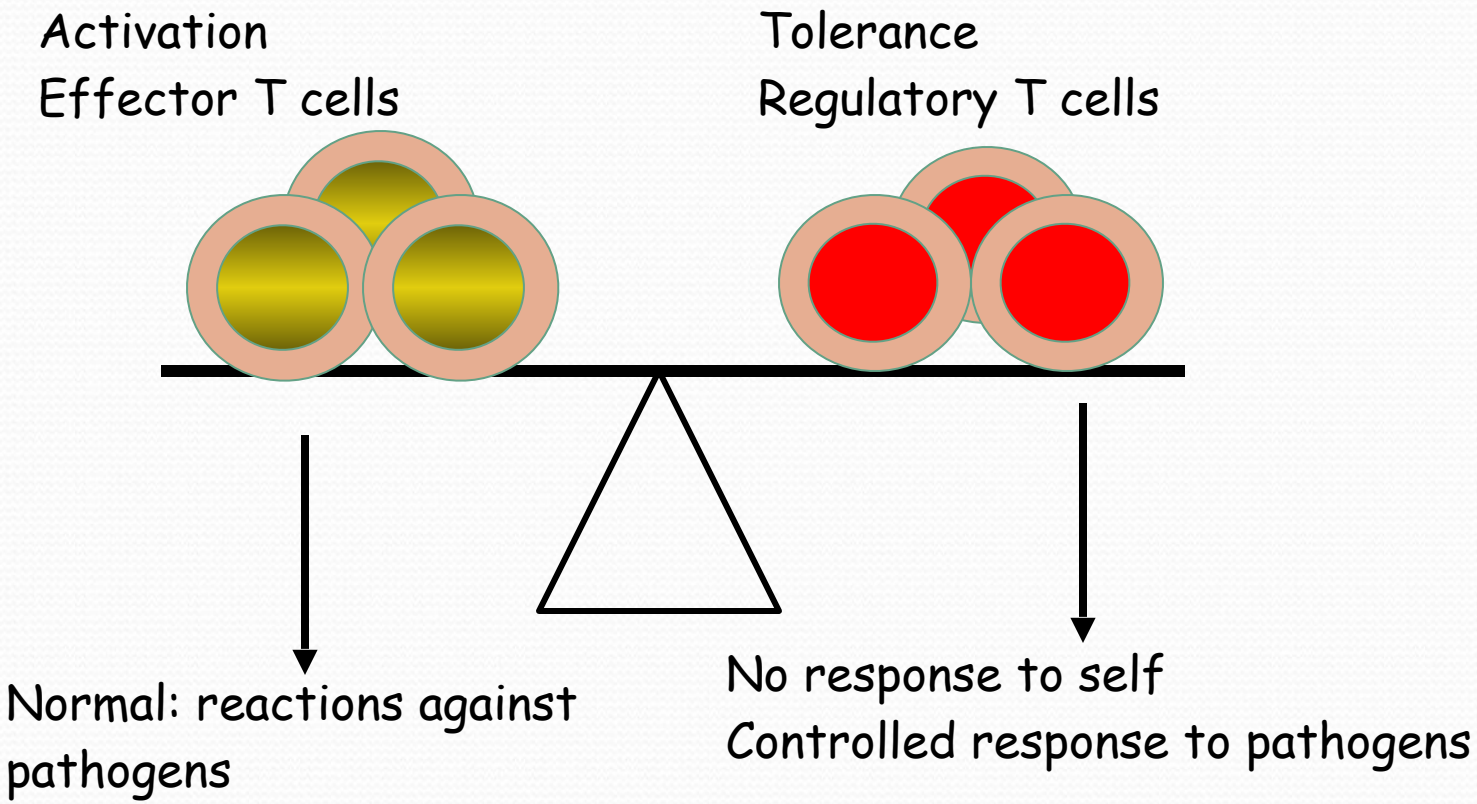
Tolerance and Autoimmunity

Mohammad Altamimi, MD, PhD
Faculty of Medicine

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

Balancing lymphocyte activation and control



Inflammatory disease, e.g. reactions against self

The importance of immune regulation

- To avoid excessive lymphocyte activation and tissue damage during normal protective responses against infections
- To prevent inappropriate reactions against self antigens ("self-tolerance")
- Failure of control mechanisms is the underlying cause of immune-mediated inflammatory diseases (autoimmune diseases)

General principles of controlling immune responses

- Responses against pathogens decline as the infection is eliminated
  - Apoptosis of lymphocytes that lose their survival signals (antigen, etc)
  - Memory cells are the survivors

- Active control mechanisms may function to limit responses to persistent antigens (self antigens, possibly tumors and some chronic infections)
  - Often grouped under "tolerance"

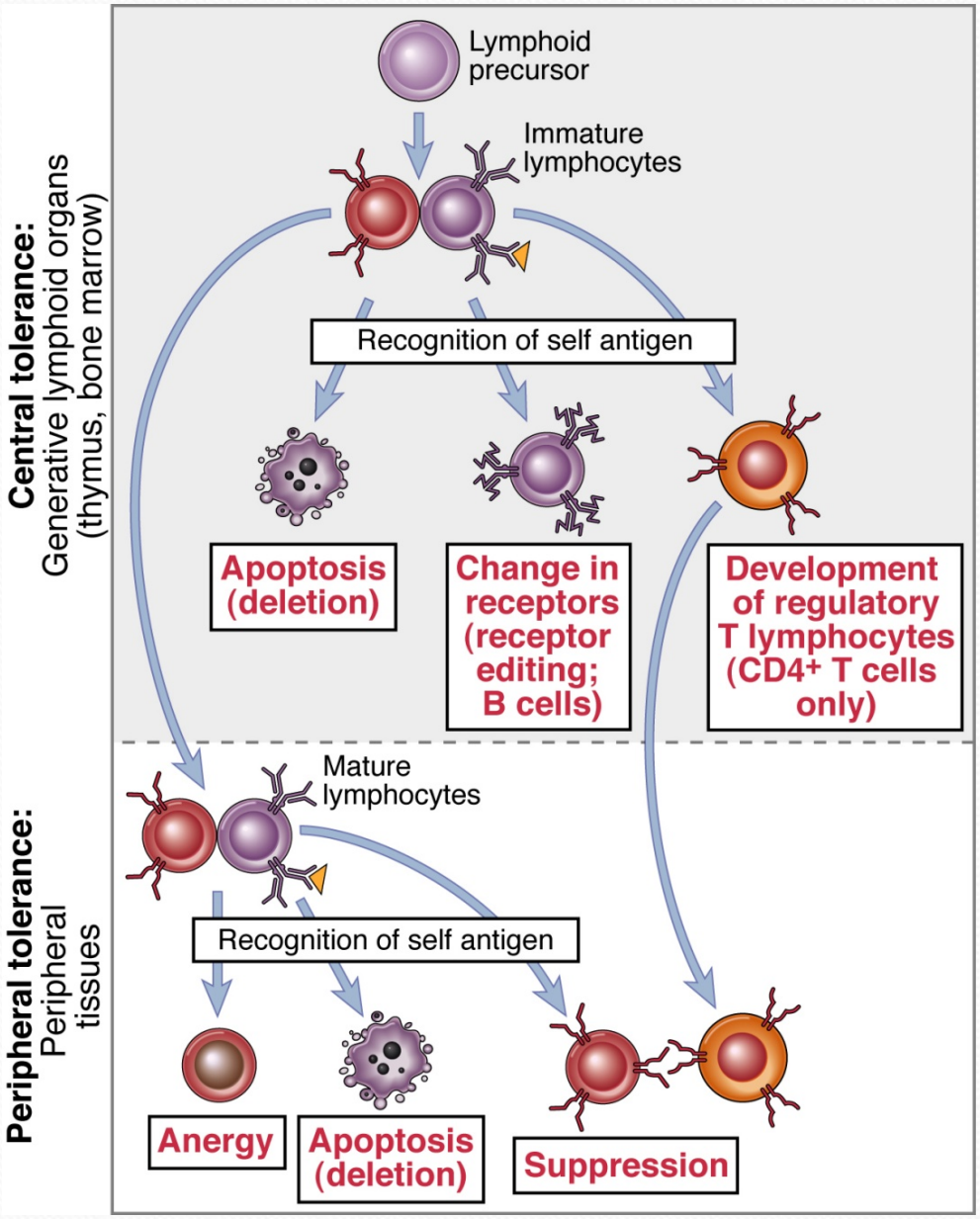
- Immunological tolerance: specific unresponsiveness to an antigen that is induced by exposure of lymphocytes to that antigen (tolerogen vs immunogen)
- Autoimmunity: immune response against self (auto-) antigen, by implication pathologic
  - Disorders are often classified under "immune-mediated inflammatory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

Toerogen versus Immunogen

- Tolerogen: antigen that induce tolerance
- Immunogen: antigen that induce immune response
- The same chemical compound can be an immunogen or tolerogen depending on how it is presented to the immune system
- Factors promoting tolerance rather than stimulation of immune system include:

1. High dose of antigen
2. Persistence of antigen in host
3. Intravenous or oral introduction
4. Absence of adjuvents
5. Low level of costimulation

Central and peripheral tolerance



Central tolerance

- Lymphocytes that see self antigens before they are mature are either eliminated or rendered harmless
- Probably continues to occur at some level throughout life (as new lymphocytes are produced from bone marrow stem cells)
- Role of the AIRE protein in thymic expression of some tissue antigens

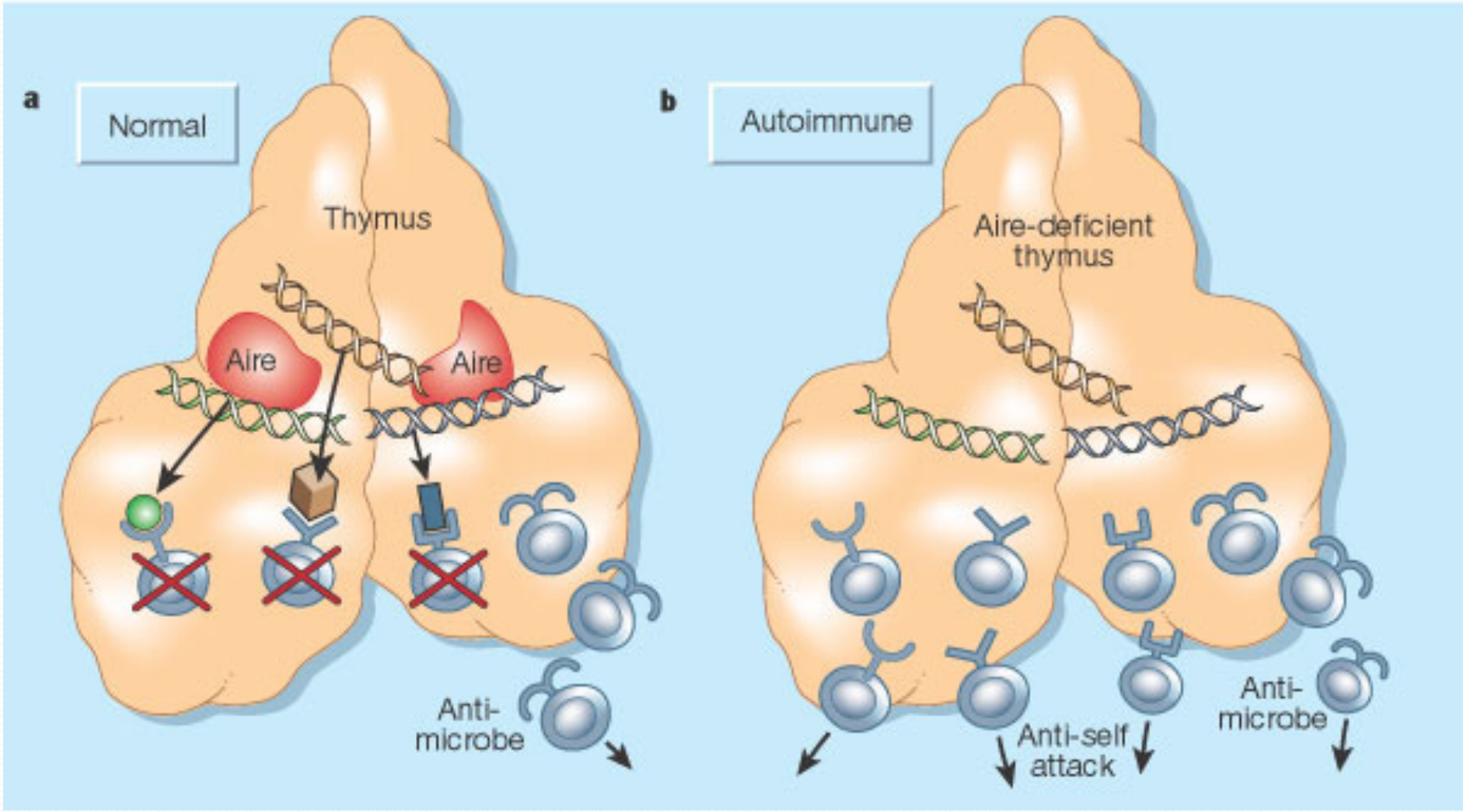
Mechanism of Central tolerance

- 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

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

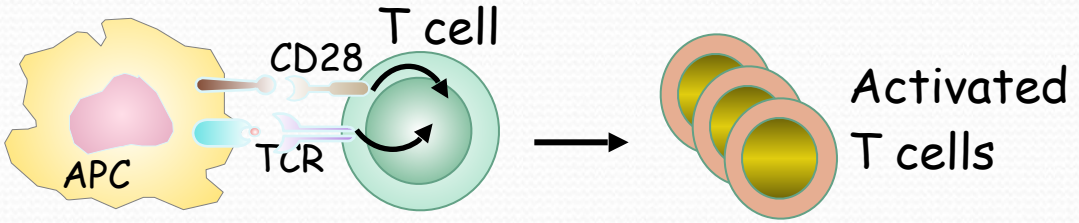
- Development requires recognition of self antigen during T cell maturation
- Reside in peripheral tissues to prevent harmful reactions against self

Autoimmune Regulator (AIRE)

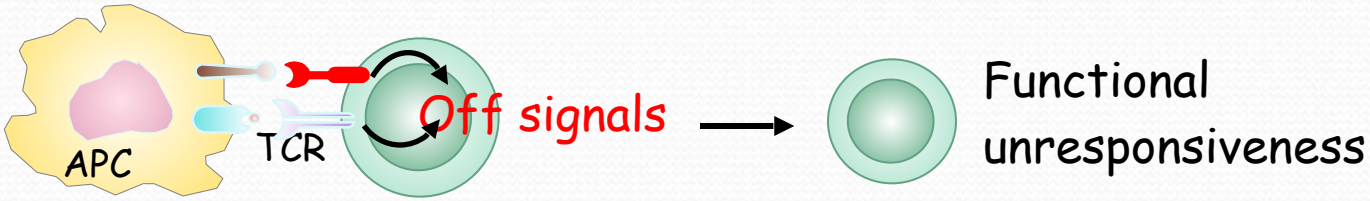


Peripheral tolerance

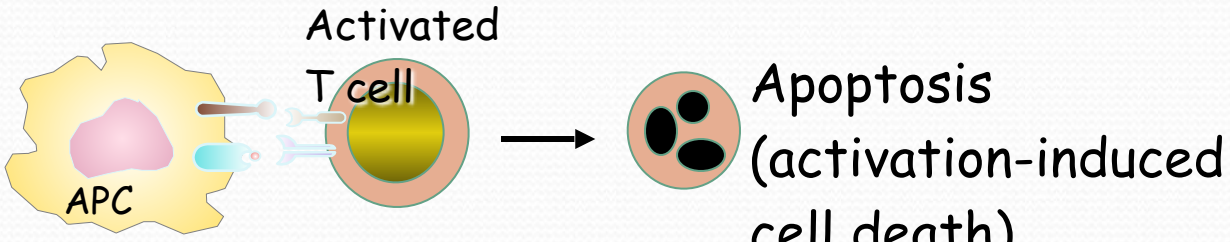
Normal T cell response



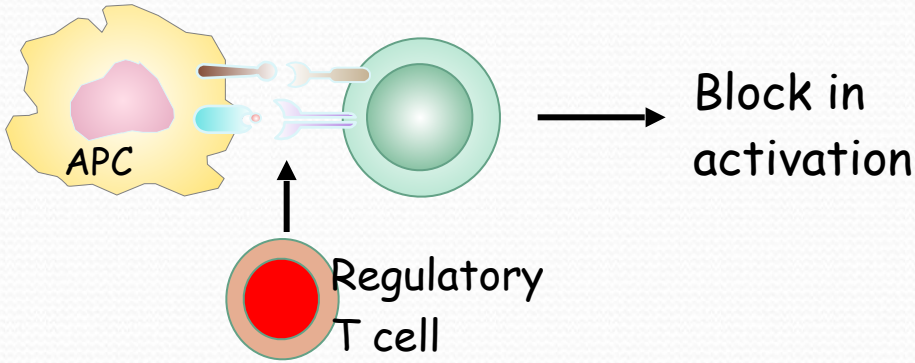
Anergy



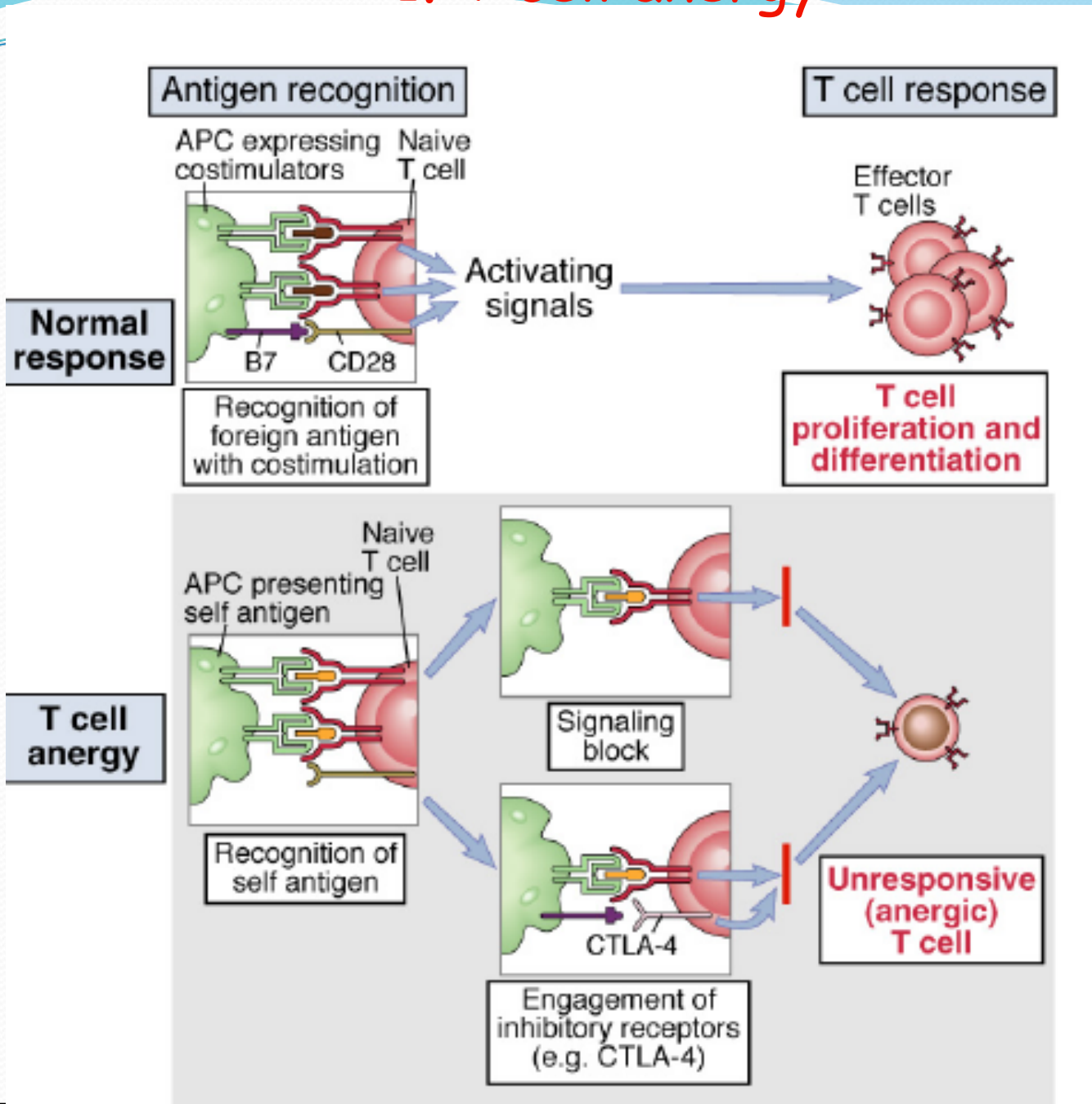
Deletion



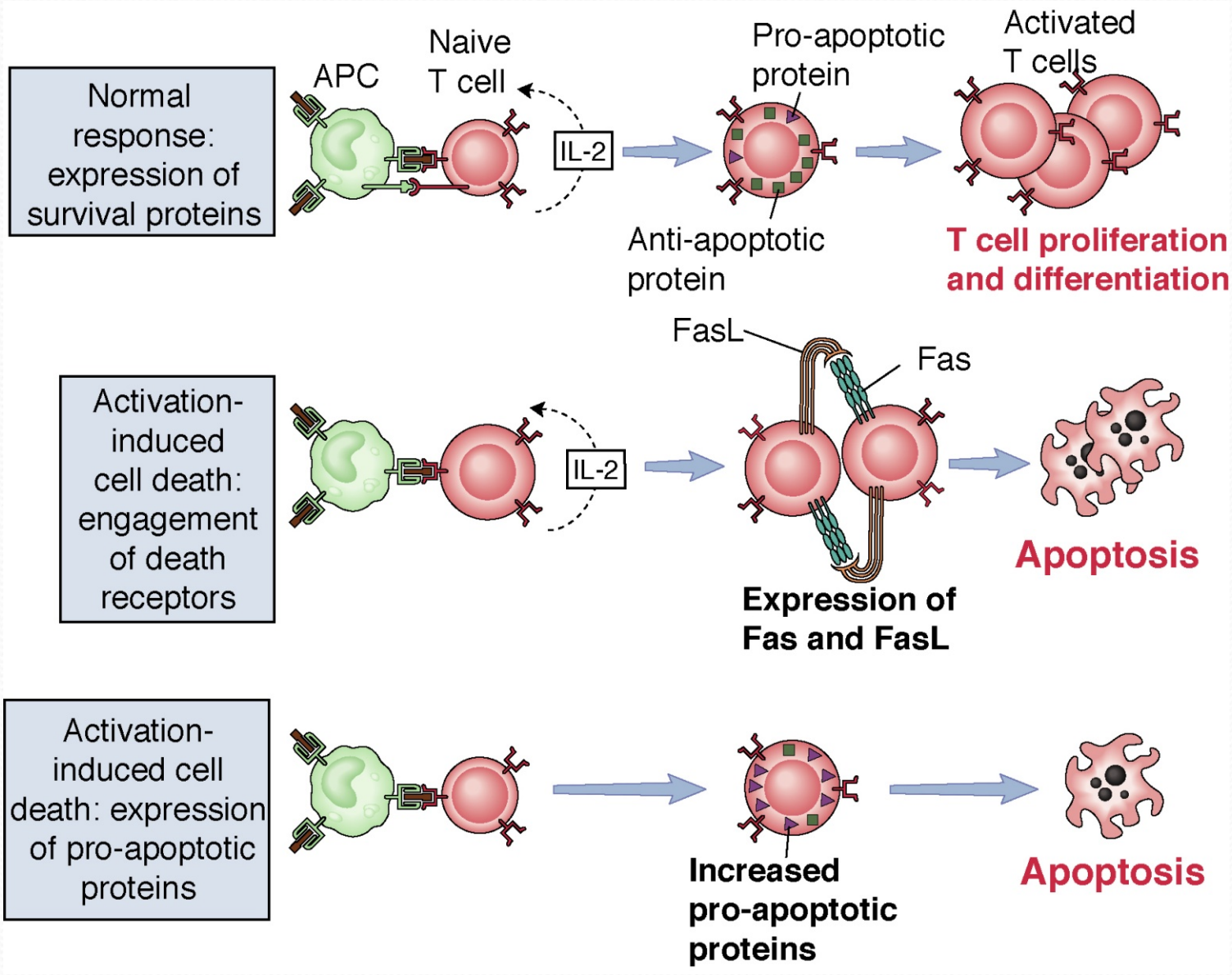
Suppression



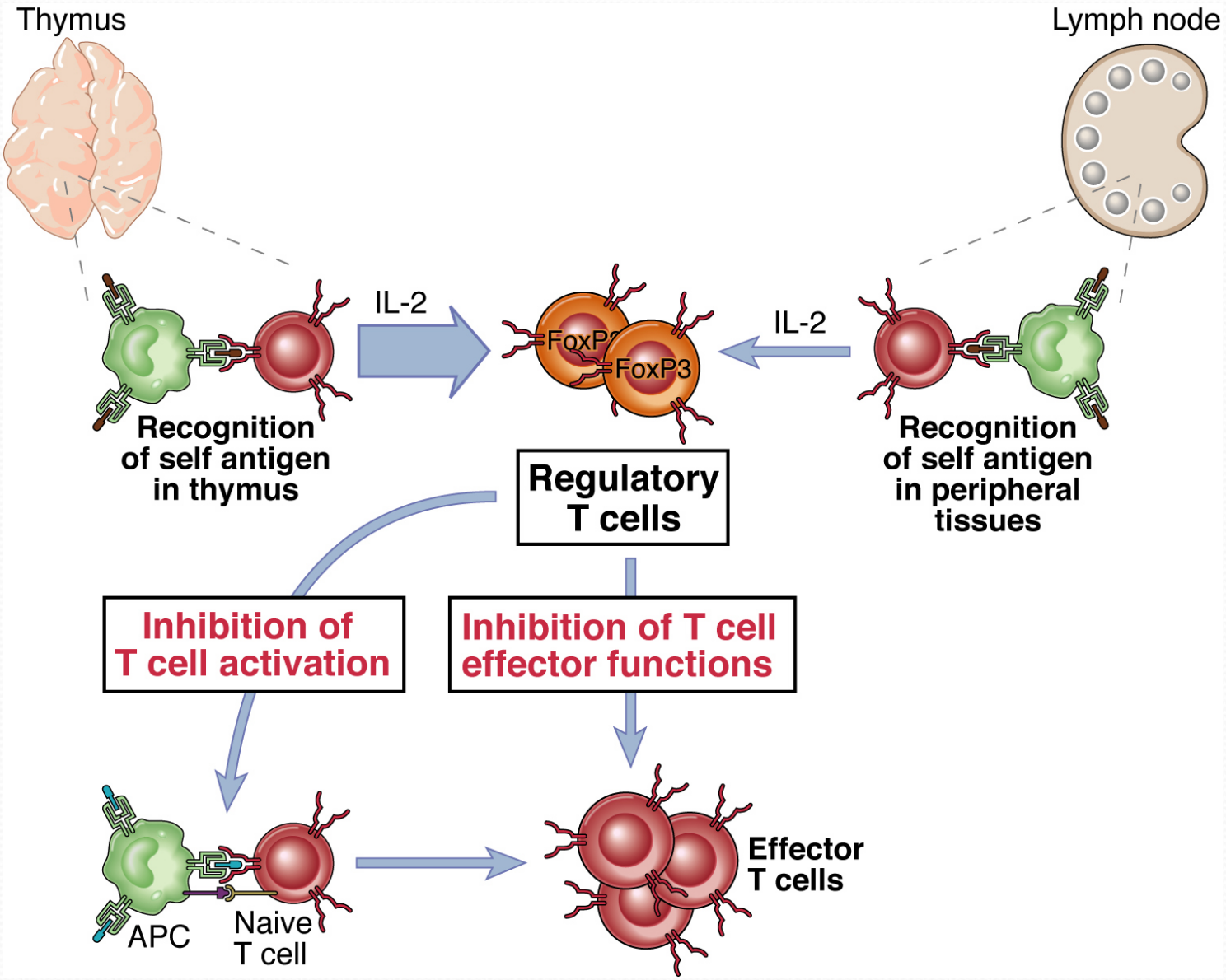
1. T cell anergy



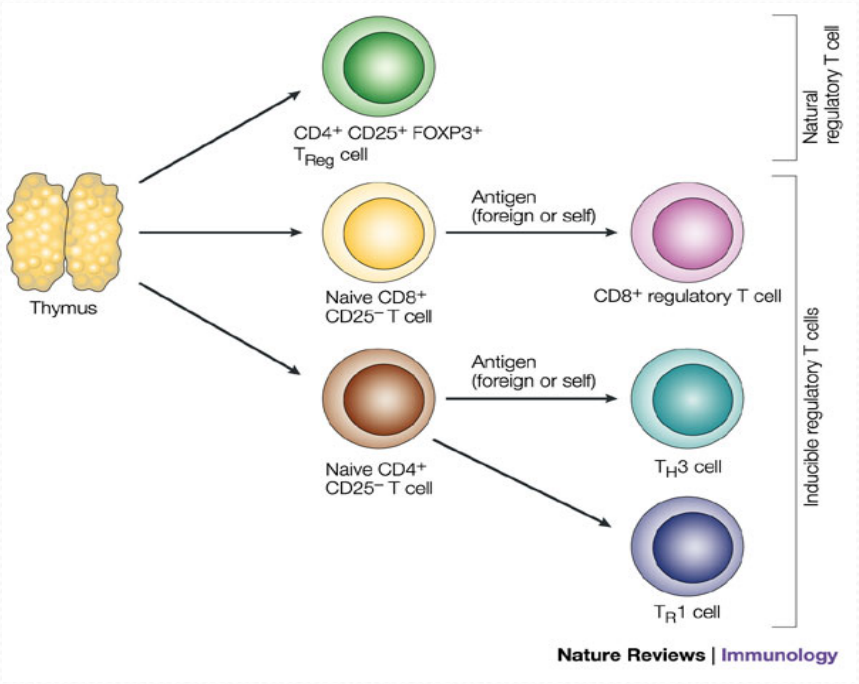
2. Apoptosis "Activation-induced cell death"



3. Regulatory T cells



Rregulatory T cell subsets



- Natural regulatory T cells express the cell-surface marker CD25 and the transcriptional repressor FOXP3 (forkhead box P3).
- regulatory T cells include distinct subtypes of $CD4^+$ T cell:

1.T regulatory 1 (T_R1) cells, which secrete high levels of IL-10, no IL-4 and no or low levels of IFN

2.T helper 3 (T_H3) cells, which secrete high levels of TGF

3.$CD8^+$ T cells a subtype of these cells can secrete IL-10 and have been called $CD8^+$ regulatory T cells.

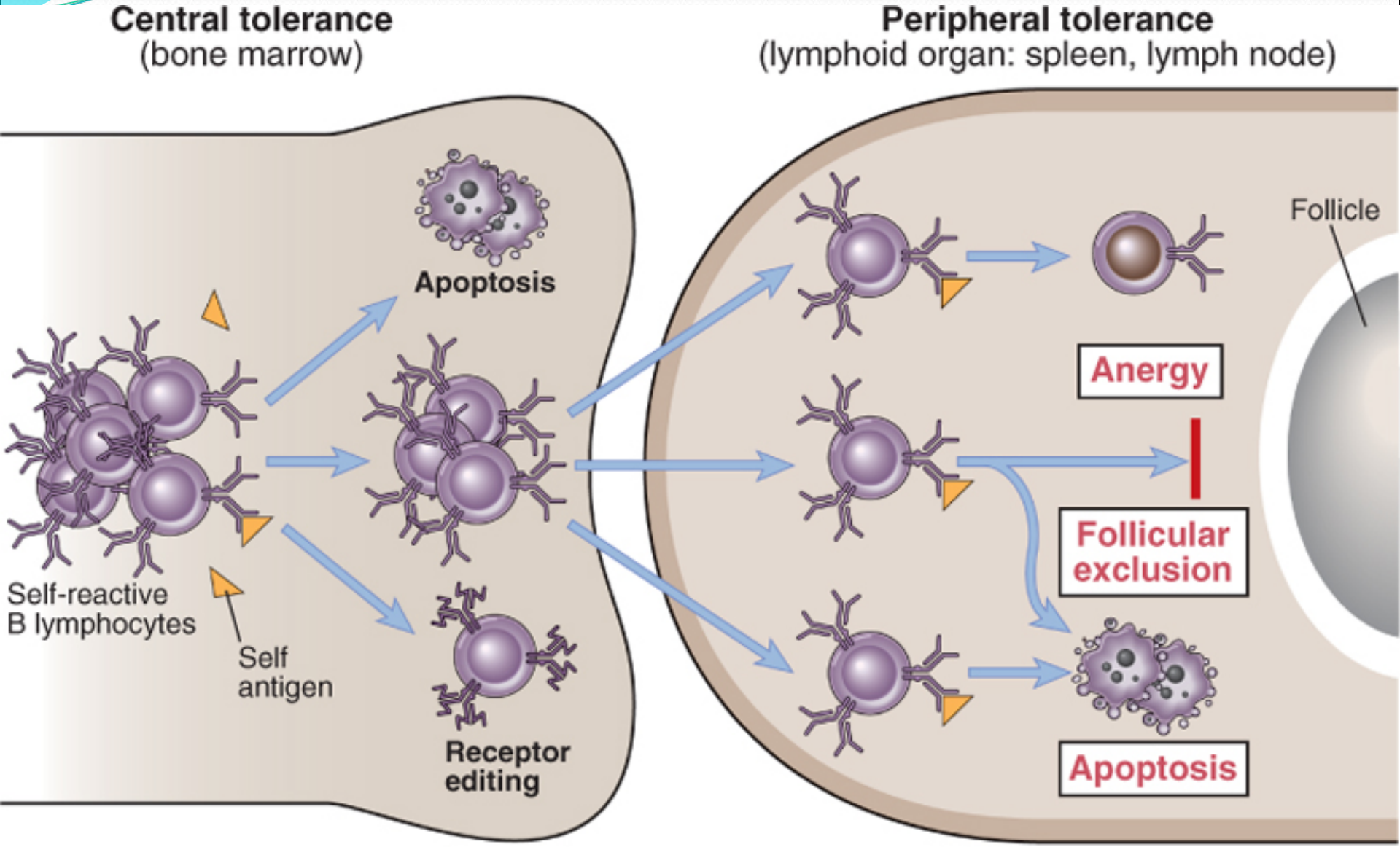
Properties of peripheral regulatory T cells

- Phenotype: CD4, high IL-2 receptor (CD25), low IL-7 receptor
- Develop from mature CD4 T cells that are exposed to persistent antigen in the periphery
- May be generated in all immune responses, to limit collateral damage
- Mechanisms of action:
  - secretion of immune-suppressive cytokines (TGFβ, IL-10, IL-35)
  - inactivation of dendritic cells or responding lymphocytes
  - Some autoimmune diseases are associated with defective generation or function of Tregs or resistance of effector cells to suppression by Tregs

Signals for the generation and maintenance of regulatory T cells

- Antigen recognition, with or without inflammation?
- TGF-β (source?)
- Interleukin-2 (originally identified as T cell growth factor; major function is to control immune responses by maintaining functional Treg; works via Stat5)
- Low levels of B7: CD28 costimulation
- Transcription factor Foxp3
  - Many activated T cells (not only Treg) may transiently express Foxp3

Central and peripheral Tolerance in B cells

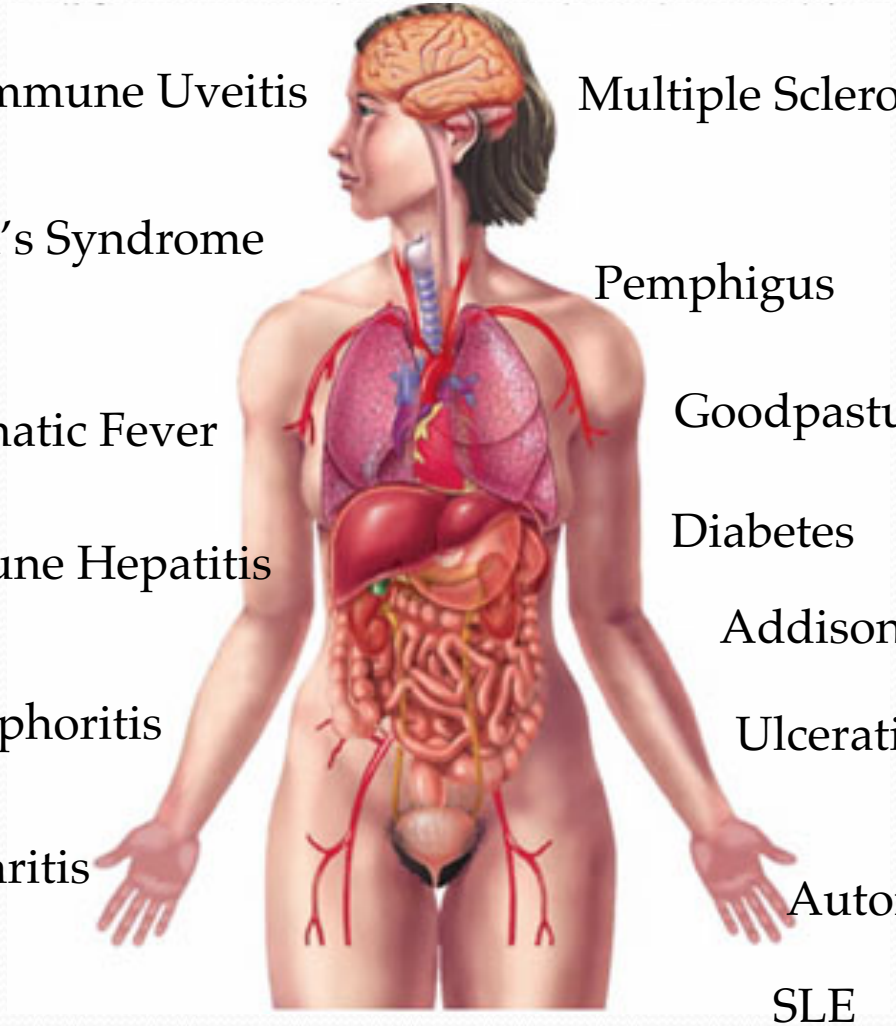


Autoimmune Diseases

Introduction

- Chronic diseases with prominent inflammation, often caused by failure of tolerance or regulation
- Affect 2-5% of people, incidence increasing
- Autoimmune diseases are a major threat to the health of all peopls.
- At least 10 millions Americans suffer from more than eighty illnesses caused by autoimmunity.
- 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

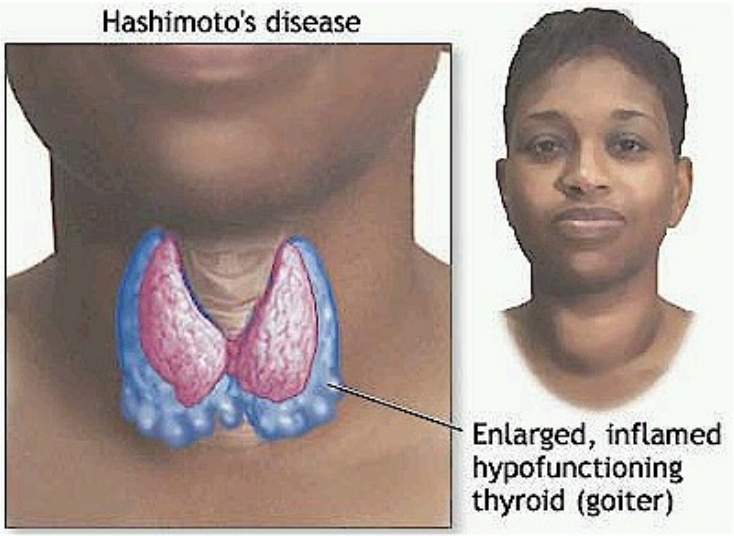
Can be classified into clusters that are either ***organ-specific*** or ***systemic***

Organ-specific autoimmune diseases
Type I diabetes mellitus
Goodpasture's syndrome
Multiple sclerosis
Graves' disease Hashimoto's thyroiditis Autoimmune pernicious anemia Autoimmune Addison's disease Vitiligo Myasthenia gravis

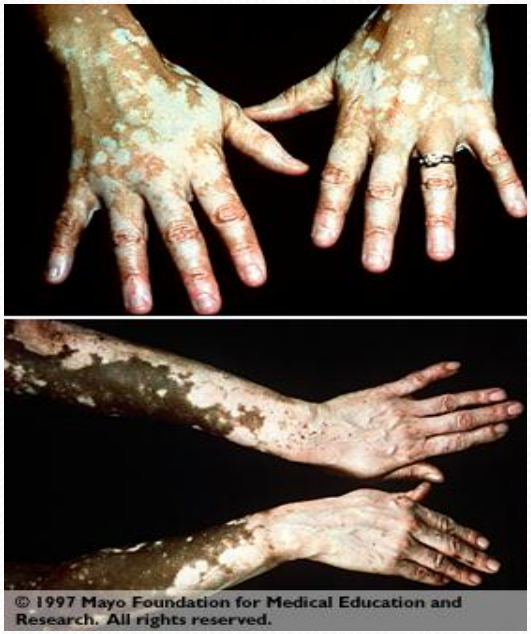
Systemic autoimmune diseases
Rheumatoid arthritis
Scleroderma
Systemic lupus erythematosus Primary Sjögren's syndrome Polymyositis

Examples of organ specific

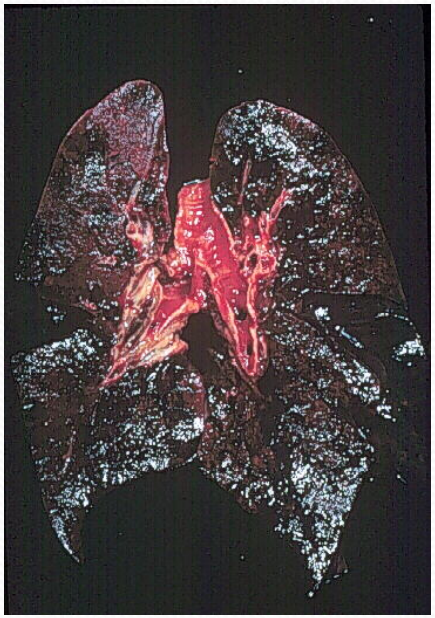
Hashimoto's disease (thyroiditis)



Vitiligo

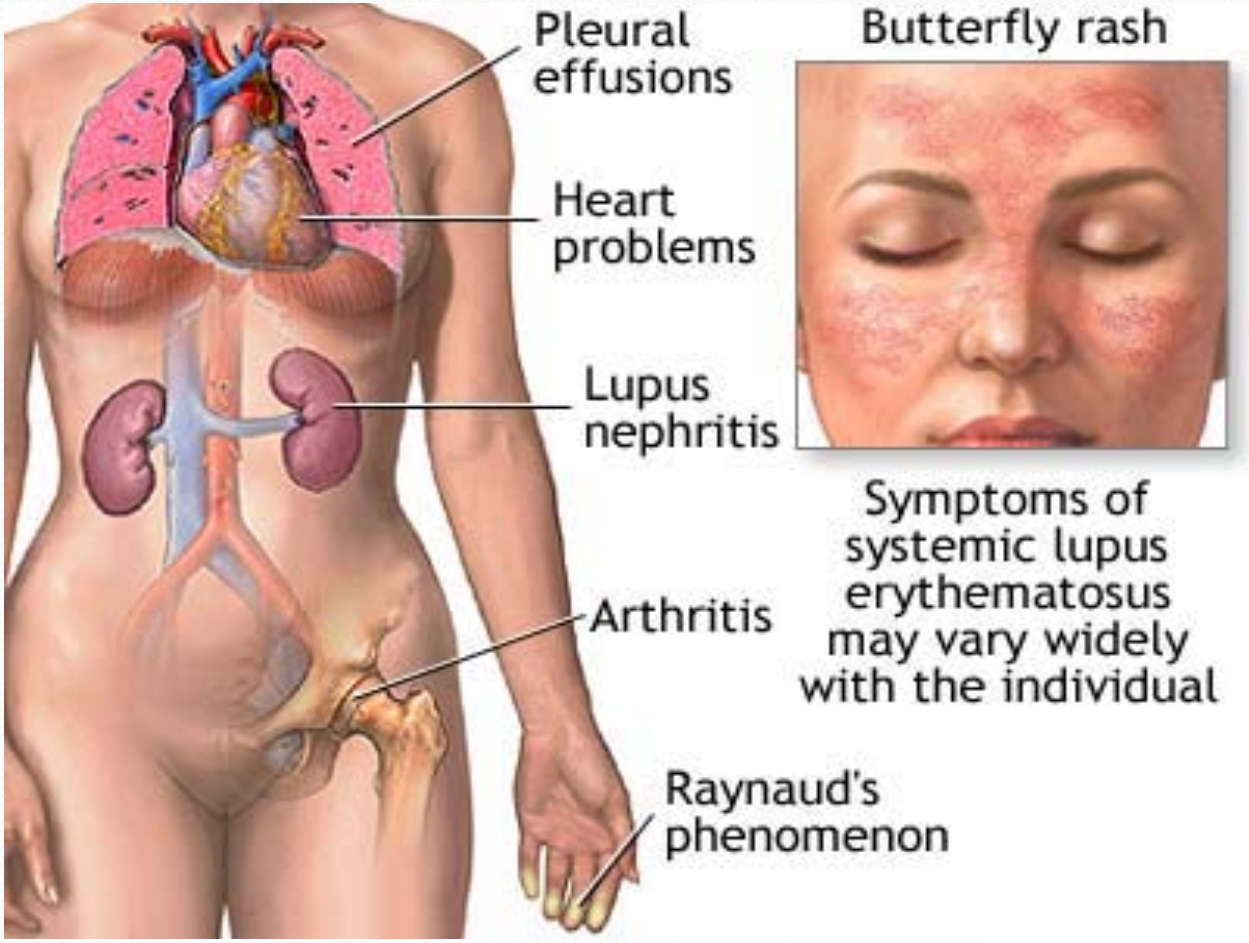


Lungs of a patient with Goodpasture's

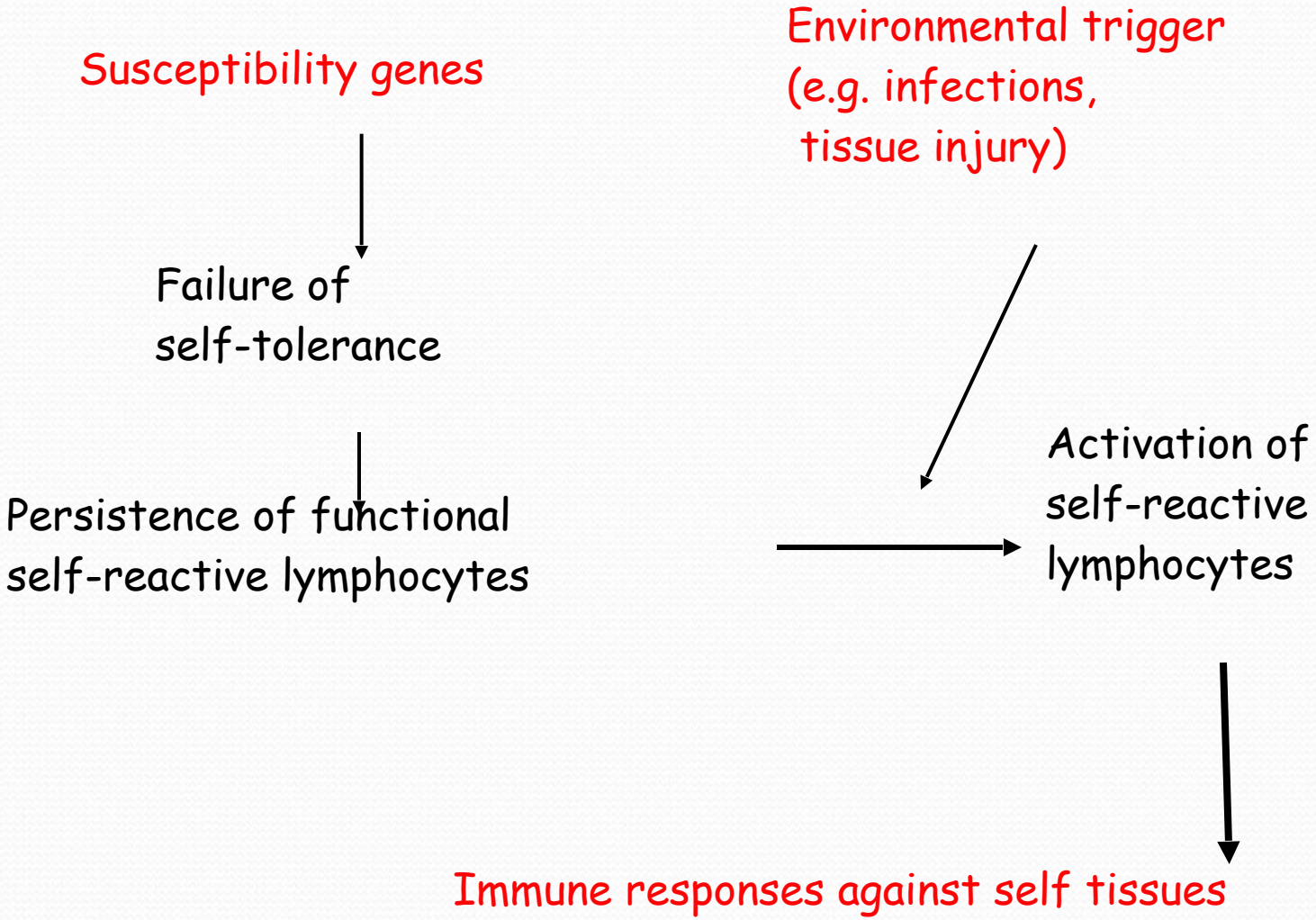


Example of systemic Autoimmunity

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
- Examples:
- NOD2: polymorphism associated with ~25% of Crohn's disease
- PTPN22: polymorphism in RA,SLE

2. Environment

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

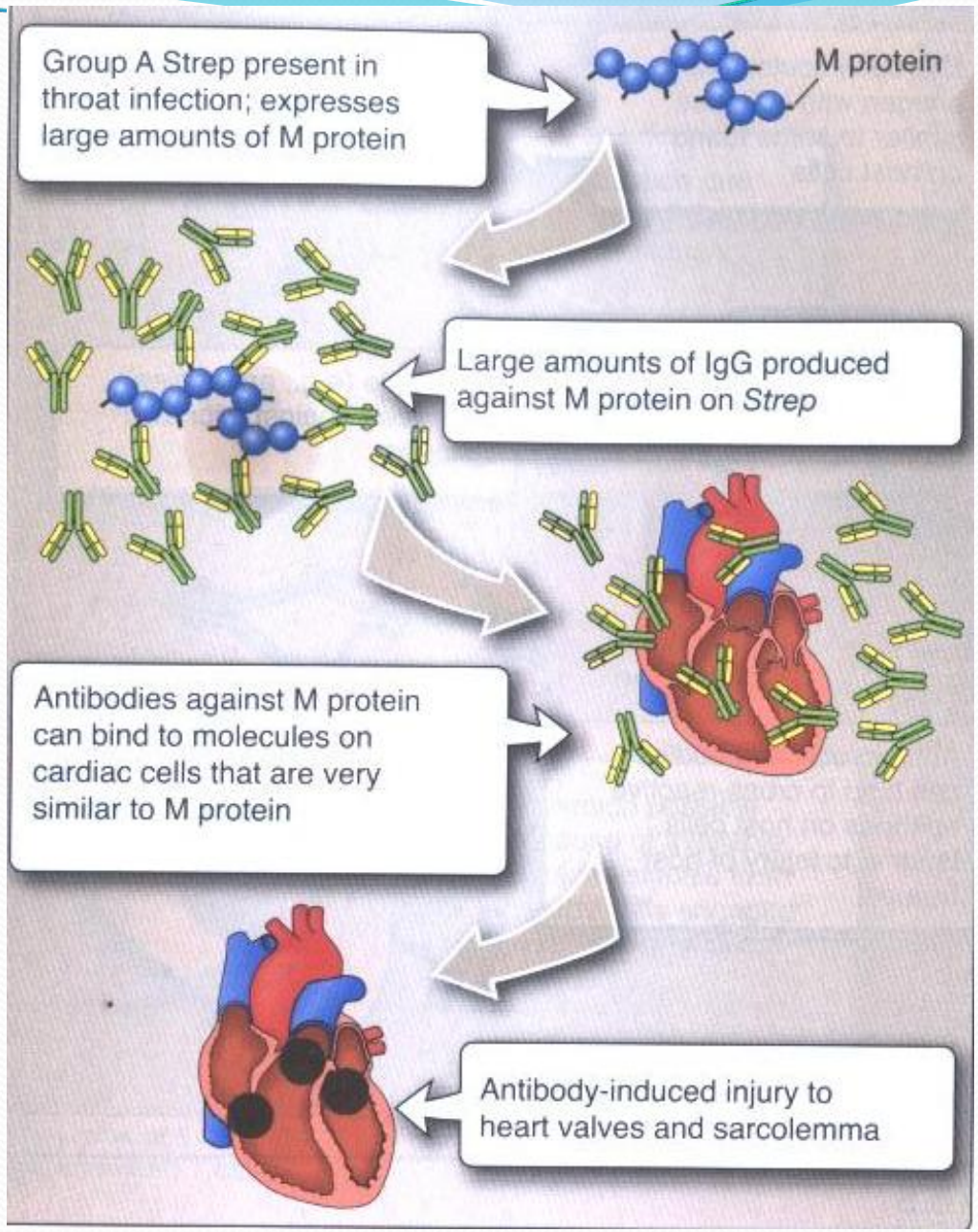
1. Drugs: Drug induced lupus
2. Toxins: Toxic Oil Syndrome
   - Occurred in Spain in 1981 after people ate contaminated olive oil
   - People developed unique illness marked by lung disease, eosinophilia, and excessive IgE
3. Hormones: Females are much more likely to develop autoimmune illness
   - Hypothesis: 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)

- Some autoimmune diseases are prevented by infections (type 1 diabetes, multiple sclerosis, others? -- increasing incidence in developed countries): mechanism unknown
  - The "hygiene hypothesis"

Rheumatic fever is a classic example of molecular mimicry



Pathophysiology of Immune-mediated diseases

- The nature of the disease is determined by the type of dominant immune response
  - Th1 response: inflammation, autoantibody production; autoimmune diseases
  - Th2 response: IgE+eosinophil-mediated inflammation; allergic reactions
  - Th17 response: acute or chronic inflammation; increasingly recognized in immune-mediated diseases

1. Hashemot's thyroditis

- Individual produce autoantibodies and sensitize Th1 cells specific for thyroid antigen
- Antibodies re 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 syndrom

- 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 attache 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