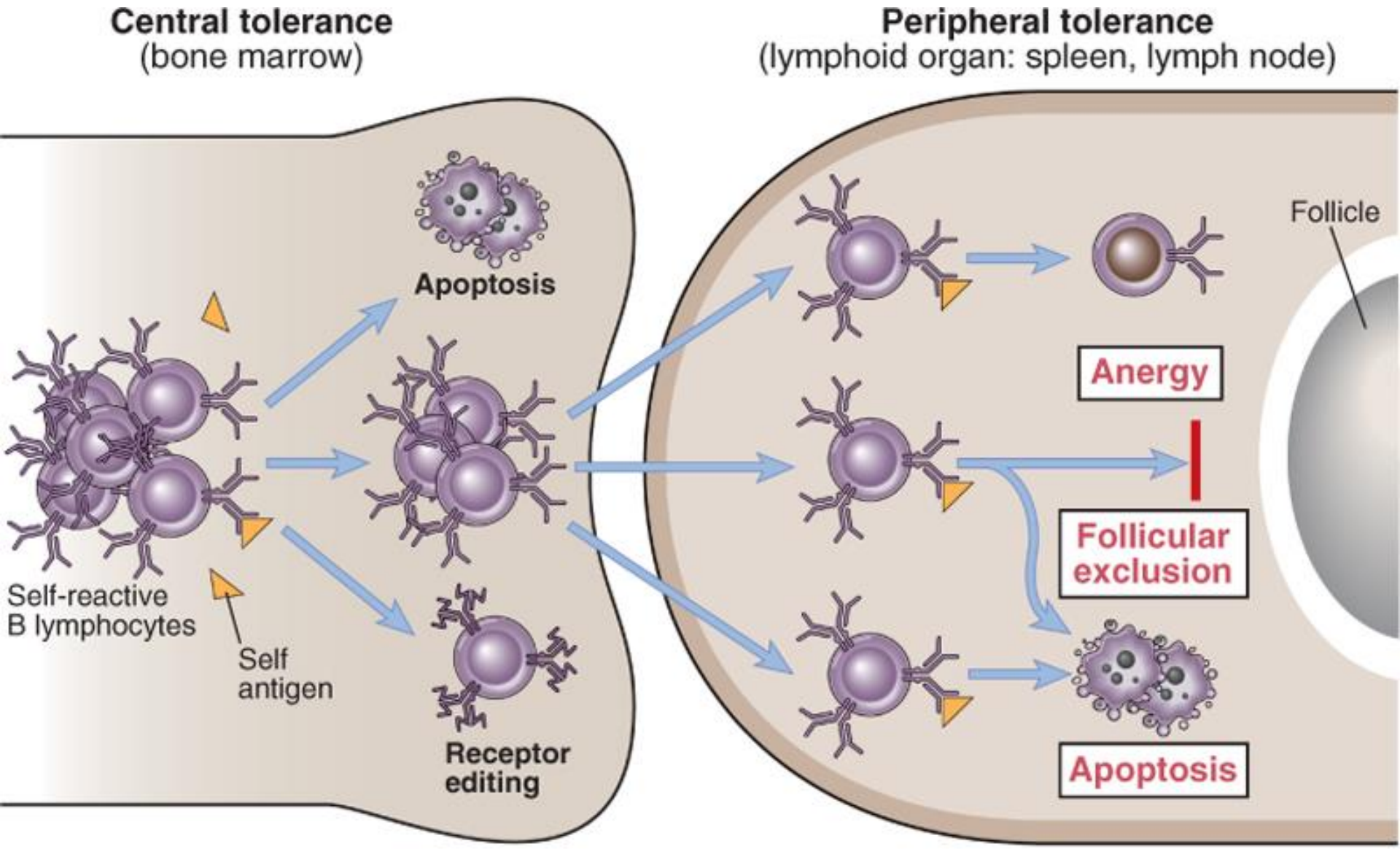
Fas ligand (FasL or CD95L) is a type-II transmembrane protein that belongs to the tumor necrosis factor (TNF) family. Its binding with its receptor induces apoptosis

3. Regulatory T cells



Regulatory T cells develop in the thymus or peripheral tissues on recognition of and block the activation of potentially harmful lymphocytes specifi c for these self antigens

Central and peripheral Tolerance in B cells

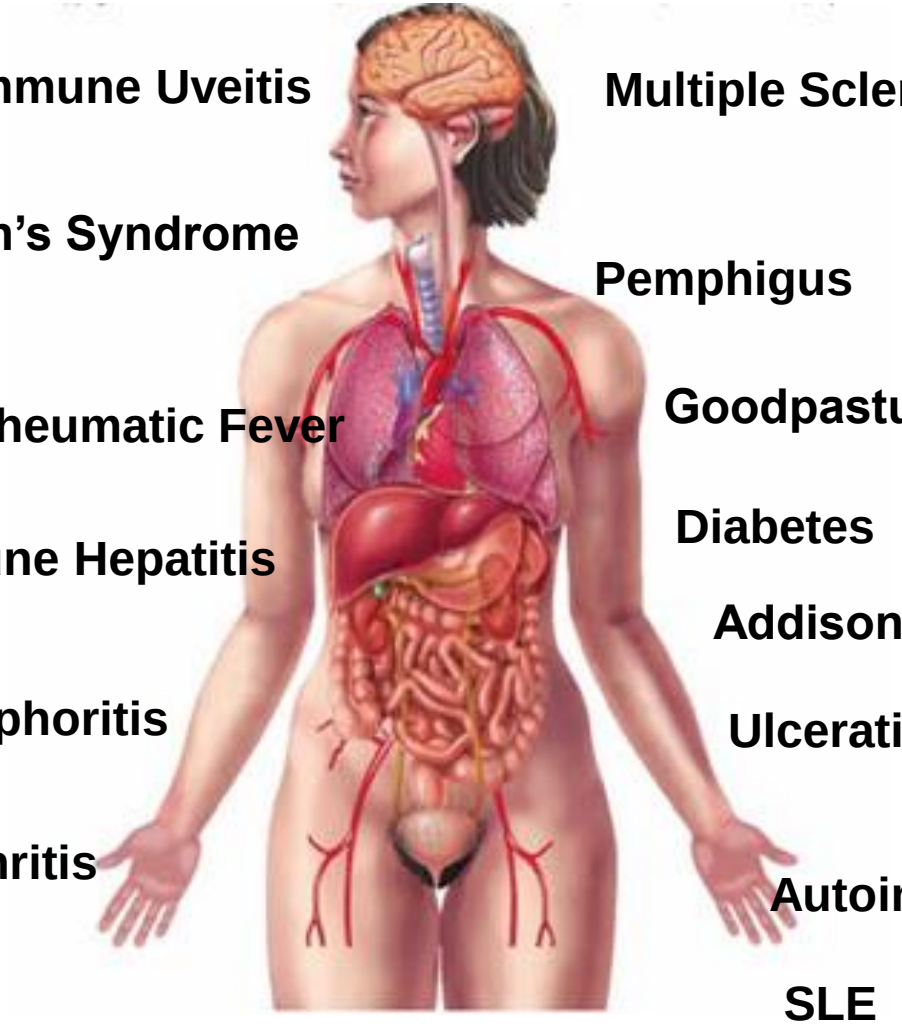


Autoimmune Diseases

Introduction

- Autoimmunity is defined as an immune response against self (autologous) antigens.
- It is an important cause of disease, estimated to affect at least 1% to 2% of persons in developed countries, and with an apparently increasing prevalence.
- Result from immune responses against self antigens (autoimmunity)
- May be caused by T cells and/or antibodies
- May be systemic or organ-specific
- These diseases often become chronic and self-perpetuating

Examples of Autoimmune diseases



Autoimmune Uveitis

Multiple Sclerosis

Sjogren's Syndrome

Pemphigus

Rheumatic Fever

Goodpasture's Syndrome

Autoimmune Hepatitis

Diabetes

Addison's Disease

Autoimmune Oophoritis

Ulcerative Colitis

Rheumatoid Arthritis

Autoimmune hemolytic Anemia

SLE

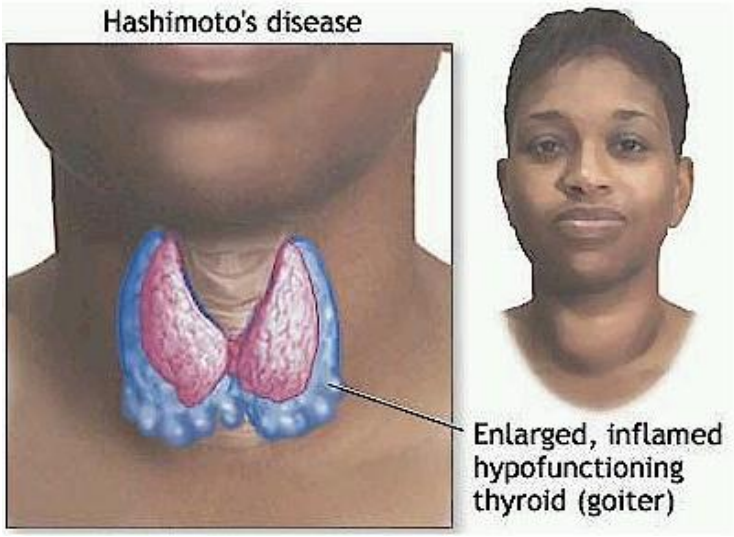
Classification of Autoimmune diseases

Can be classified into clusters that are either ***organ-specific*** or ***systemic***

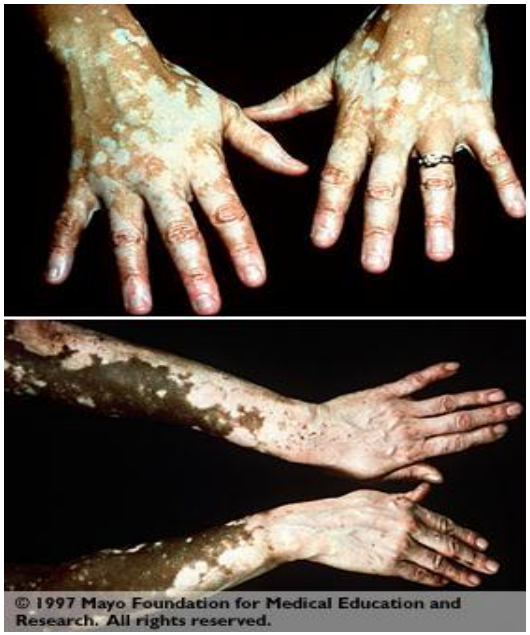
Organ-specific autoimmune diseases	Systemic autoimmune diseases
Type I diabetes mellitus	Rheumatoid arthritis
Goodpasture's syndrome	Scleroderma
Multiple sclerosis	Systemic lupus erythematosus Primary Sjögren's syndrome Polymyositis
Graves' disease Hashimoto's thyroiditis Autoimmune pernicious anemia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

Examples of organ specific

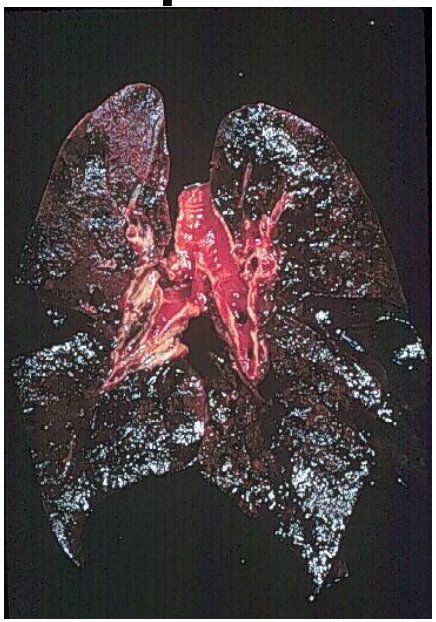
Hashimoto's disease (thyroiditis)



Vitiligo

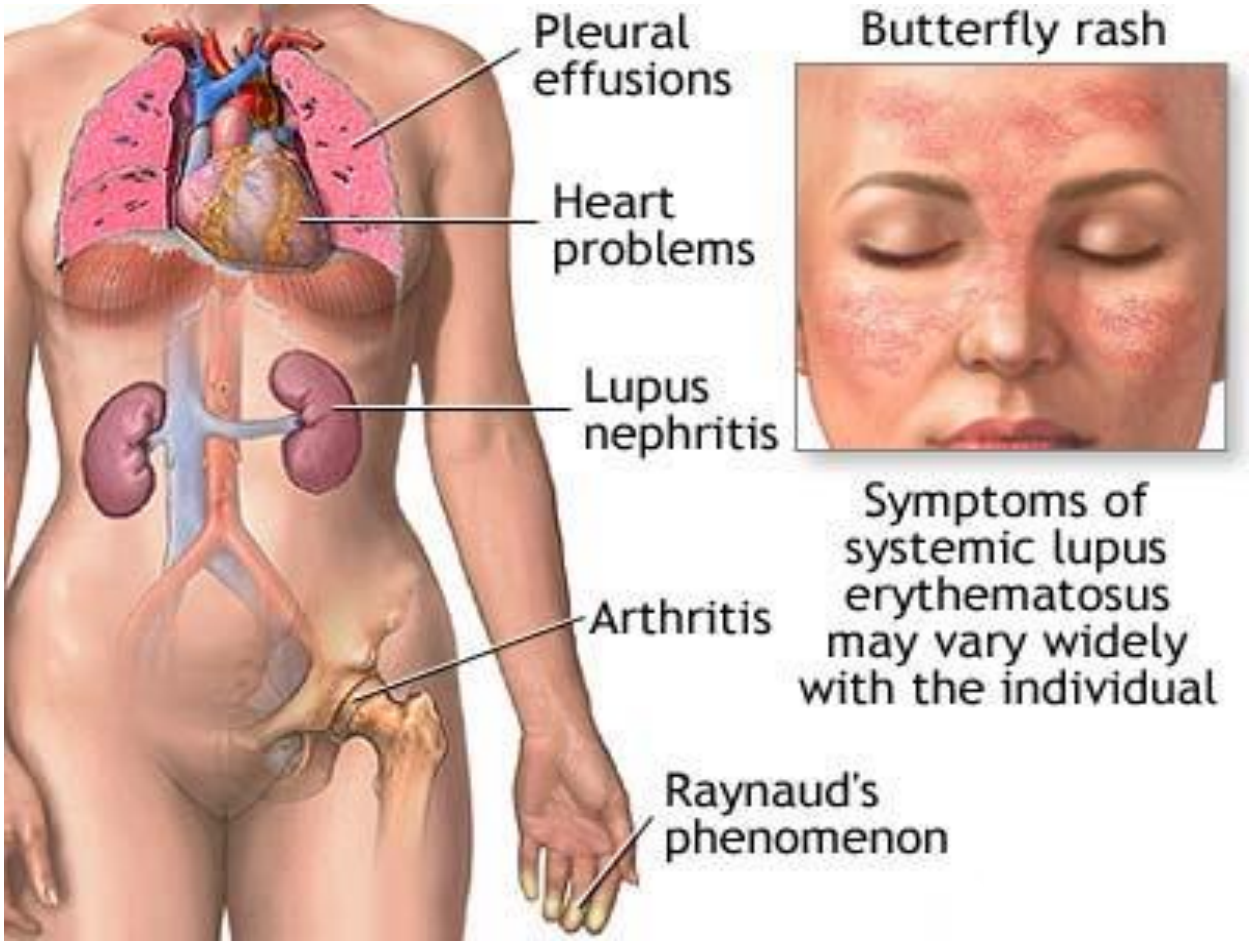


Lungs of a patient with Goodpasture's

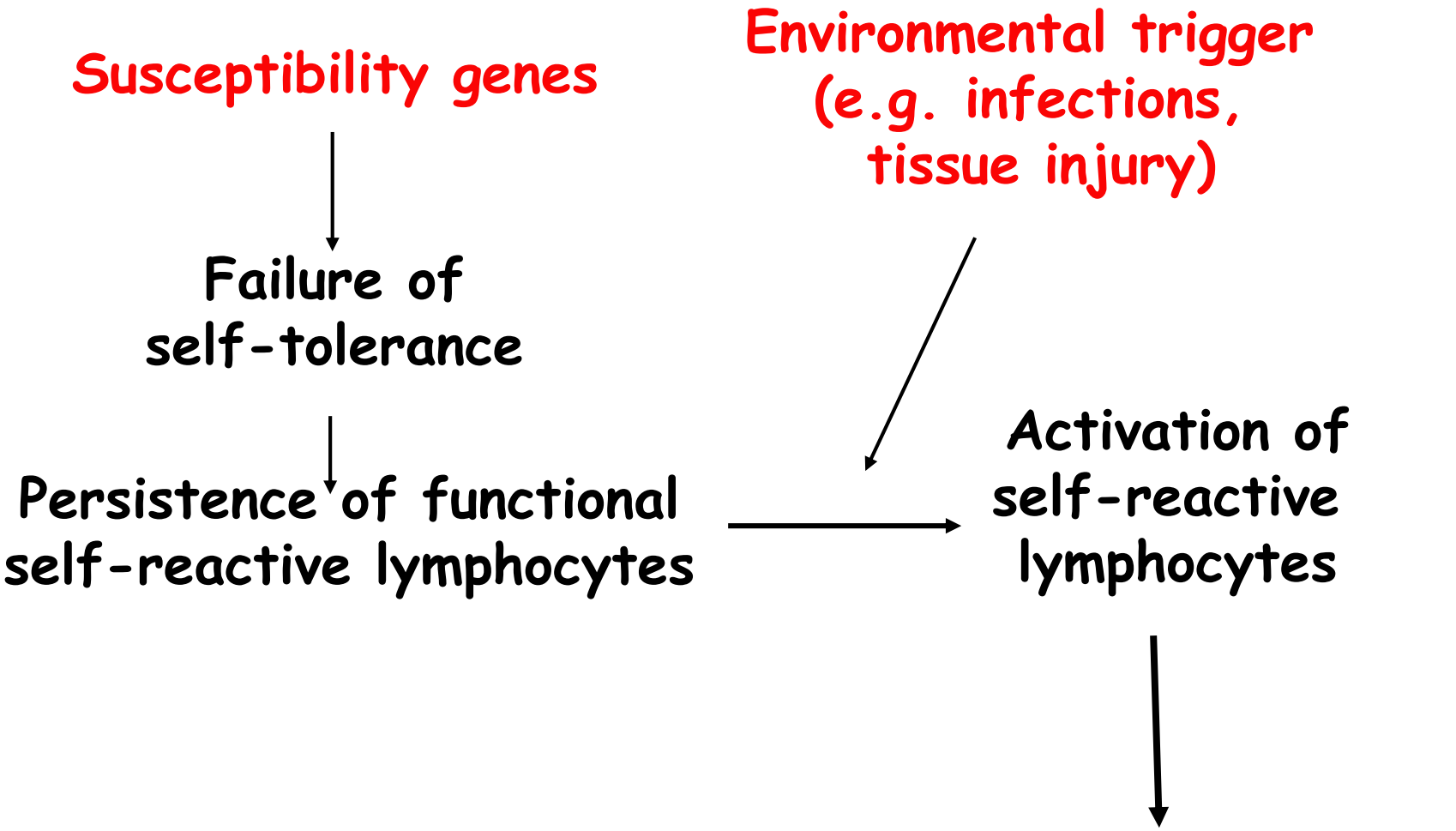


Example of systemic Autoimmunity

SLE (systemic Lupus Erythrematosus)



Pathogenesis of autoimmunity



1. Genetics of autoimmunity

- Human autoimmune diseases are complex polygenic traits
- Some polymorphisms are associated with multiple diseases. Other genetic associations are disease-specific

2. Environment

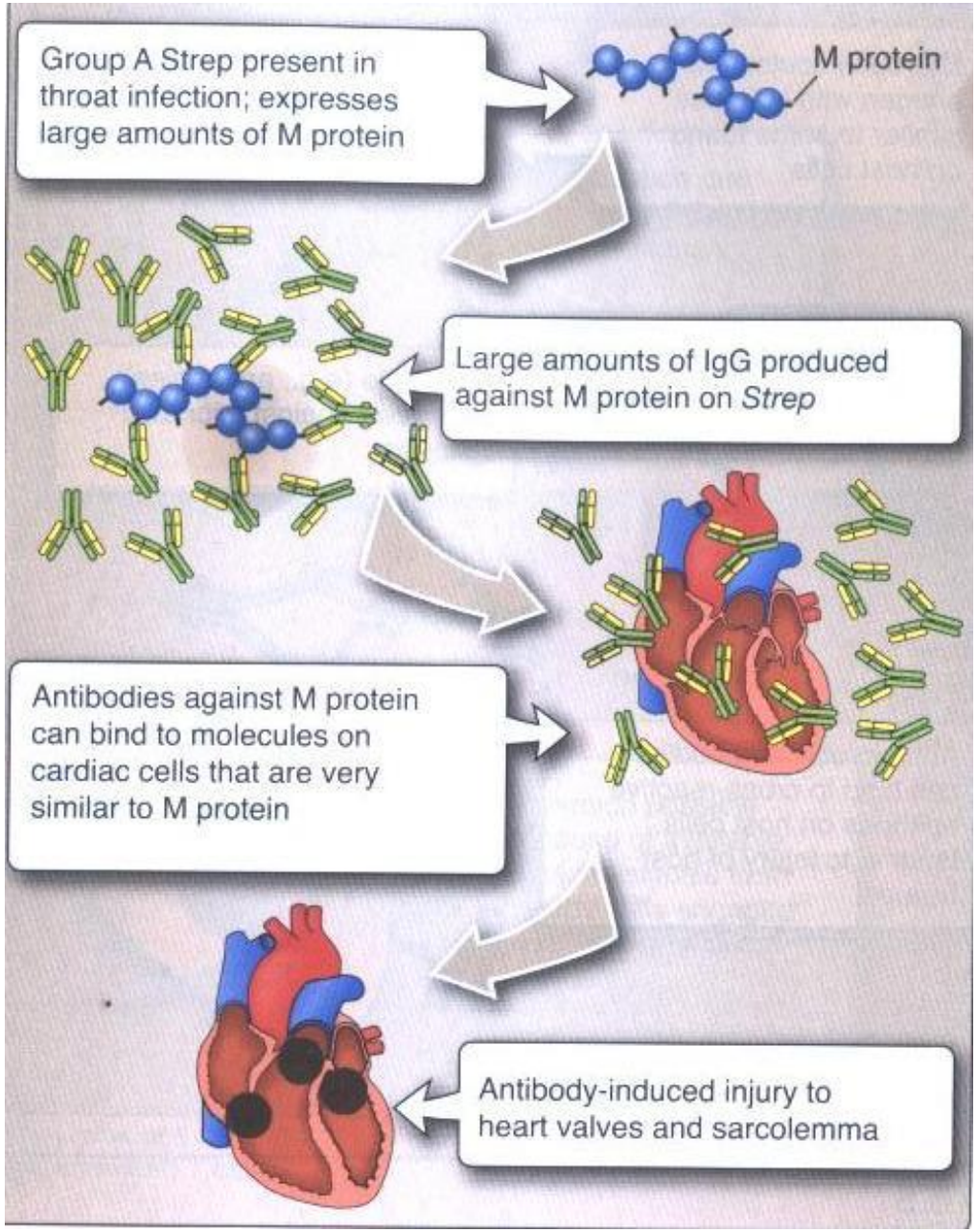
- Pathogens, drugs, hormones, and toxins are just a few ways that the environment can trigger autoimmunity

1. Drugs: Drug induced lupus
2. Toxins:
3. Hormones: Females are much more likely to develop autoimmune illness
    - Hypothesis: estrogen response elements (EREs) in several genes

3. Infections and autoimmunity

- **Infections trigger autoimmune reactions**
- **Autoimmunity develops after infection is eradicated (i.e. the autoimmune disease is precipitated by infection but is not directly caused by the infection)**

Rheumatic fever is a classic example of molecular mimicry



1. Hashemot's thyroditis

- Individual produce autoantibodies and sensitize Th1 cells specific for thyroid antigen
- Antibodies are formed against thyroid proteins including thyroglobulin and thyroid peroxidase.
- Binding of these antibodies to these proteins interferes with iodine uptake leading to hypothyroidism
- Intense infiltration of thyroid gland with lymphocytes, macrophages, and plasma cells
- Inflammatory response leads to goiter and hypothyroidism

2. Autoimmune anemias

- It includes pernicious anemia, autoimune hemolytic anemia and drug induced hemolytic anemia
- **Pernicious anemia** is caused by antibodies to intrinsic factors on gastric parietal cells which blocks vit B12 absorption necessary for haematopoiesis.
- **Autoimmune hemolytic anemia** results from autoantibodies to RBCs antigens triggering complemnt mediated lysis or antibody mediated opsonization and phagocytosis
- Certain drugs like penicillin or methyldopa induce hemolysis of RBCs

3. Goodpastuare's syndrome

- Autoantibodies specific for basement membrane antigens of kidney glomeruli and alevoli
- Complement activation and inflammatory response induce cellular damage leading to progressive kidney damage and lung hemorrhage

4. IDDM

- Immune response against beta cells of langehans islets in pancreas
- The autoimmune attack induce damage of beta cells with decrease production of insulin which leads to increased levels of blood glucose

5. Graves' disease

- In Graves' disease autoantibodies binds receptors for TSH and mimic the normal action of TSH resulting in the production of thyroid hormones

6. Myasthenia gravis

- Autoantibodies that bind the acetycholine receptors on the motor end of muscles blocking the normal binding of acetycholine and induce compliment mediated lysis of cells
- This results of progressive weakness of the muscles

7. SLE

- Autoantibodies against DNA, histones, RBCs, WBCs, platelets manifested mainly by systemic vasculitits and glomeulonephritis

8. Rheumatoid arthritis

- Autoantibodies called rheumatic factor of IgM class react with determinants on the FC portion of IgG. IgM/ IgG complex deposited on joint surface leading to arthritis