Kazan (Volga region) Federal University
Institute of Fundamental Medicine and Biology
Department of Morphology and General Pathology

AUTOIMMUNE DISEASES

Lecturer
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Immunologic tolerance

is unresponsiveness to an antigen that is induced by exposure of specific lymphocytes to that antigen

***Central tolerance*:** Immature lymphocytes that recognize self antigens in the central (generative) lymphoid organs are killed by apoptosis; in the B cell lineage, some of the self-reactive lymphocytes switch to new antigen receptors that are not self-reactive.

***Peripheral tolerance*:** Mature lymphocytes that recognize self antigens in peripheral tissues become functionally inactive (anergic), or are suppressed by regulatory T lymphocytes, or die by apoptosis.

Immunologic tolerance

The *factors that lead to a failure of self-tolerance and the development of autoimmunity* include:

1) inheritance of susceptibility genes that may disrupt different tolerance pathways

2) infections and tissue alterations that may expose self-antigens and activate APCs and lymphocytes in the tissues.

Autoimmunity

- Specific adaptive immune response mounted against a self-antigen

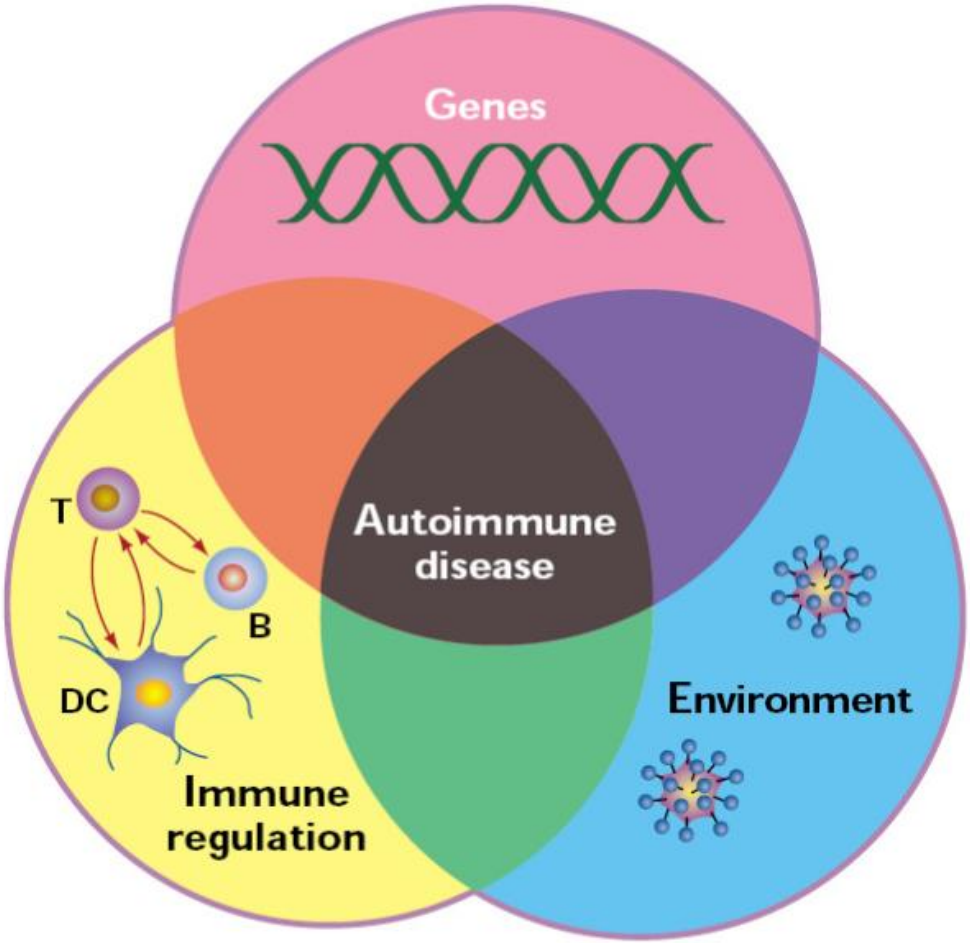
- Loss of Self-tolerance to self-antigens
  - *Loss of central and peripheral tolerance*

- Loss of central tolerance likely occurs all the time
  - *May have a physiological role to clear defective or denatured molecules through the RE system*
  - *Normally kept in check by mechanisms of peripheral tolerance*

- May be triggered by infections or aging

- May or may not cause disease

Autoimmune Disease



Genetic Predisposition

↓

Initiation

↓

Perpetuation and Progression

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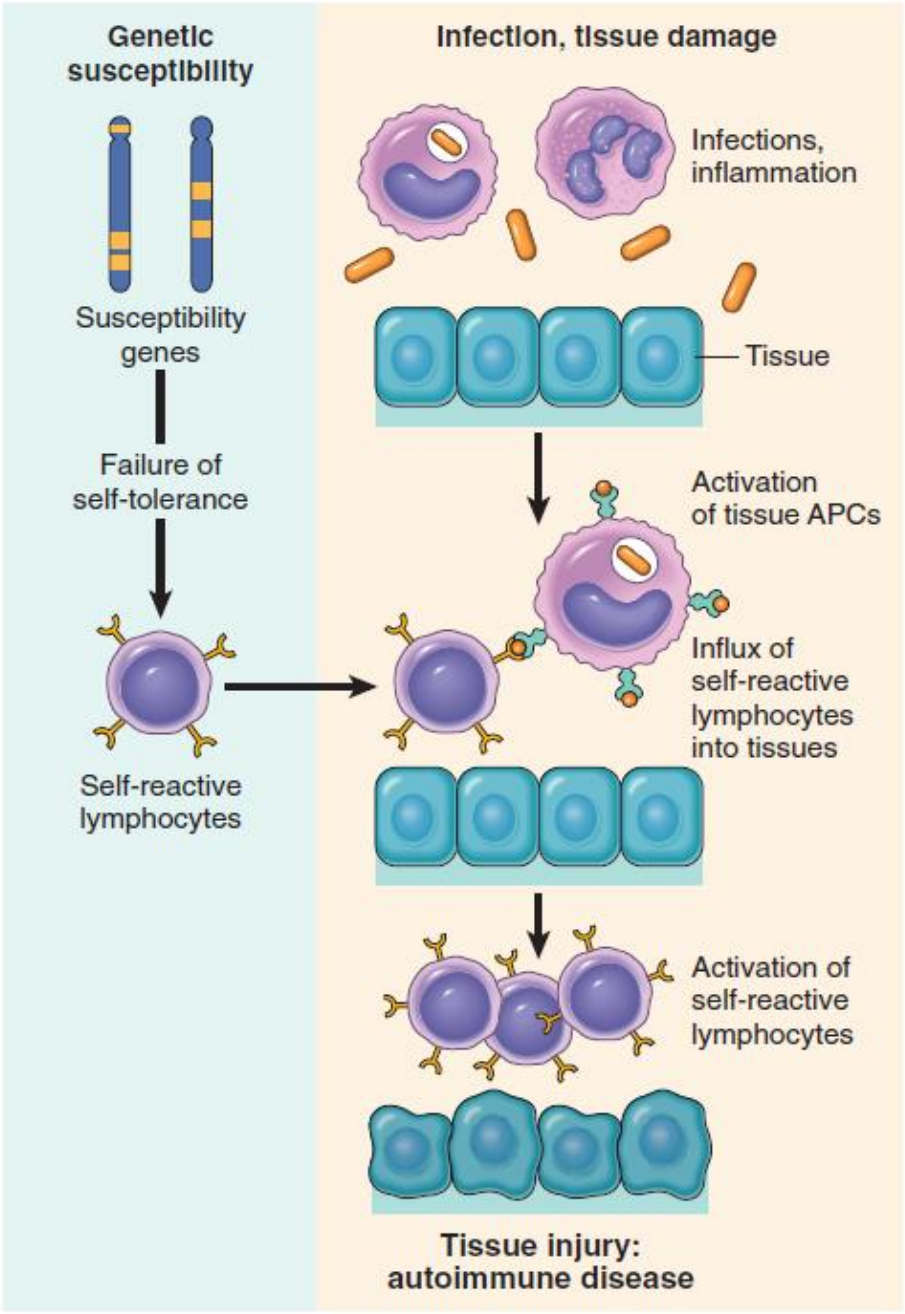
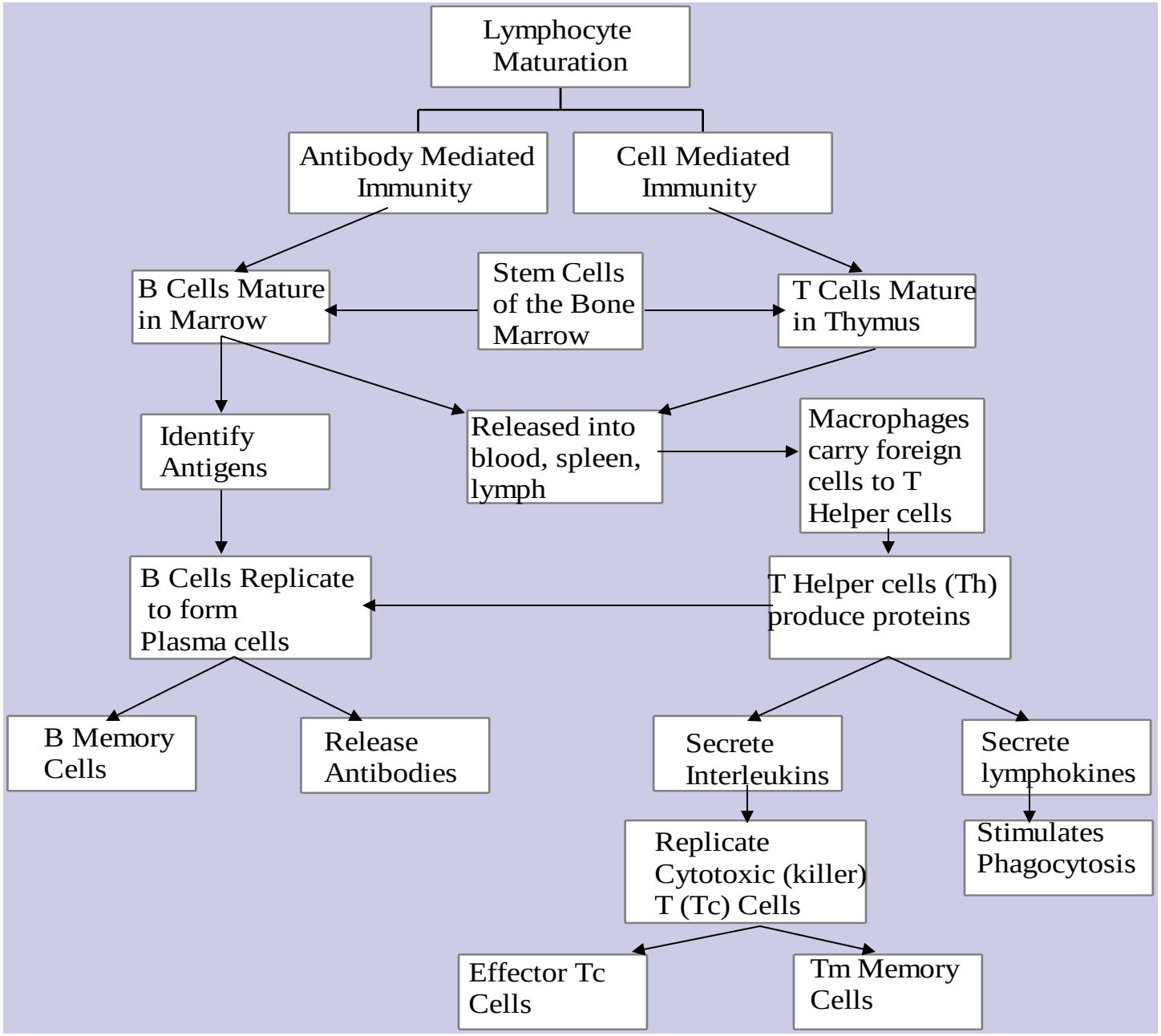
Clinical Disease

J Ermann et al. Nature Immunology 2001

AUTOIMMUNE DISEASE	CLINCAL PHENOTYPE
Systemic Lupus Erythematosus	Rash; inflammation of joints and serosal linings; glomerulonephritis; hemolytic anemia, systemic symptoms
Rheumatoid Arthritis	Inflammation of synovium of diarthroidal joints, systemic inflammation
Scleroderma	Inflammation, dermal fibrosis, internal organ fibrosis, vasculopathy
Ankylosing Spondylitis	Inflammation of spine, joints, and tendon insertions; uveitis
Multiple Sclerosis	Demyelination, optic neuritis, neurological deficits
Myasthenia Gravis	Skeletal muscle weakness, diplopia, dysarthria, dysphagia
Hashimoto's Thyroiditis	Hypothyroidism
Graves Disease	Hyperthyroidism, opthalmopathy
Celiac Disease	Diarrhea and malabsoprtion
Autoimmune hemolytic anemia	Anemia through lysis of red blood cells
Type I diabetes	Failure of insulin production and glycemic control


Genetic susceptibility
Infection, tissue damage
Susceptibility genes
Failure of self-tolerance
Self-reactive lymphocytes
Infections, inflammation
Tissue
Activation of tissue APCs
Influx of self-reactive lymphocytes into tissues
Activation of self-reactive lymphocytes
Tissue injury: autoimmune disease


Lymphocyte Maturation
Antibody Mediated Immunity
Cell Mediated Immunity
B Cells Mature in Marrow
Stem Cells of the Bone Marrow
T Cells Mature in Thymus
Identify Antigens
Released into blood, spleen, lymph
Macrophages carry foreign cells to T Helper cells
B Cells Replicate to form Plasma cells
T Helper cells (Th) produce proteins
B Memory Cells
Release Antibodies
Secrete Interleukins
Secrete lymphokines
Replicate Cytotoxic (killer) T (Tc) Cells
Stimulates Phagocytosis
Effector Tc Cells
Tm Memory Cells

Immune Deficiencies

- **Inherited:**
  - **Cellular** - when the defective gene is only in T cells;
  - **Humoral** - when the defective gene is only in B cells;
  - **Combined** - when the defect is in a gene common to all lymphocytes, e.g., RAGs (recombination activation genes).
- **Acquired** - due to:
  - Hemopoietic **diseases**;
  - **Treatments**: chemotherapy, irradiation;
  - **Infection**: **AIDS** - caused by the Human Immunodeficiency Virus (**HIV**) which attacks helper T cells. The virus gradually kills more T cells than the body can produce, the immune system fails, and the patient dies from infections that are normally not dangerous.

Immune Hypersensitivity

- **Hypersensitivity** is an improperly strong response.
- **Immediate** hypersensitivity:
  - Mediated by **antibodies**.
  - Types:
    - allergy - up to anaphylactic shock.
    - Induction of antibody-mediated cytotoxicity.
    - Sickness due to accumulation of immune complexes.
- **Delayed** hypersensitivity:
  - Mediated by **T cells.**
  - Hyper-activity of CTLs and macrophages.
  - Contact sensitivity.

Autoimmune diseases

- Normally, the immune system **does not attack the self**.
- This is ensured by **elimination of auto-reactive lymphocytes** during their development (**negative selection**).
- However, there is a large group of diseases in which the immune system does attack self-cells: **autoimmune diseases**.
- The attack can be either **humoral (by auto-antibodies)** or **cellular (by auto-reactive T cells).**
- The attack can be directed either against a very **specific** tissue, or to a large number of tissues (**systemic** autoimmune disease), depending on the self-antigen which is attacked.

Autoimmune diseases

- **Specific:**
  - **Juvenile diabetes** (attacks insulin-producing cells)
  - **Multiple sclerosis** (attacks myelin coating of nerve axons)
  - **Myasthenia gravis** (attacks nerve-muscle junction)
  - **Thyroiditis** (attacks the thyroid)
  - …
- **Systemic:** Immune complexes accumulate in many tissues and cause inflammation and damage.
  - **Systemic Lupus Erythematosus** (anti-nuclear antibodies): harms kidneys, heart, brain, lungs, skin…
  - **Rheumatoid Arthritis** (anti-IgG antibodies): joints, hearts, lungs, nervous system…
  - **Rheumatic fever**: cross-reaction between antibodies to streptococcus and auto-antibodies.

What could cause the immune system to attack the self?

- **Changes in self-antigens**, that make them look like non-self to the immune system, due to:
  - Viral or bacterial infection
  - Irradiation
  - Medication
  - Smoking …
- **Changes in the immune system**:
  - Normal auto-antibodies exist; mutations in B cells producing them may create pathogenic auto-antibodies.
  - Problems with control of lymphocyte development and differentiation.

Transplant Rejection

- The T lymphocyte repertoire is selected to **tolerate** cells expressing **self-MHC-I + self-peptide** complexes, and **attack non-self (altered)** complexes.
- **Normally,** altered complexes would be the result of infection or transformation of the cell expressing the MHC, that is, the **peptide will be non-self**.
- However, transplantation of tissues from a **non-MHC-matched donor** will present to the immune system a **non-self-MHC** (with self-peptides, usually).
- The immune system will react vigorously against this “altered self”.
- **Prevention:** finding a matched donor or immune suppression.

Failure to detect Cancer cells

- Cancer is uncontrolled proliferation of self-cells. Cancer cells have lost the mechanisms of cell cycle control, dependence on resources or cell density, etc. Later on, some of the tumor cells may migrate to other body sites (metastasis).
- **Transformation** from normal to cancerous cells involves many genetic, biochemical, metabolic **changes in the cells.**
- The **immune system** sometimes recognizes these changes and regards the transformed cells as **" altered self "** to be attacked.
- When will the immune system fight cancer:
  - **When it's different enough from self,**
  - **When the quantity of non-self cells is large enough,**
  - **When the system functions well, and is not suppressed.**

Development of Autoimmune Disease

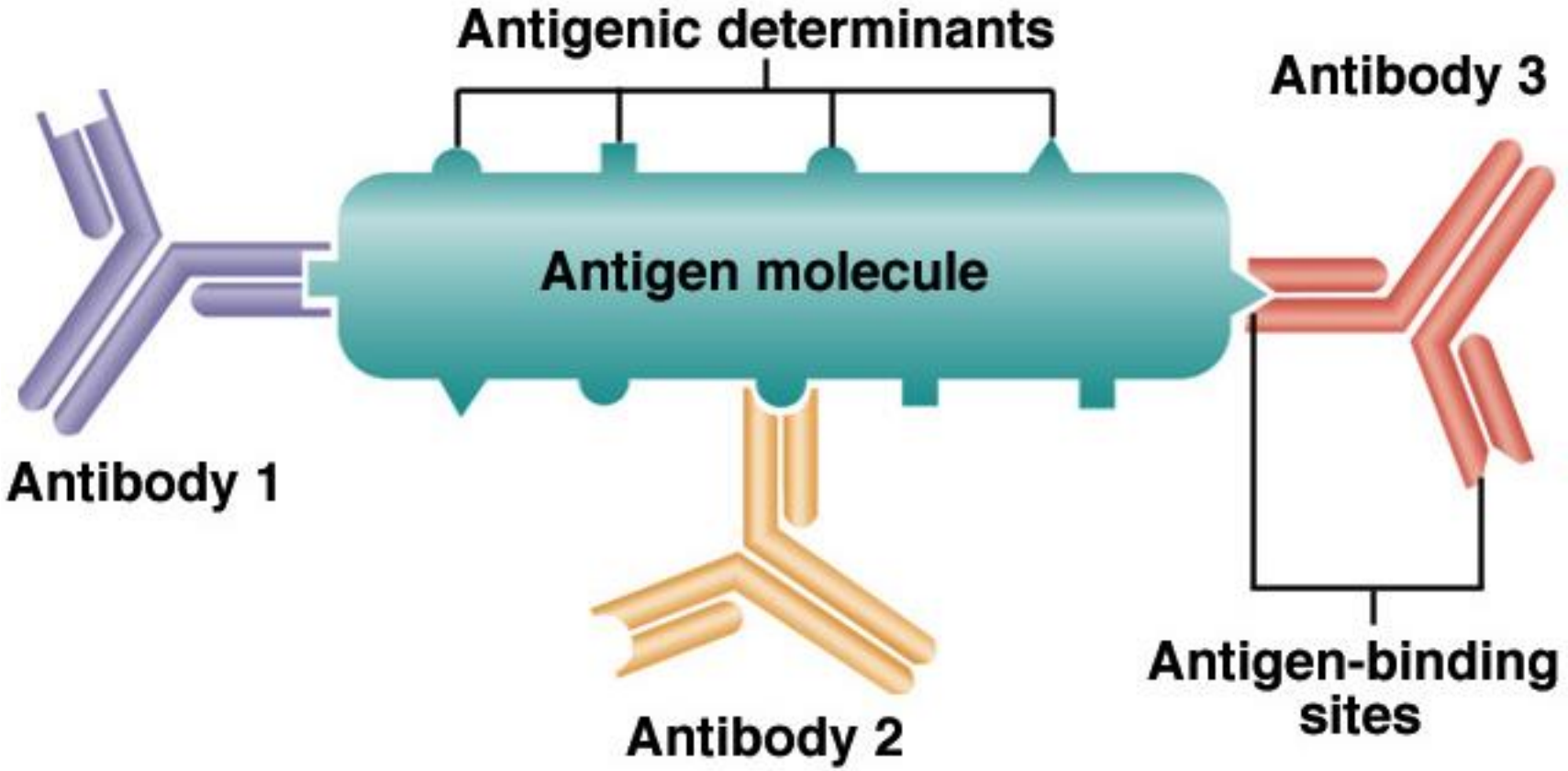
- Autoimmune disease occurs as a result of breakdown in tolerance to self
- Autoimmune disease is characterized by immune system "attack" against self antigens that lead to tissue damage
  – Inflammation and hypersensitivity reactions
- Mediated by B-lymphocytes that produce antibodies to self antigens

  And / or
- T-lymphocytes with T-cell receptors that recognize selfantigens
  – Autoreactive CD4 Th and autoreactive CD8 cytotoxic T cells

Mechanisms of tissue injury

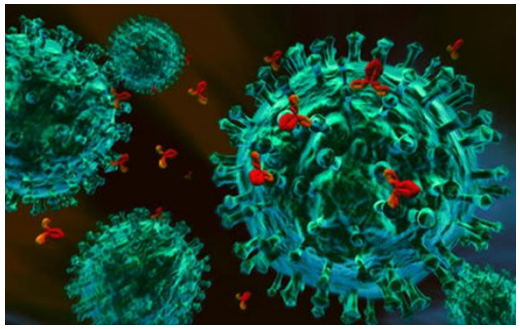
- Auto-antibodies circulating in blood or at site of tissue injury
- Autoreactive B and T cells in blood and at site of tissue injury
- Hypersensitivity reactions occurring at sites of tissue injury
- Histology- chronic inflammation
- Pathway for cell death- apoptosis

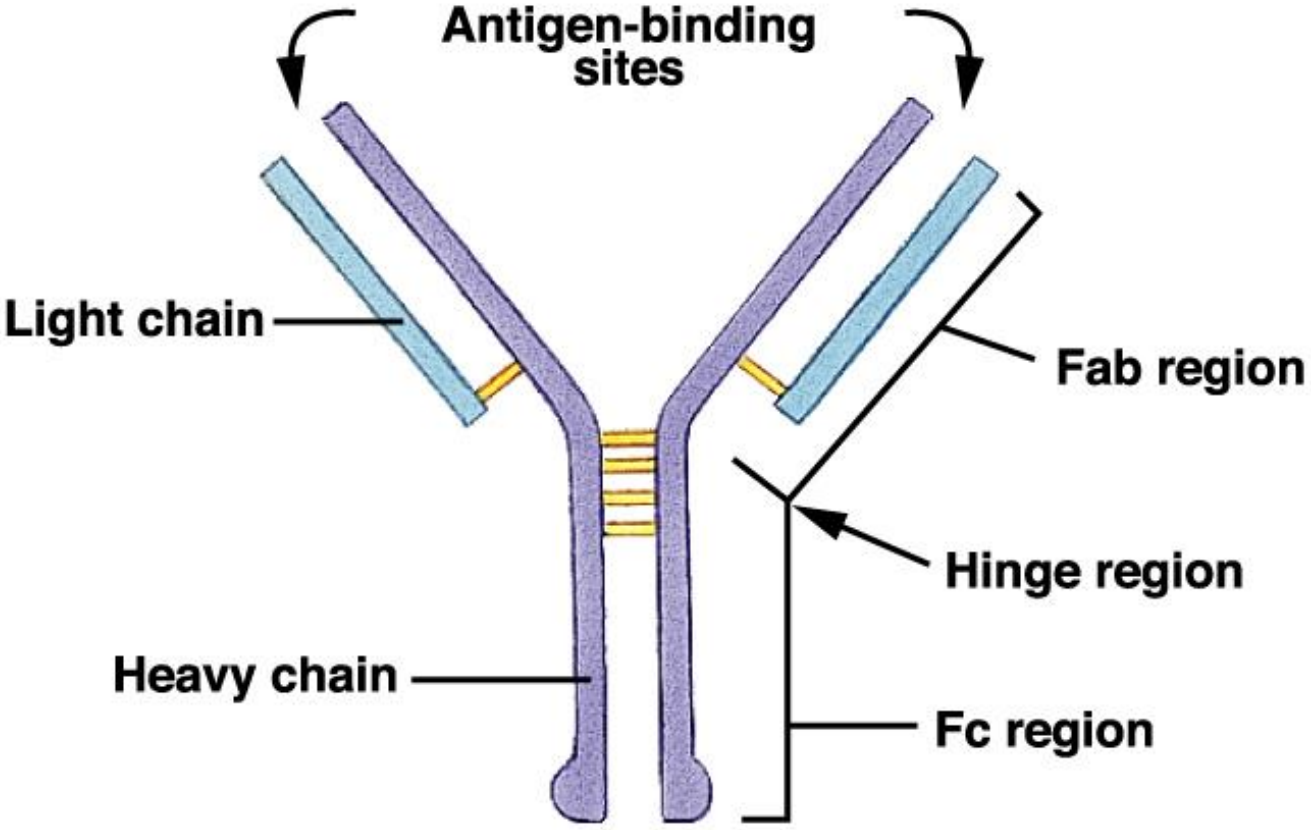
Antigenic Determinants

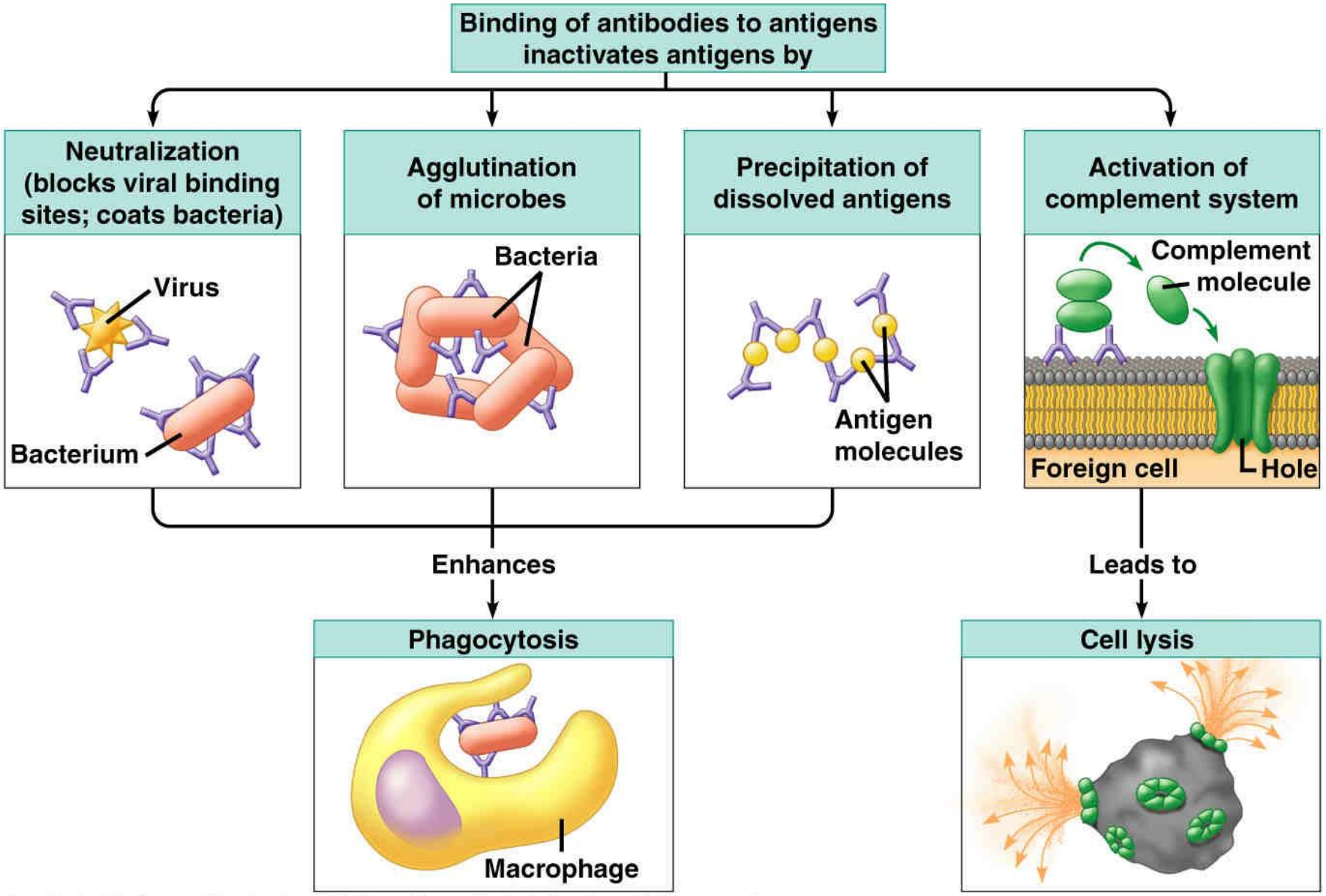


- The antibody is 4 polypeptides forming a Y-shaped structure.
- Each side of the Y is composed of one light chain and 1 heavy chain.
- The 2 arms (Fab regions) contain antigen binding sites.
- The stem of the Y is the Fc region.

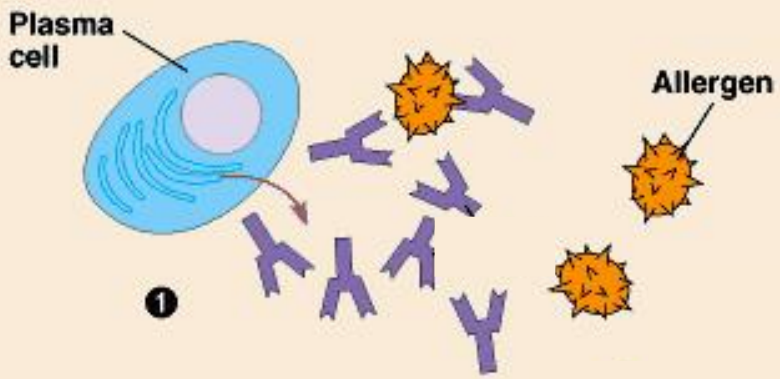
Antibody Structure





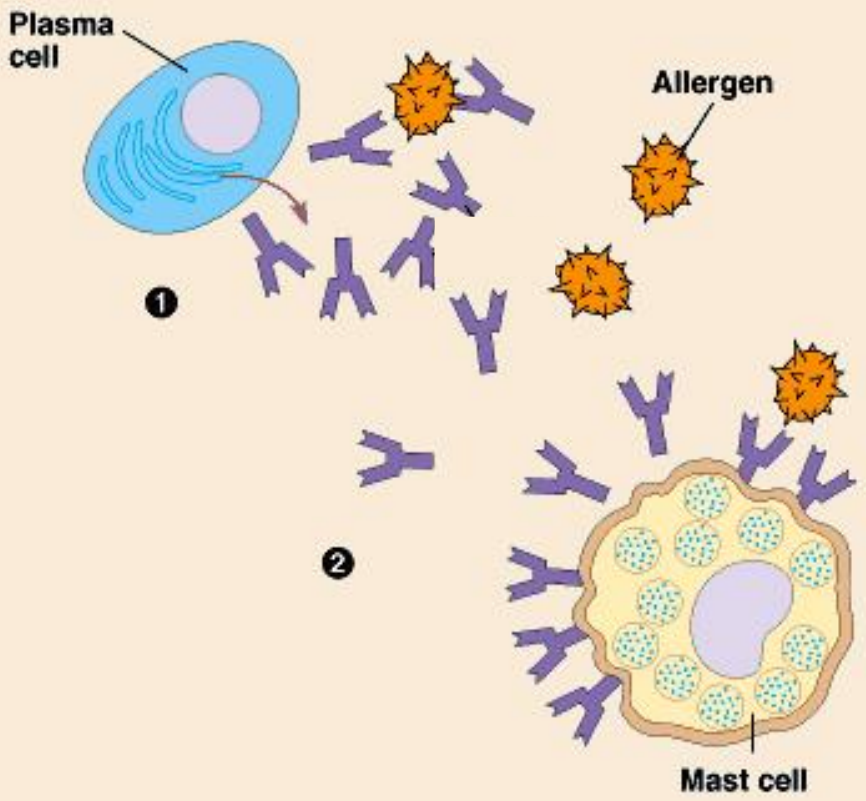


What happens when the immune system malfunctions?



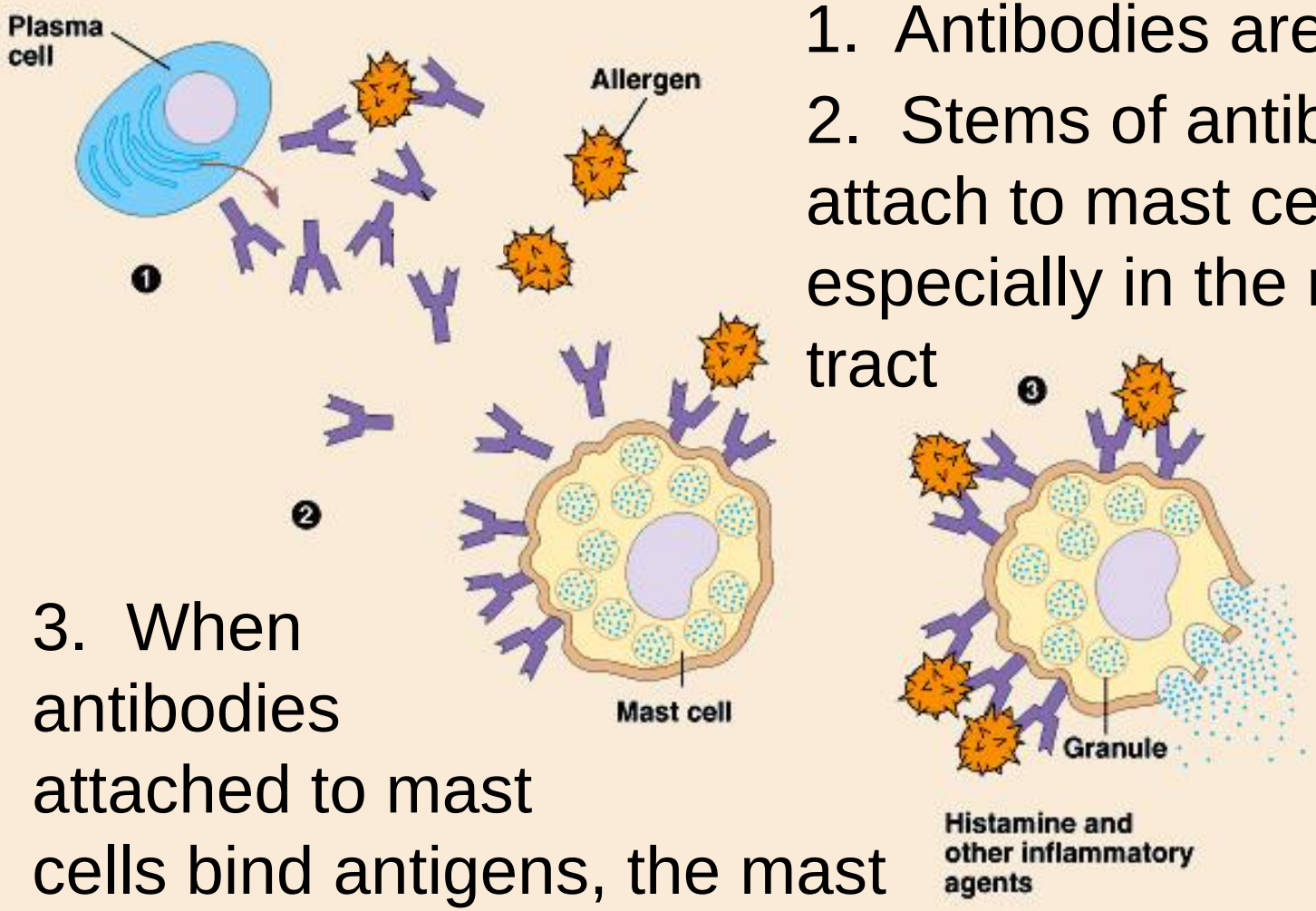
1. Antibodies are produced

What happens when the immune system malfunctions?



1. Antibodies are produced
2. Stems of antibodies attach to mast cells, especially in the respiratory tract

What happens when the immune system malfunctions?



1. Antibodies are produced
2. Stems of antibodies attach to mast cells, especially in the respiratory tract
3. When antibodies attached to mast cells bind antigens, the mast cells release histamine, which causes inflammation

What happens when the immune system malfunctions?

Autoimmune diseases

The immune system lacks or loses its ability to distinguish self vs. non-self molecules, *i.e*., it loses its self-tolerance and produces anti-self antibodies

- Rheumatoid arthritis (cartilage of joints)
- Multiple sclerosis (mylein sheaths of neurons)
- Insulin-dependent diabetes mellitus (insulin-secreting cells of the pancreas)

What happens when the immune system malfunctions?

Immunodeficiency diseases

Inhibit effective immune response; either inherited or acquired

Severe Combined Immunodeficiency (SCID)

An inherited disorder

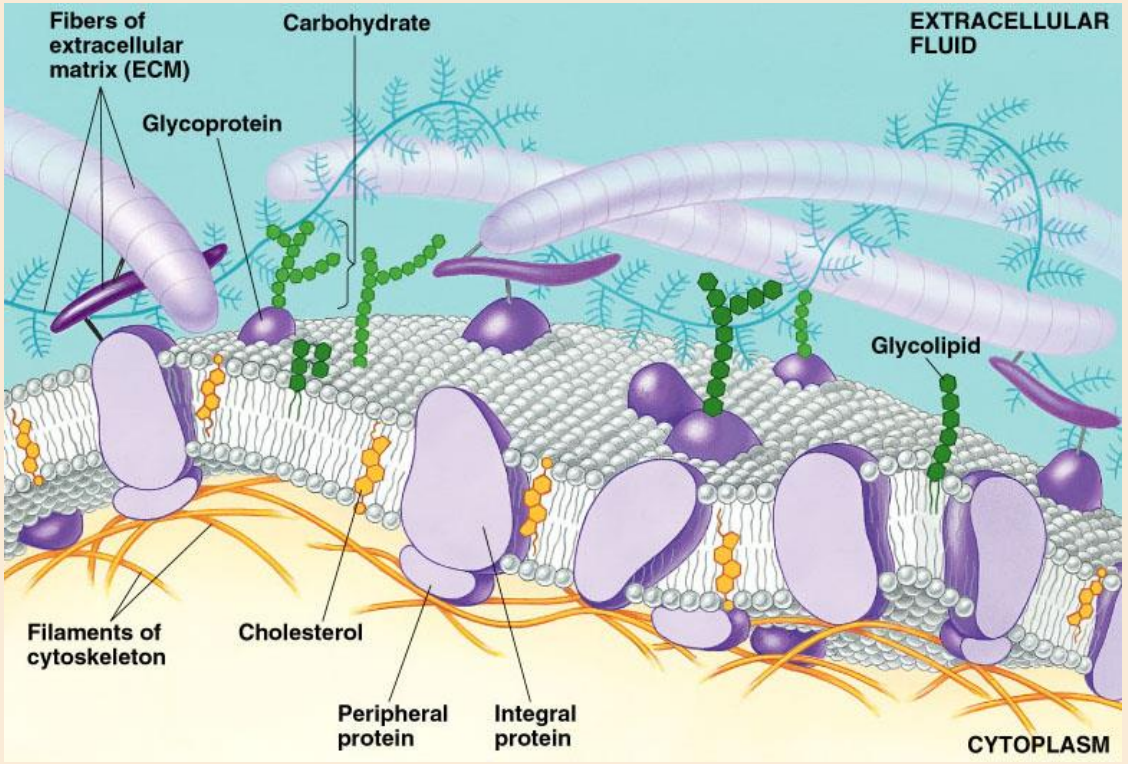
Acquired Immunodeficiency Syndrome (AIDS)

Caused by retroviruses (Human Immunodeficiency Viruses – HIV) that especially infect helper T cells

RECOGNITION

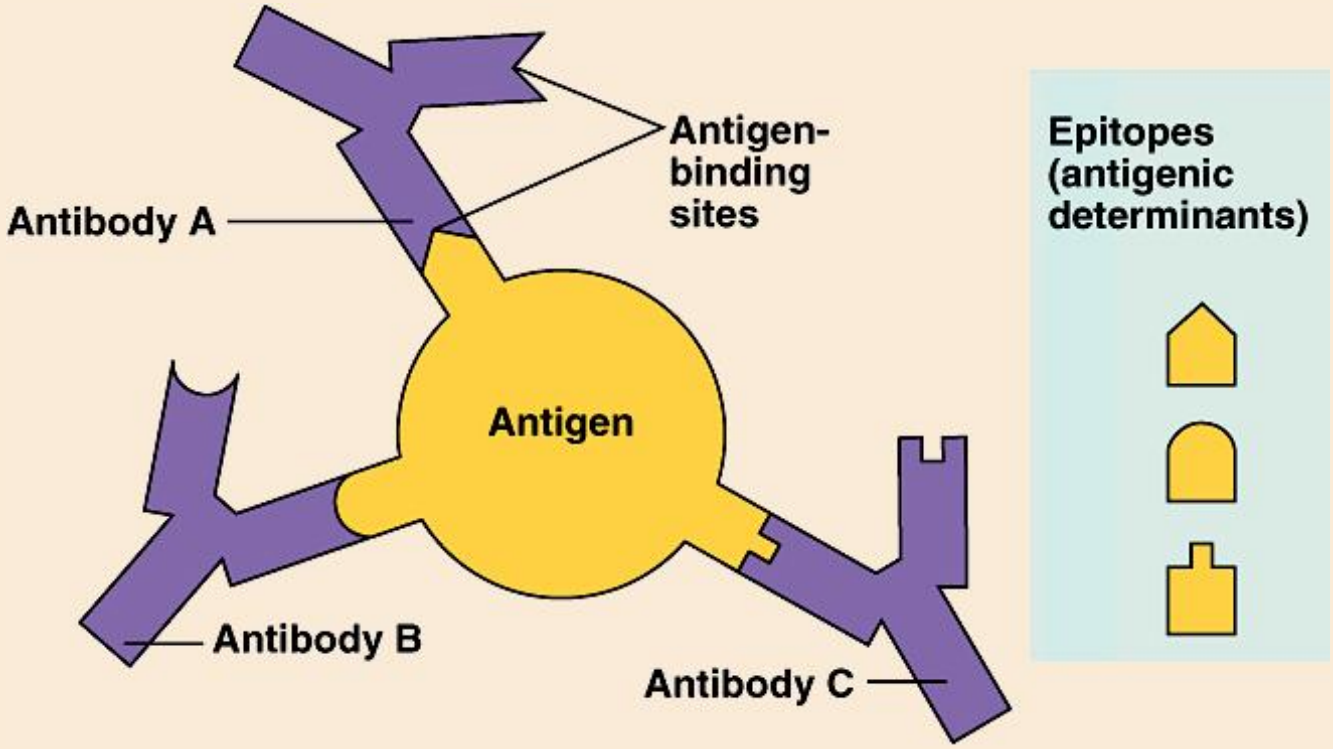
Lymphocytes recognize and respond to particular microbes and foreign molecules, *i.e.*, they display specificity

A foreign molecule that induces an immune response is known as an antigen



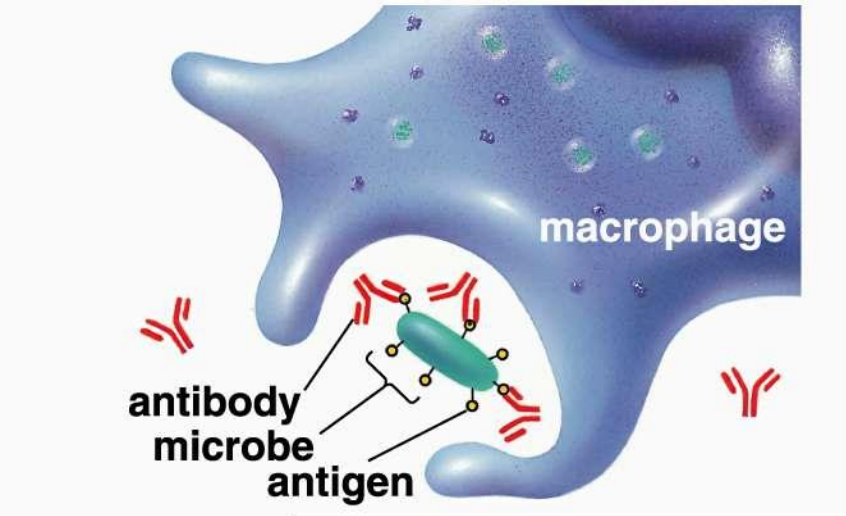
RECOGNITION

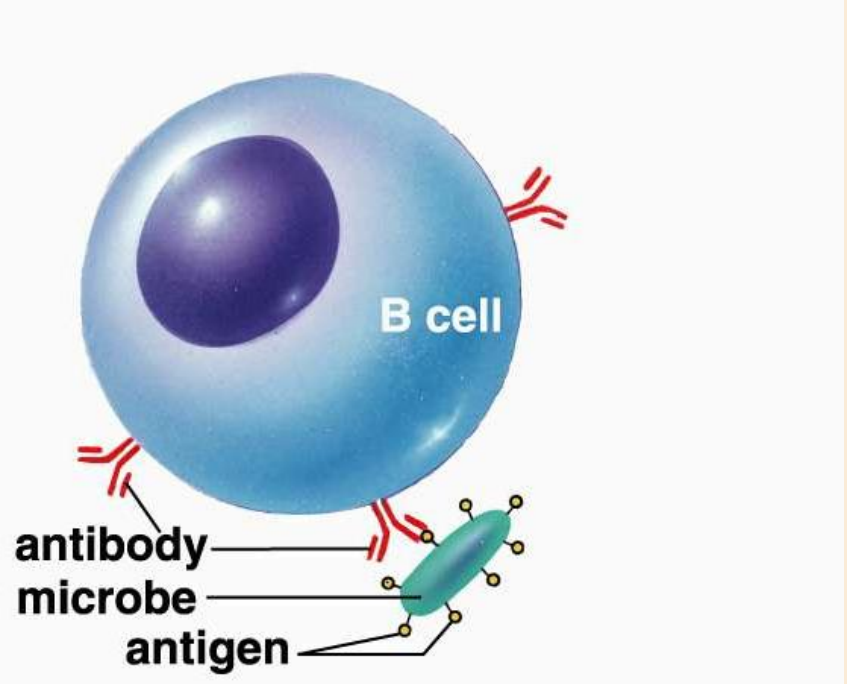
Multiple antibodies may recognize the same antigen by different epitopes (small accessible portions of the larger molecule)



RECOGNITION

B cells produce antibodies, that are either secreted out of the cells or remain embedded in the B cell membranes, and that bind to antigens

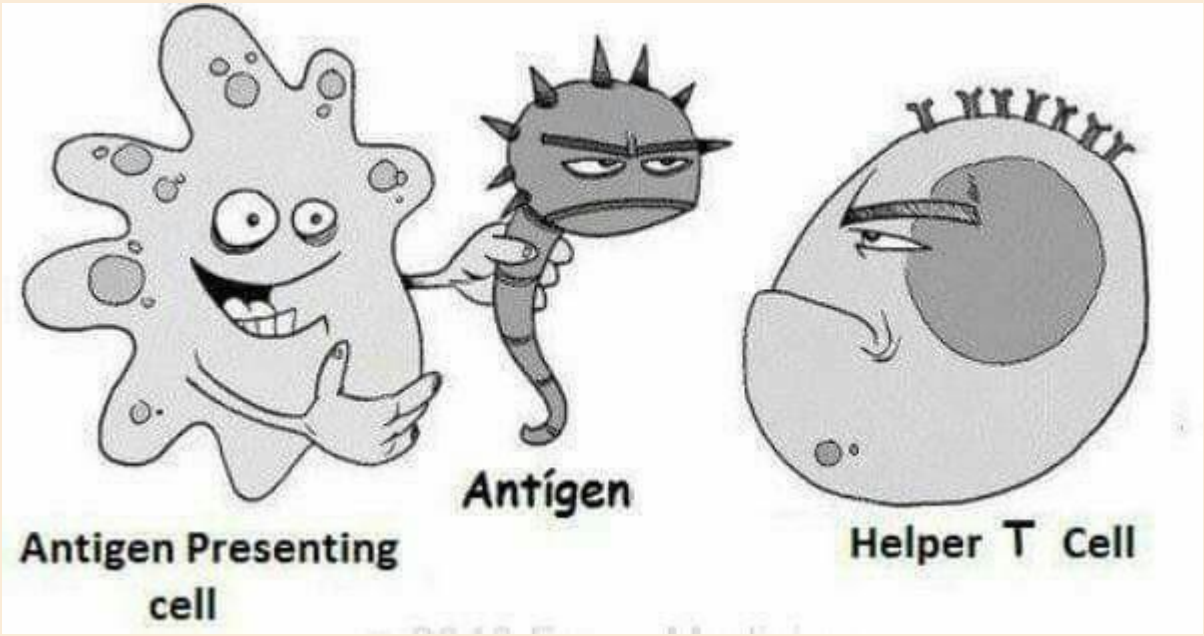




RECOGNITION

B cells produce antibodies, that are either secreted out of the cells or remain embedded in the B cell membranes, and that bind to antigens

T cells have T-cell receptors, embedded in their cell membranes, that bind to antigens



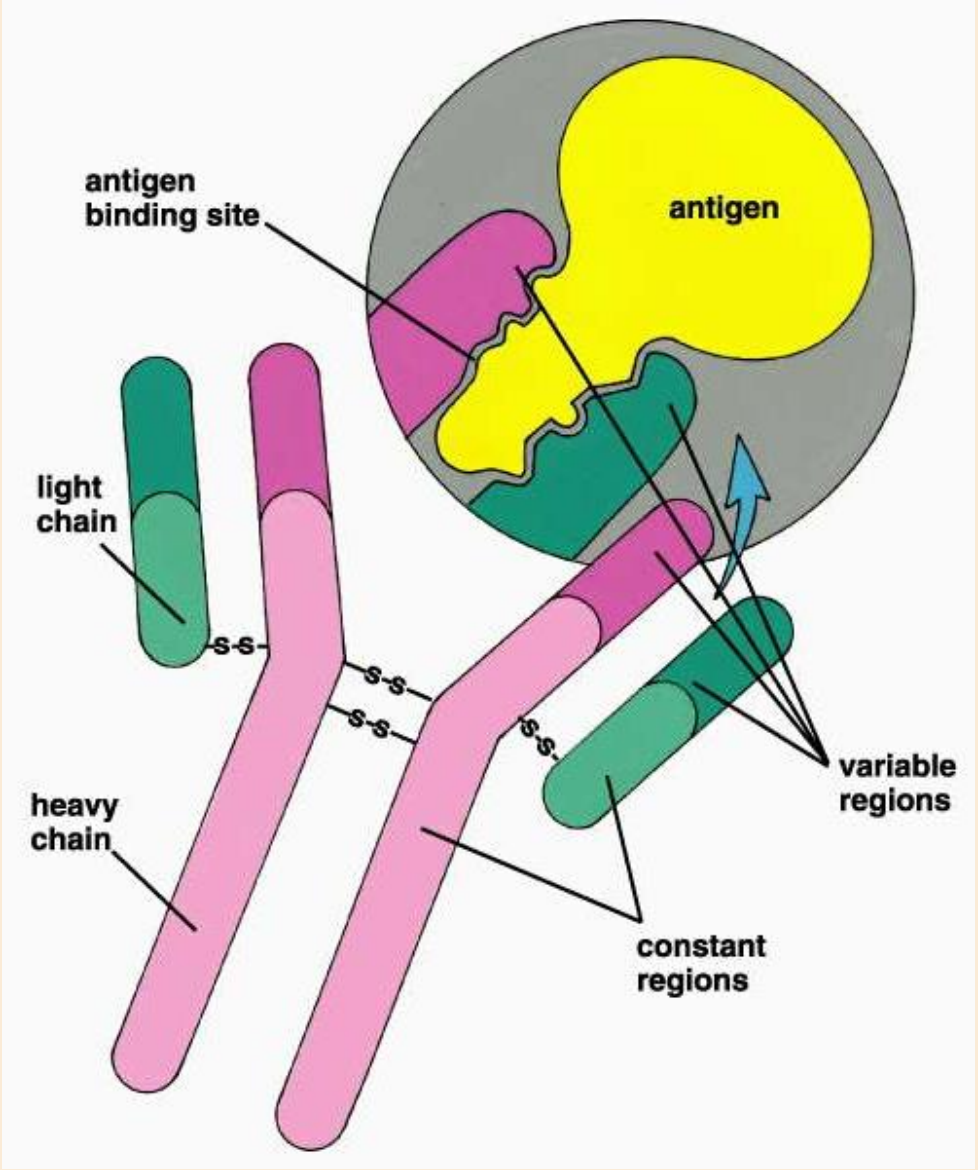
RECOGNITION

Secreted antibodies constitute a group of proteins called immunoglobulins

Antibodies have 2 heavy chain and 2 light chain subunits

Each subunit has a constant region and a variable region

The variable region can bind to an antigen



RECOGNITION of non-self molecules

Construction of antibodies
(and T-cell receptors)

Millions of antigens are recognized by randomly combining the protein products of hundreds of genes

Card analogy: although there are only 52 cards in the deck, random combinations can produce an enormous number of different hands

RECOGNITION of self molecules

In a healthy immune system, as B and T cells mature they are destroyed by apoptosis if they attack self molecules

Healthy, mature B and T cells then have the capacity to distinguish self from non-self molecules

RECOGNITION of self molecules

Almost all cells in an individual human's body have major histocompatibility complex (MHC) glycoproteins embedded in their cell membranes

Class I MHC molecules are found on almost every nucleated cell

Class II MHC molecules are restricted to a few specialized cells, including macrophages, dendritic cells, B cells, *etc*.

RECOGNITION of self molecules

MHC glycoproteins migrate to the cell membrane after they are produced

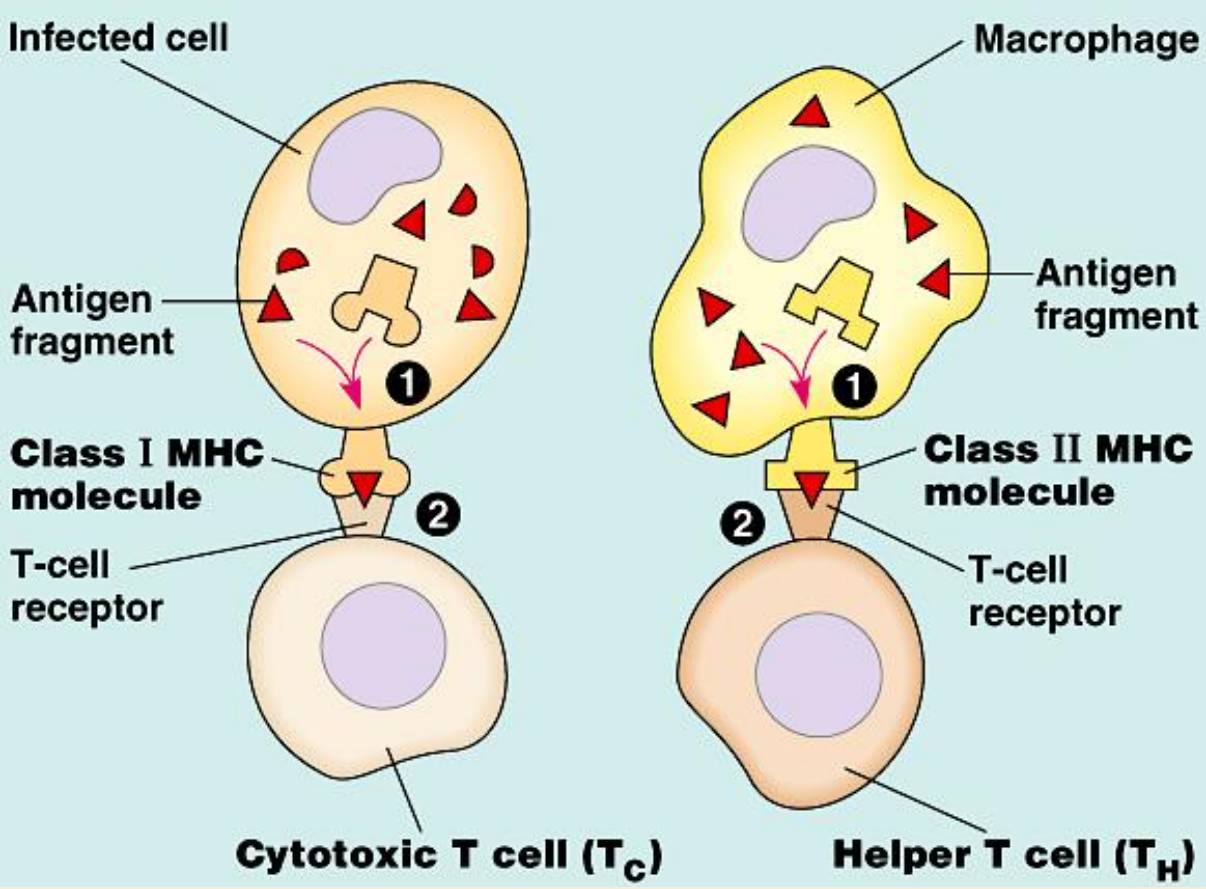
MHC glycoproteins pick up molecules from the cytosol that are presented at the cell's surface

T cells bind to MHC glycoproteins and the molecules they present

An individual's own MHC glycoproteins, and molecules of its own body that the MHC glycoproteins present, are treated as self

RECOGNITION of non-self molecules

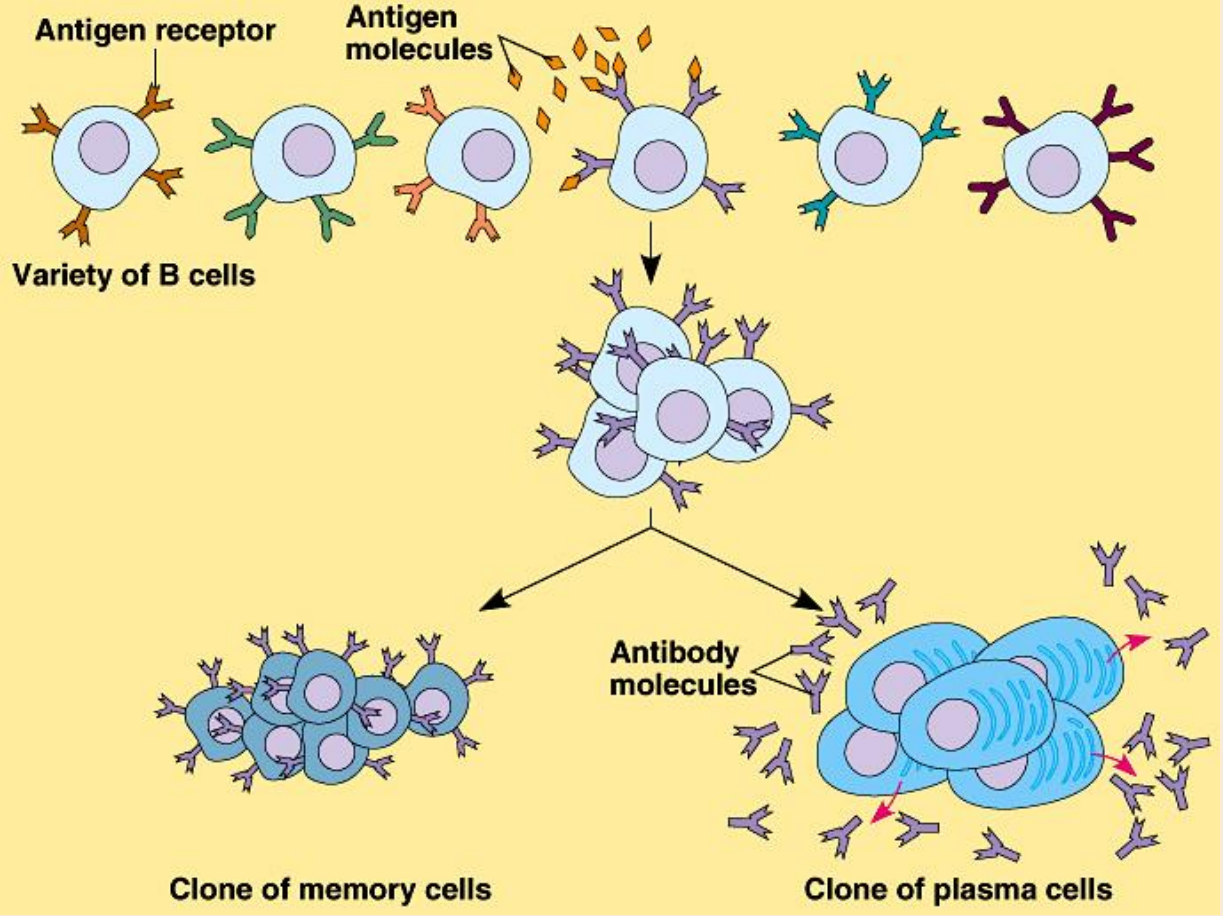
Helper T cells bind to cells that carry Class II MHC glycoproteins



ATTACK & MEMORY

The B and T cells that first recognize a given foreign antigen are short lived, whereas immune memory cells can have long lifetimes

Illustrated here for B cells, but the process for T cells is similar



TYPES OF HYPERSENSITIVITY

- Type II
  - Autoimmune hemolytic anemias
  - Anti-insulin receptor antibody (insulin-dependent diabetes mellitus)
- Type III
  - Systemic lupus erythematosus (SLE)
  - Rheumatoid arthritis

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- Chronic systemic autoimmune disease
- Cause unknown
- Affects almost any organ(s)
- Characterized by chronic inflammation
- Immunologically, the disease is associated with an enormous array of autoantibodies, classically including antinuclear antibodies (ANAs).

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- Auto-antibodies formed against variety of self antigens
- Anti-double stranded DNA,RNA and histones
- Antibodies against cell surface antigens on RBC’s and/or platelets
- Tissue damage caused by Type III hypersensitivity reactions
- Immune circulating complexes formed against self deposit on tissues
- Vasculitis, synovitis, glomerulonephritis

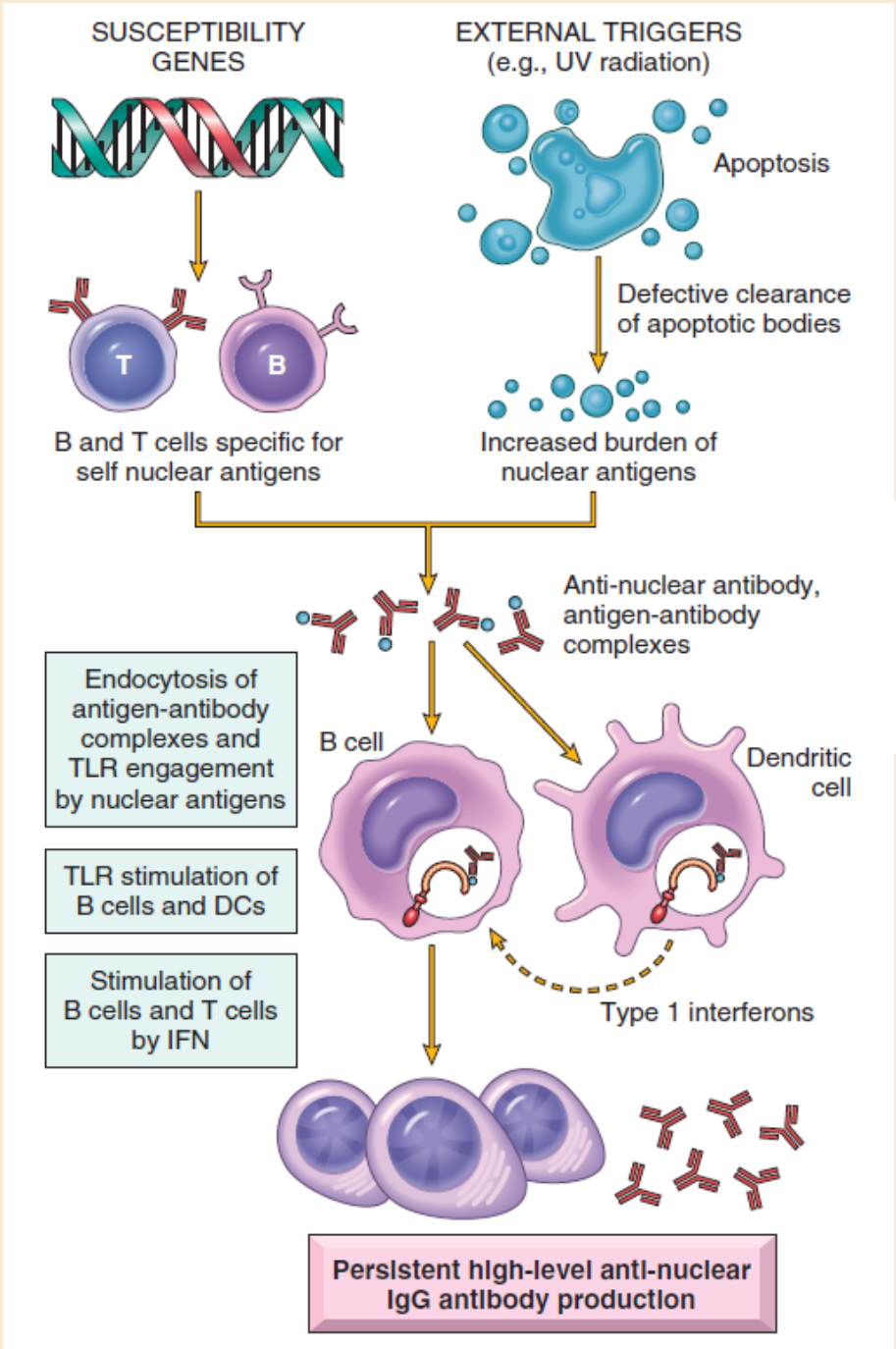


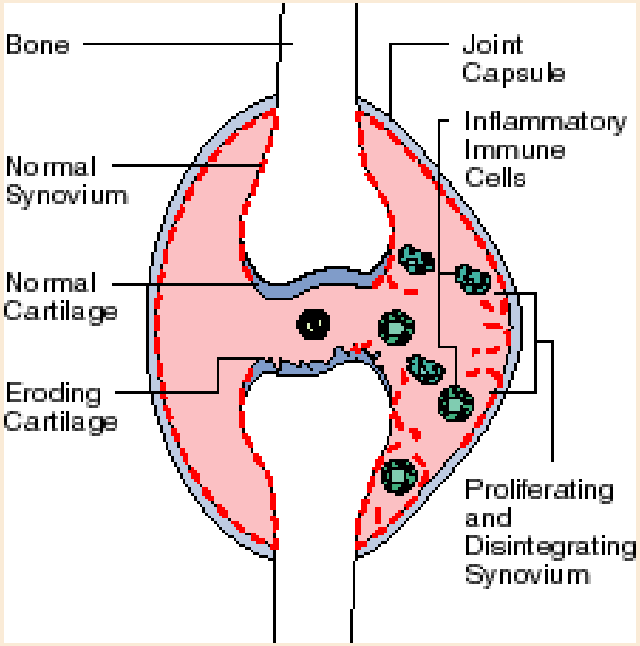
Figure 4–17 Model for the pathogenesis of systemic lupus erythematosus. Genetic susceptibility and exposure result in failure of self-tolerance and persistence of nuclear antigens. Autoantibodies serve to internalize nuclear components, which engage TLRs and stimulate IFN production. IFN may stimulate B and T cell responses to the nuclear antigens. IFN, interferon; IgG, immunoglobulin G; MHC, major histocompatibility complex; TLRs, Toll-like receptors; UV, ultraviolet.

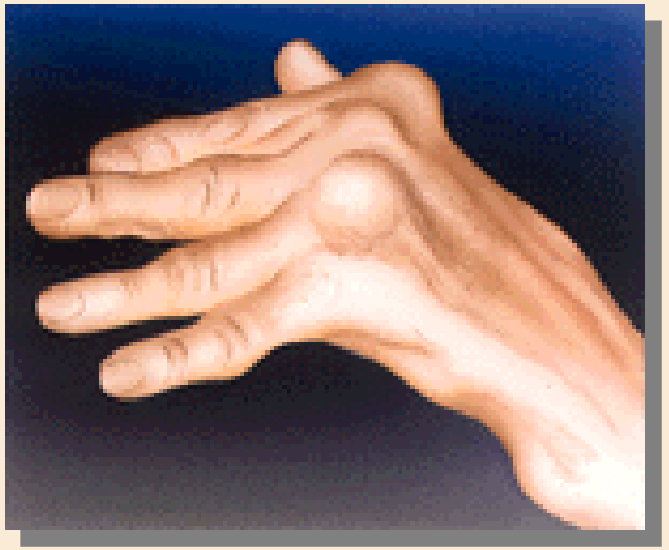
Rheumatoid Arthritis

- Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease affecting many tissues but principally attacking the joints to produce a nonsuppurative proliferative synovitis that frequently progresses to destroy articular cartilage and underlying bone with resulting disabling arthritis.
- Genetic factors (HLA-DR1, HLA-DR4) Autoreactive B-cells synthesize auto antibody against Fc portion of IgG
- Rheumatoid factor (RF)
- Chronic inflammation of synovial joints
- Proliferation of synovial lining cells
- Erosion of articular cartilage and adjacent bone

Rheumatoid arthritis (RA) affects peripheral joints and may cause destruction of both cartilage and bone. The disease affects mainly individuals carrying the **DR4** variant of MHC genes.

This fact can lead to better prognoses and in aiding efforts to change immune reactions that involve the DR4 variant while leaving other reactions intact.





Systemic Sclerosis (Scleroderma)

- *Systemic sclerosis (SS) is an immunologic disorder characterized by excessive fibrosis in multiple tissues, obliterative vascular disease, and evidence of autoimmunity, mainly the production of multiple autoantibodies.*
- *Fibrosis may be the result of activation of fibroblasts by cytokines produced by T cells, but what triggers T cell responses is unknown.*
- *Endothelial injury and microvascular disease are commonly present in the lesions of SS, causing chronic ischemia, but the pathogenesis of vascular injury is not known.*