

9 Oct 2023,
BT 304
Lecture 25

BT 304 Syllabus

Instructor: Manish Kumar

Properties and Overview of Immune Responses, Cells and Tissue of the immune system, Leukocyte migration into tissues, Antibodies and antigen. Innate Immunity: Major histocompatibility complex. Antigen processing and presentation to T lymphocyte. Antigen receptors gene rearrangement and lymphocyte development, Immune receptors and signal transduction, Activation of T lymphocytes.

Adaptive Immunity: Effector mechanisms, B cell activation and antibody production, Regional Immunity, Immune memory response. Immunologic Tolerance: Autoimmunity, Immunity to Microbes, Transplantation immunology, Tumor Immunology. Hypersensitivity: IgE dependent Immune response, Allergic disease, Congenital and acquired immune deficiencies.

18 -to- 24 Sept: Mid-Sem and 19 -to- 25 Nov: End-Sem

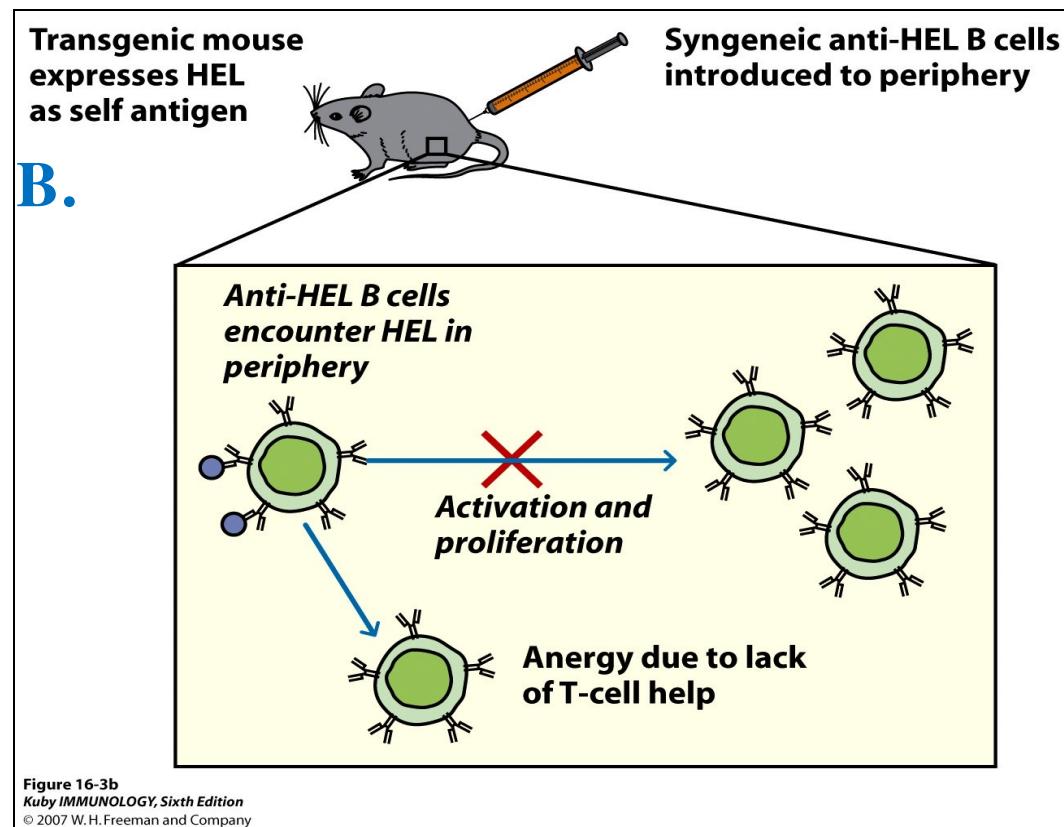
17 Nov : Last date of instruction

Text Books

1. Cellular and Molecular Immunology: 7th Updated Edition by **Abul K. Abbas**
Andrew H. Lichtman & Shiv Pillai
2. **Kuby Immunology**. 4th Edition by W. H. Freeman & Co., 2000.

Experimental evidence for central and peripheral tolerance

B. Mouse experiment demonstrating existence of peripheral tolerance



Peripheral tolerance occurs when, as a consequence of recognizing self antigens, mature lymphocytes become incapable of responding to that antigen, or are induced to die by apoptosis, or mature T cells are actively suppressed by regulatory T cells.

The word "sygenic" or "syngeneic" (from the Greek word for a relative) means genetically identical, or sufficiently identical and immunologically compatible as to allow for transplantation.

• Peripheral Tolerance

- May be induced by T_{reg} cells
 - Unique group of CD4+ T cells
 - Recognize self-antigens on immune system cells and seem to be able to suppress immune system
 - Induce cell death in some immune cells

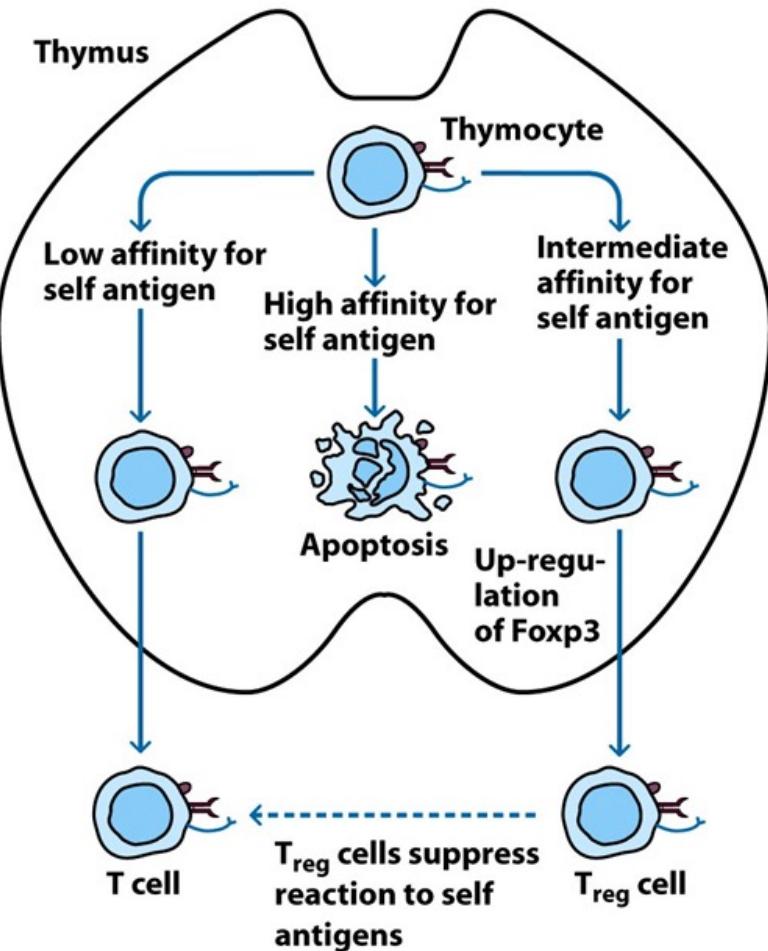
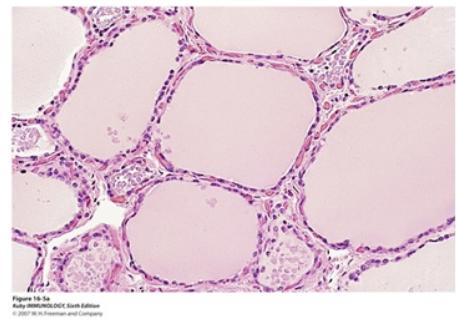


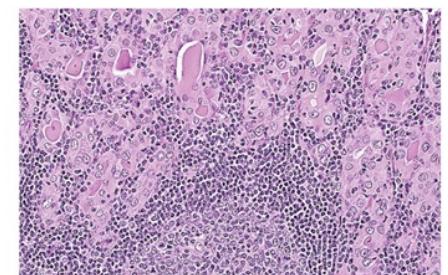
Figure 16-4
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Organ-specific autoimmune diseases

- Target antigen specific to organ or gland
- Cellular lysis and chronic inflammation that can damage organ
- Hashimoto's Thyroiditis
 - Mainly middle-aged women
 - Target is thyroid antigens
 - Goiter can form
 - Hypothyroidism - decrease



Normal



Intense lymphocyte infiltration

Organ-specific autoimmune diseases...

- Autoimmune anemias
 - Pernicious anemia
 - Ab against membrane bound intestinal protein that uptakes B_{12} - needed for hematopoiesis
 - Hemolytic anemia
 - Abs to red-blood cell antigens
 - Drug-induced anemia

Organ-specific autoimmune diseases...

- Goodpasture's syndrome
 - Abs against basement membranes in **glomeruli** and **alveoli**
 - Leads to **kidney** damage and
 - **pulmonary** hemorrhage

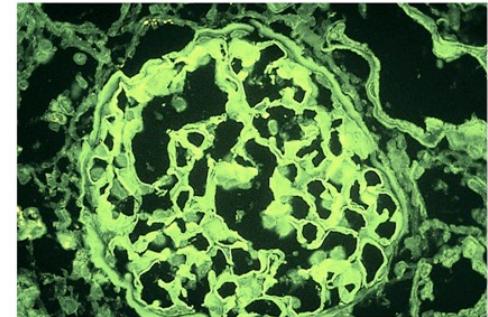
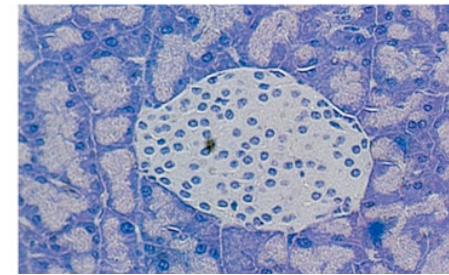


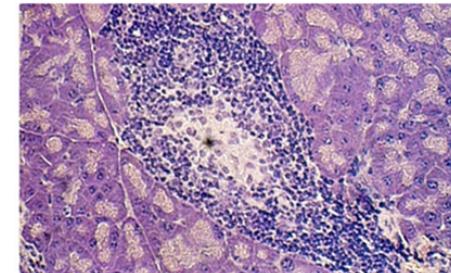
Figure 16-6
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Glomerulus of kidney – fluorescent labeled anti-IgG reveals a large amount of IgG (autoantibodies) attached to glomerulus

- Insulin-Dependent Diabetes Mellitus
 - Abs against beta cells (pancreas) that produce insulin
 - Insulin is needed by cells to uptake glucose needed for cellular respiration



Normal islet with beta cell in pancreas



Islet infiltrated by lymphocytes

- In some autoimmune diseases, antibodies act as agonists or antagonist
 - Bind inappropriately to receptors, resulting in overproduction or blocking
 - (Overproduction) Up-regulating a hormonal response without the presence of that hormone, for example,
 - Grave's Disease – auto-Ab binds to receptor for thyroid stimulating hormone (TSH) resulting in over-stimulation of thyroid
 - (Blocking) For example,
 - Myasthenia gravis
 - Blocking Auto-Abs bind acetylcholine receptors on motor end plate of muscles – progressively weakened skeletal muscles

STIMULATING AUTO-ANTIBODIES (Graves' disease)

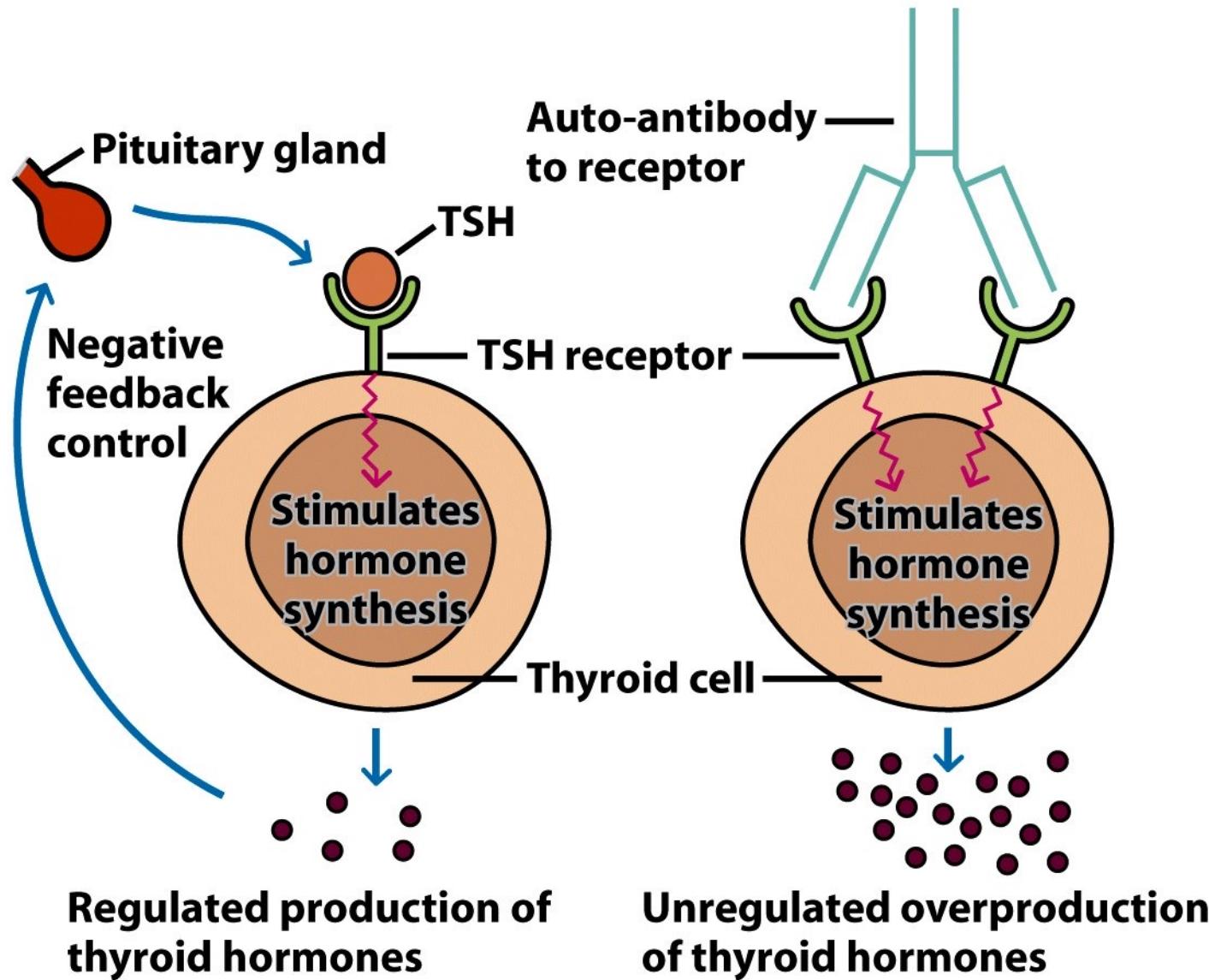


Figure 16-8

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BLOCKING AUTO-ANTIBODIES (Myasthenia gravis)

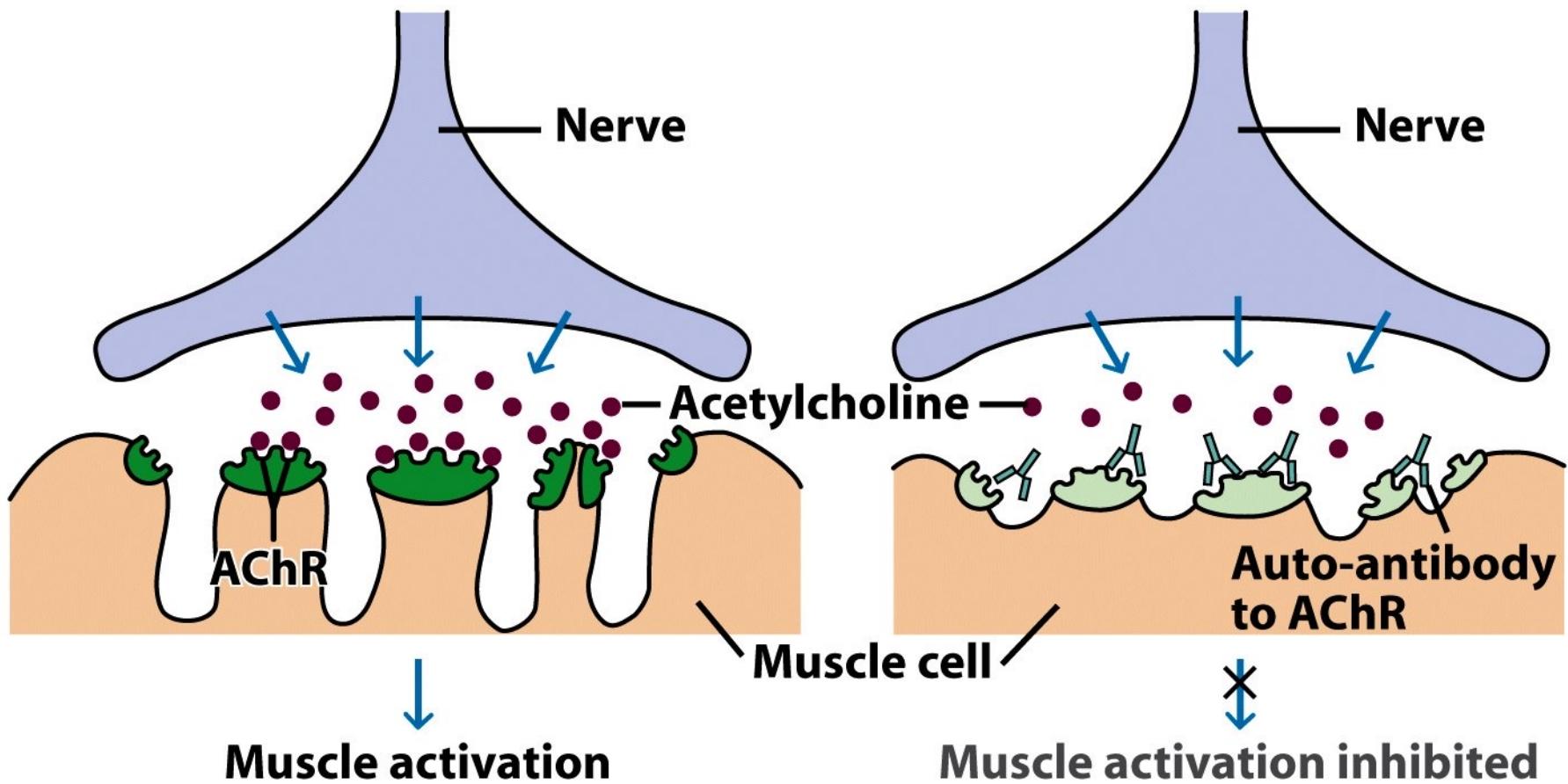


Figure 16-9
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Systemic Autoimmune Diseases

- Response is directed toward wide range of target antigens
- Systemic Lupus Erythematosus
 - Typically middle-aged women
 - Fever, weakness, arthritis, skin rash, kidney problems
 - Produce auto-Abs to DNA, histones, platelets, leukocytes, clotting factors
 - Excessive complement activation

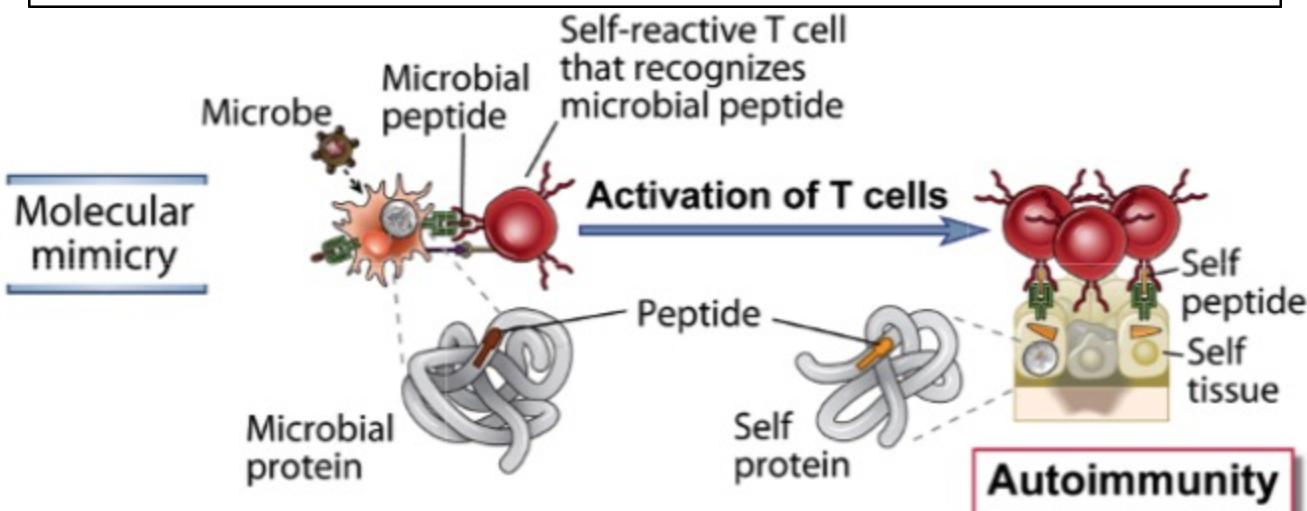
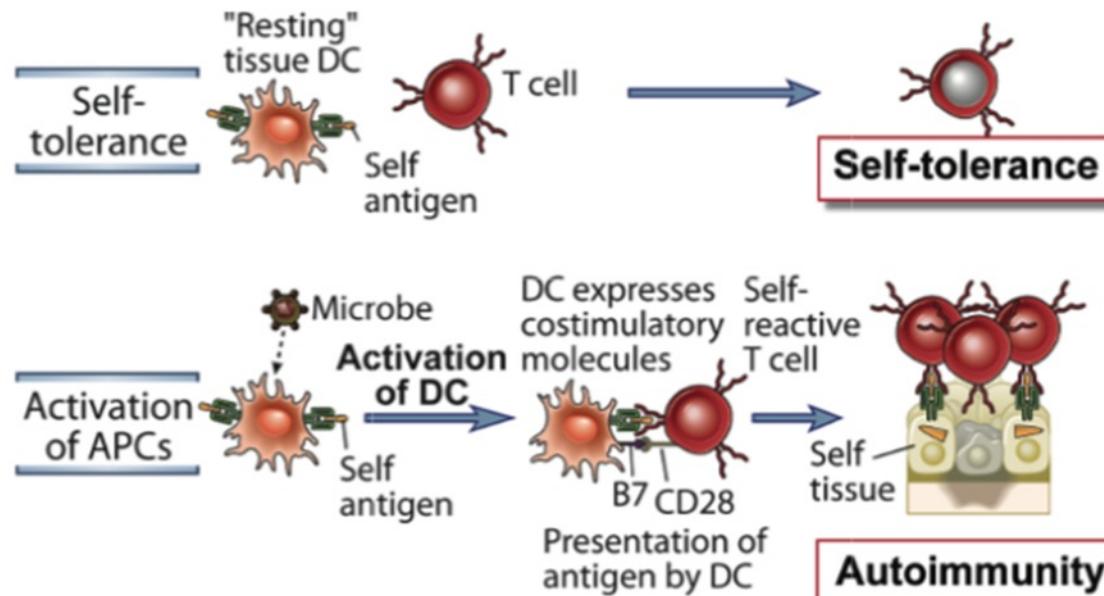
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Systemic Autoimmune Diseases...

- Multiple sclerosis
 - Numbness, paralysis, vision loss
 - Inflammatory lesions in myelin sheath (brain) caused by T-cells
- Rheumatoid Arthritis
 - Chronic inflammation of joints
 - Produce auto-Abs that bind Fc portion of IgG circulating in blood that creates immune complexes

- **Proposed mechanisms for induction of autoimmunity**
 - Release of sequestered antigens
 - Blood-brain barrier, sperm released into tissues during vasectomy
 - Molecular mimicry
 - Inappropriate expression of Class II MHC
 - Non-antigen presenting cells will for some reason express Class II MHC
 - » Can be caused by viral infection
 - This allows them to present self antigen to T helper cells
 - leads to inappropriate reaction

Infection and autoimmunity



Different mechanisms of autoimmunity

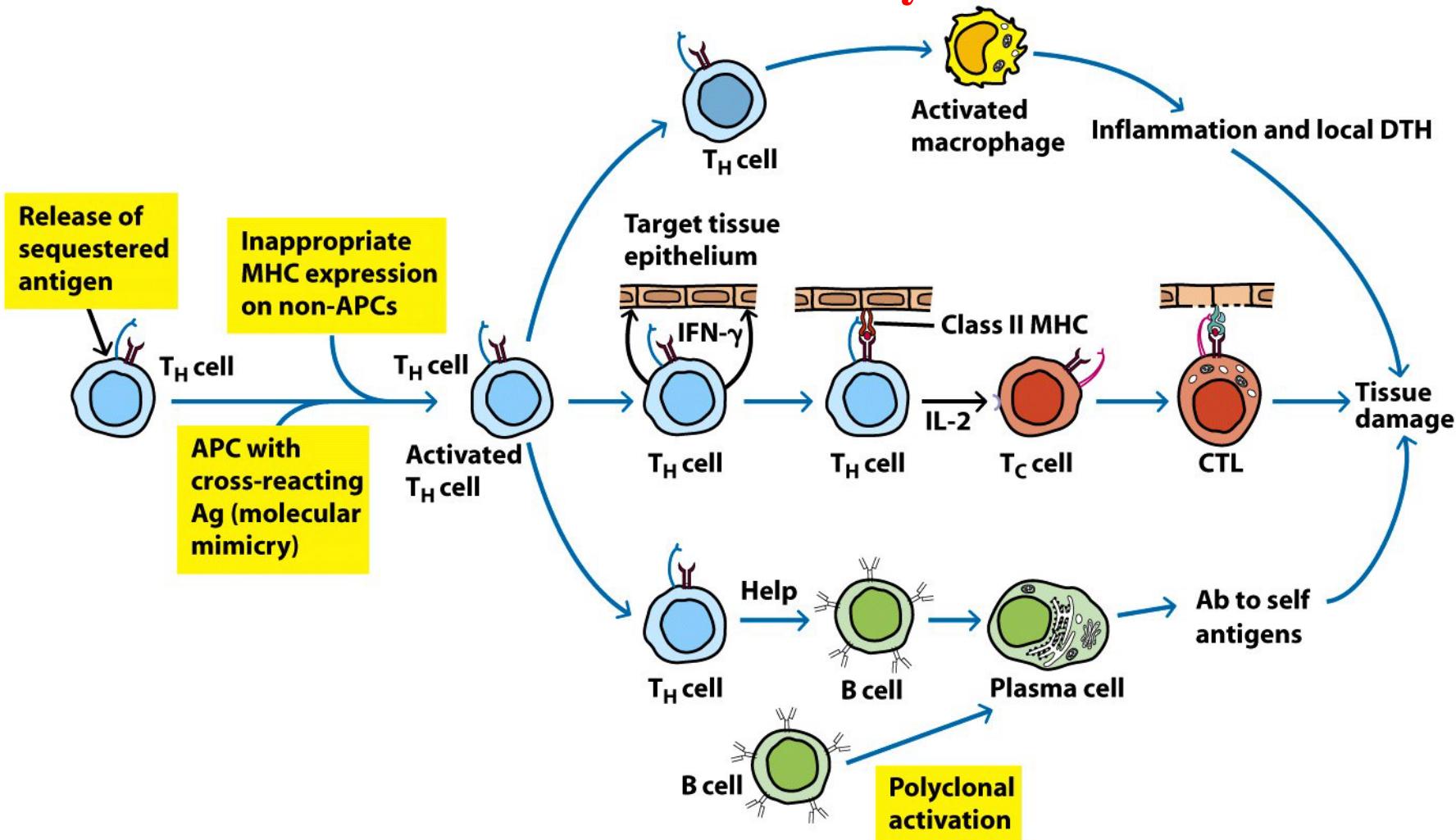


Figure 16-12

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TABLE 16-3

**Molecular mimicry between
proteins of infectious organisms
and human host proteins**

Protein*	Sequence†
Human cytomegalovirus IE2 HLA-DR molecule	79 P D P L G R P D E D 60 V T E L G R P D A E
Poliovirus VP2 Acetylcholine receptor	70 S T T K E S R G T T 176 T V I K E S R G T K
Papilloma virus E2 Insulin receptor	76 S L H L E S L K D S 66 V Y G L E S L K D L
Rabies virus glycoprotein Insulin receptor	147 T K E S L V I I S 764 N K E S L V I S E
<i>Klebsiella pneumoniae</i> nitrogenase HLA-B27 molecule	186 S R Q T D R E D E 70 K A Q T D R E D L
Adenovirus 12 E1B α-Gliadin	384 L R R G M F R P S Q C N 206 L G Q G S F R P S Q Q N
Human immunodeficiency virus p24 Human IgG constant region	160 G V E T T T P S 466 G V E T T T P S
Measles virus P3 Corticotropin	13 L E C I R A L K 18 L E C I R A C K
Measles virus P3 Myelin basic protein	31 E I S D N L G Q E 61 E I S F K L G Q E

*In each pair, the human protein is listed second. The proteins in each pair have been shown to exhibit immunologic cross-reactivity.

†Amino acids are indicated by a single-letter code. Identical residues are shown in blue. Numbers indicate amino acid position in the intact protein.

SOURCE: Adapted from M. B. A. Oldstone, 1987, *Cell* 50:819.

Table 16-3

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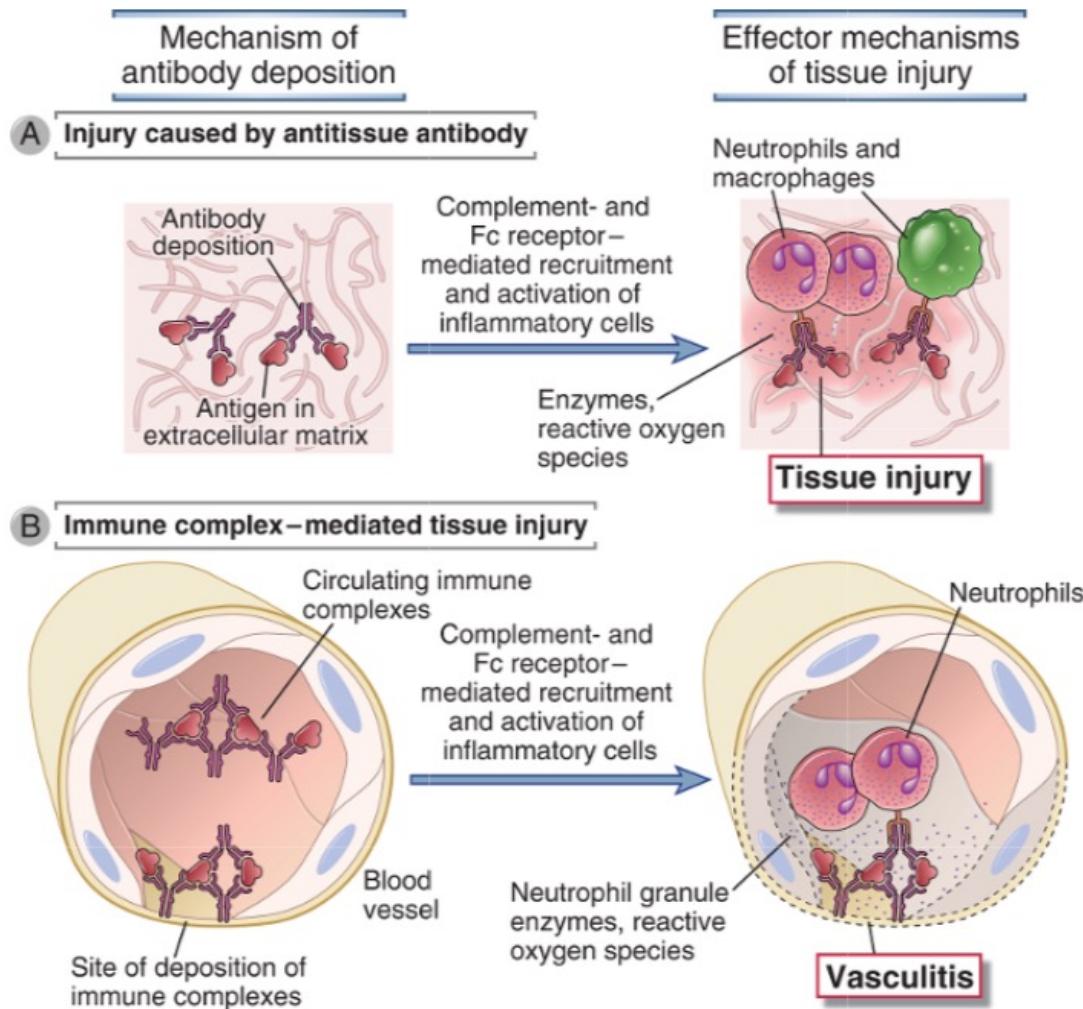
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Treatment

- Immunosuppressive drugs
- Removal of thymus (for example, with myasthenia gravis)
- Plasmapheresis – removing plasma and then returning RBCs (removes extra immune complexes)
- Treating the inflammation
- Antigen given orally can induce tolerance

Types of antibody mediated diseases:

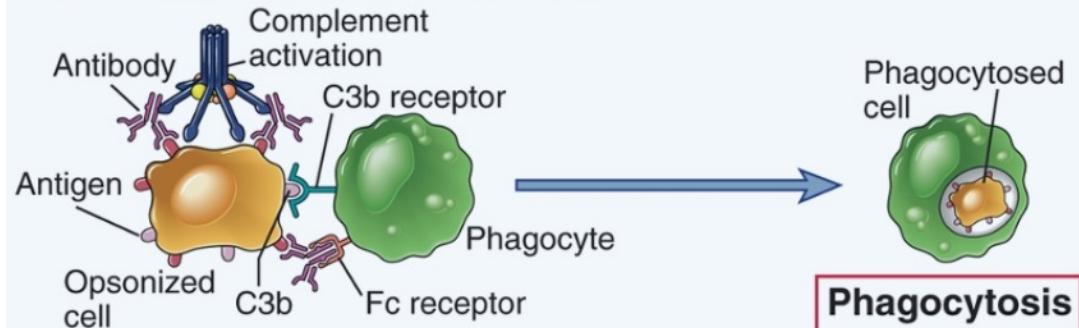
Antibodies may bind specifically to tissue antigens (A), or they may be deposited as immune complexes that are formed in the circulation (B). In both cases, the deposited antibodies induce inflammation, leading to tissue injury.



Effector mechanisms of antibody-mediated disease.

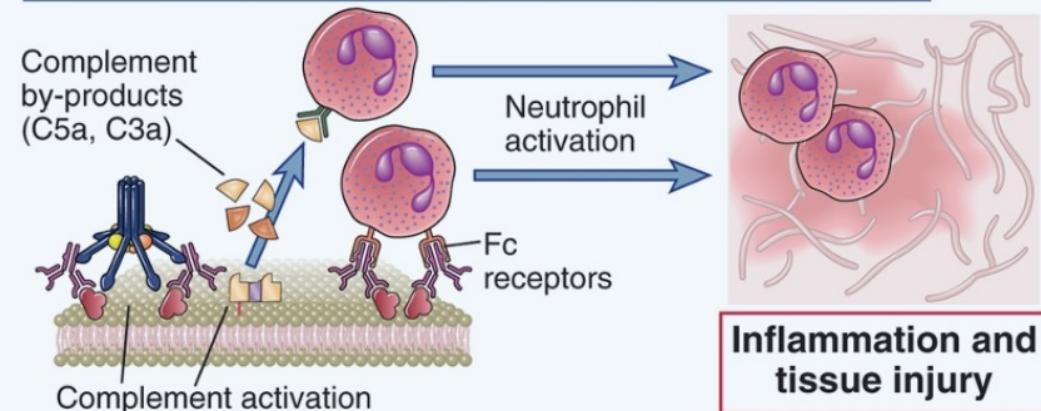
A, Antibodies opsonize cells and may activate complement, generating complement products that also opsonize cells, leading to phagocytosis of the cells through phagocyte Fc receptors or C3 receptors. **B**, Antibodies recruit leukocytes by binding to Fc receptors or by activating complement and thereby releasing byproducts that are chemotactic for leukocytes. **C**, Antibodies specific for cell surface receptors for hormones or neurotransmitters may stimulate the activity of the receptors even in the absence of the hormone (left panel) or may inhibit binding of the neurotransmitter to its receptor (right panel). TSH, thyroid-stimulating hormone.

A Opsonization and phagocytosis



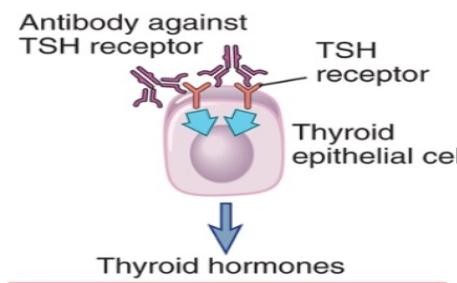
Phagocytosis

B Complement- and Fc receptor–mediated inflammation

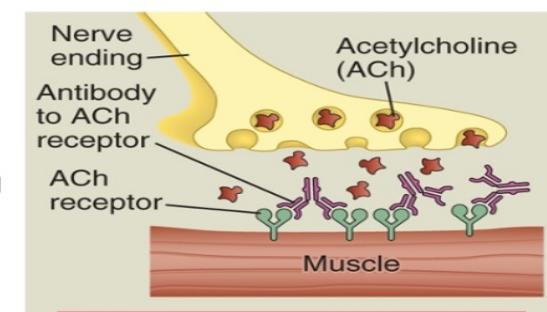


Inflammation and tissue injury

C Abnormal physiologic responses without cell/tissue injury



Antibody stimulates receptor without ligand



Antibody inhibits binding of ligand to receptor

Mechanisms of T cell-mediated diseases.

A, In cytokine-mediated inflammatory reactions, CD4+ T cells (and sometimes CD8+ cells) respond to tissue antigens by secreting cytokines that stimulate inflammation and activate phagocytes, leading to tissue injury. APC, antigen-presenting cell.

B, In some diseases, CD8+ CTLs directly kill tissue cells.

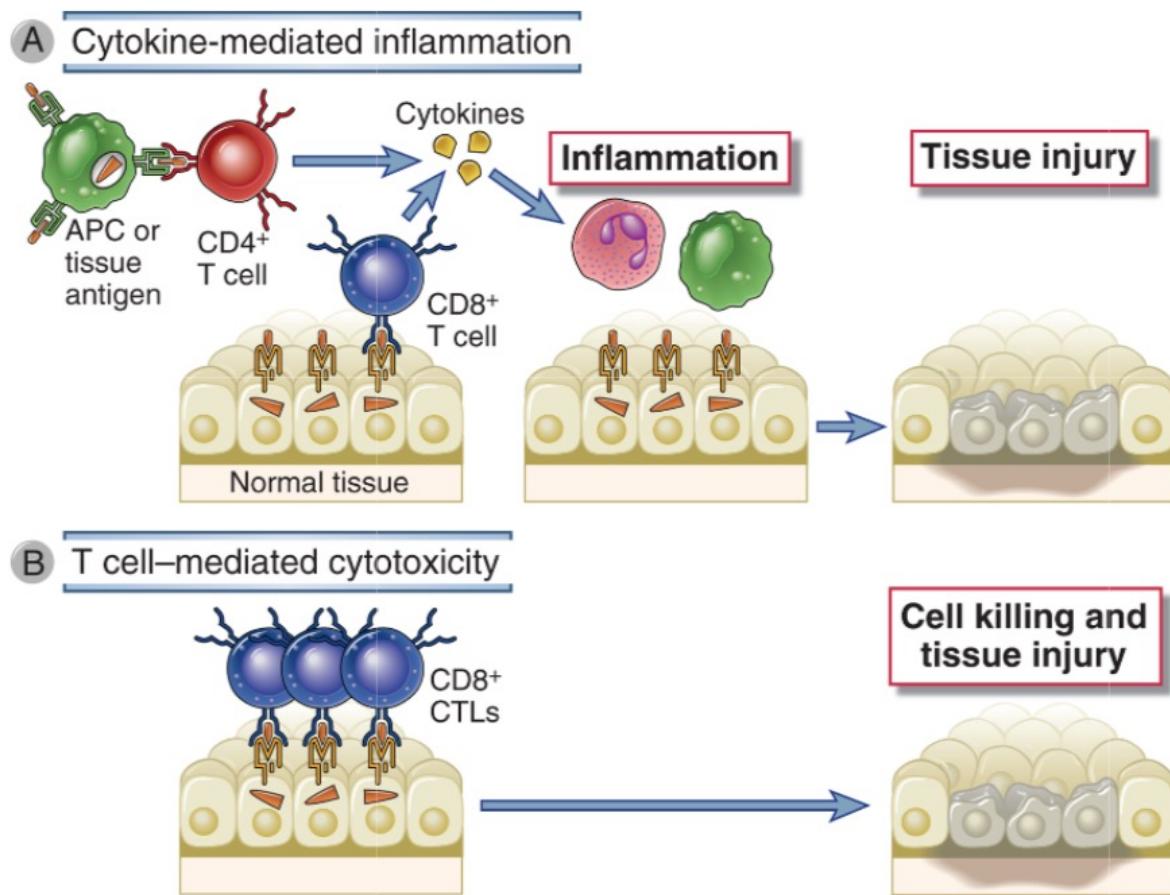


TABLE 18–4 T Cell–Mediated Diseases

Disease	Specificity of Pathogenic T Cells	Principal Mechanisms of Tissue Injury
Rheumatoid arthritis	Collagen? Citrullinated self proteins?	Inflammation mediated by $T_{H}17$ (and $T_{H}1$?) cytokines Role of antibodies and immune complexes?
Multiple sclerosis	Protein antigens in myelin (e.g., myelin basic protein)	Inflammation mediated by $T_{H}1$ and $T_{H}17$ cytokines Myelin destruction by activated macrophages
Type 1 diabetes mellitus	Antigens of pancreatic islet β cells (insulin, glutamic acid decarboxylase, others)	T cell–mediated inflammation Destruction of islet cells by CTLs
Inflammatory bowel disease	Enteric bacteria Self antigens?	Inflammation mediated by $T_{H}17$ and $T_{H}1$ cytokines
Autoimmune myocarditis	Myosin heavy chain protein	CTL-mediated killing of myocardial cells Inflammation mediated by $T_{H}1$ cytokines
Examples of human T cell–mediated diseases are listed. In many cases, the specificity of the T cells and the mechanisms of tissue injury are inferred on the basis of the similarity with experimental animal models of the diseases.		

Delayed-type hypersensitivity reaction.

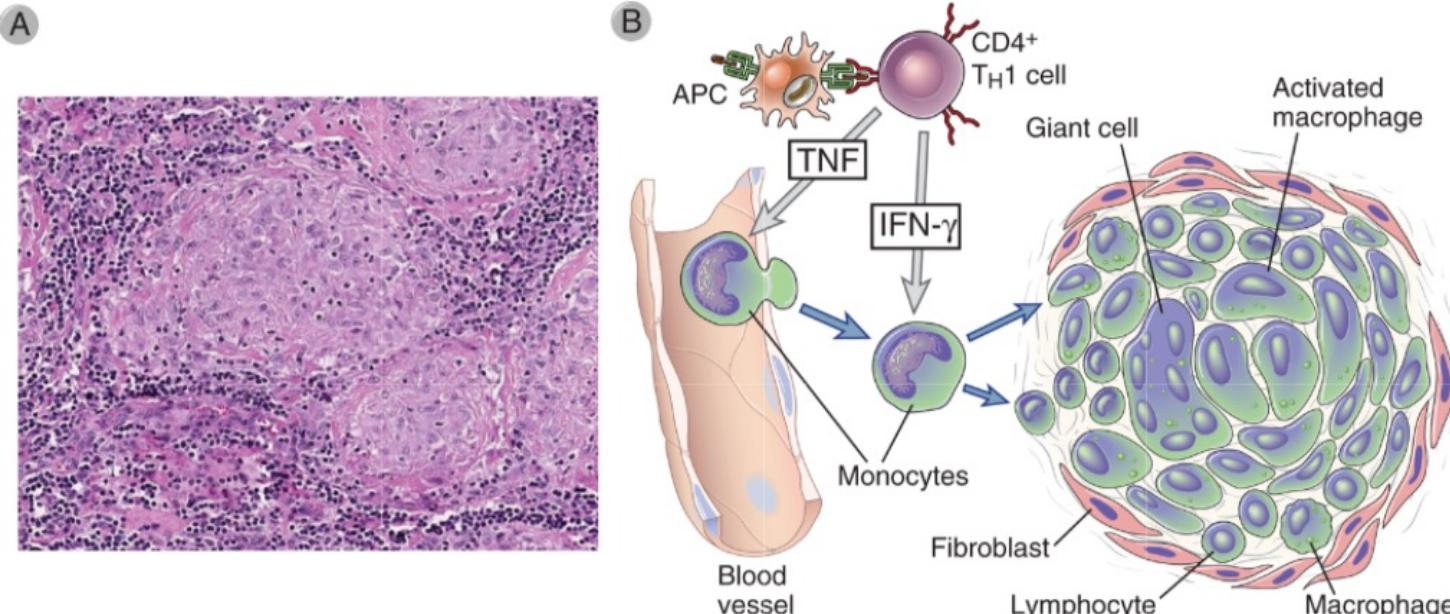
Infection or immunization (vaccination) sensitizes an individual, and subsequent challenge with an antigen from the infectious agent elicits a DTH reaction. The reaction is manifested by induration with redness and swelling at the site of the challenge, which is undetectable at ~4 hours and peaks at ~48 hours.



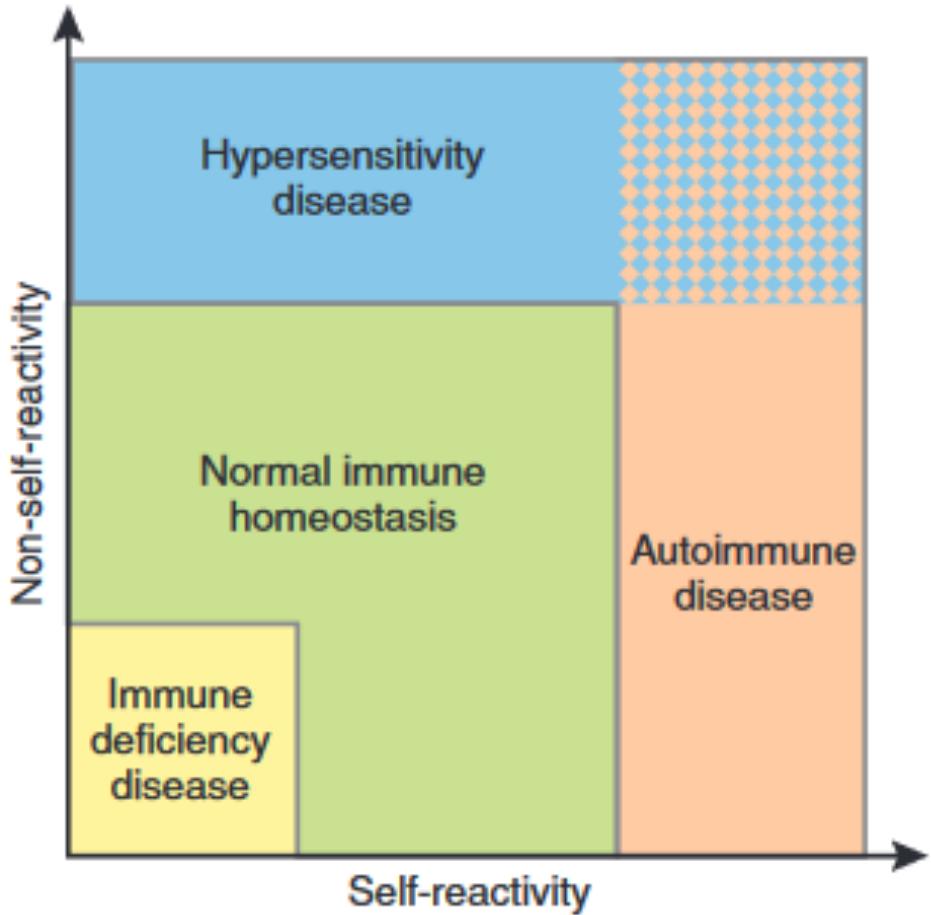
Granulomatous inflammation.

A, Lymph node from a patient with tuberculosis containing granulomas with activated macrophages, multinucleate giant cells, and lymphocytes. In some granulomas, there may be a central area of necrosis. Immunohistochemical studies would identify the lymphocytes as T cells.

B, Mechanisms of granuloma formation. Cytokines are involved in the generation of TH1 cells, activation of macrophages, and recruitment of leukocytes. Prolonged reactions of this type lead to the formation of granulomas.



- Normal immune homeostasis involves a balance between T cells, B cells, and antibodies that are reactive with self, non-self, or both.
- Disease results when there is an imbalance of immune responsiveness with either too little immune defense against foreign pathogens (immune deficiency disease), more immune response to non-self antigens than is beneficial (allergic or hypersensitivity disease), or more immune response to self antigens than is beneficial (autoimmune disease).



Hypersensitivity Reactions

- When the immune system "goes wrong".
 - Immune response should be protective.
 - In this process damage to host occurs.
- Hypersensitivity denotes a state of increased reactivity of the host to an antigen and implies that the reaction is damaging to the host.
 - The individual must first have become **sensitized** by previous exposure to the antigen.
 - On second and subsequent exposures, symptoms and signs of a hypersensitivity state occur.

Hypersensitivity Reactions

- *Immediate hypersensitivity* refers to antibody mediated reactions – symptoms develop within minutes to hours
- *Delayed hypersensitivity* refers to cell mediated immunity, symptoms not observed for 24 to 48 hours.

Four Classifications

- Type I (*Immediate*) hypersensitivity
- Type II (*cytotoxic*) hypersensitivity
- Type III (*immune complex mediated*) hypersensitivity
- Type IV (*delayed*) hypersensitivity

Type I (*Immediate*) Hypersensitivity

- Distinguishing feature short lag time.
- Key reactant is IgE
- Antigens which trigger response called *atopic antigens* or *allergens*.
- **Atopy** – inherited tendency to immunologically respond to inhaled or ingested allergens with increased IgE production.

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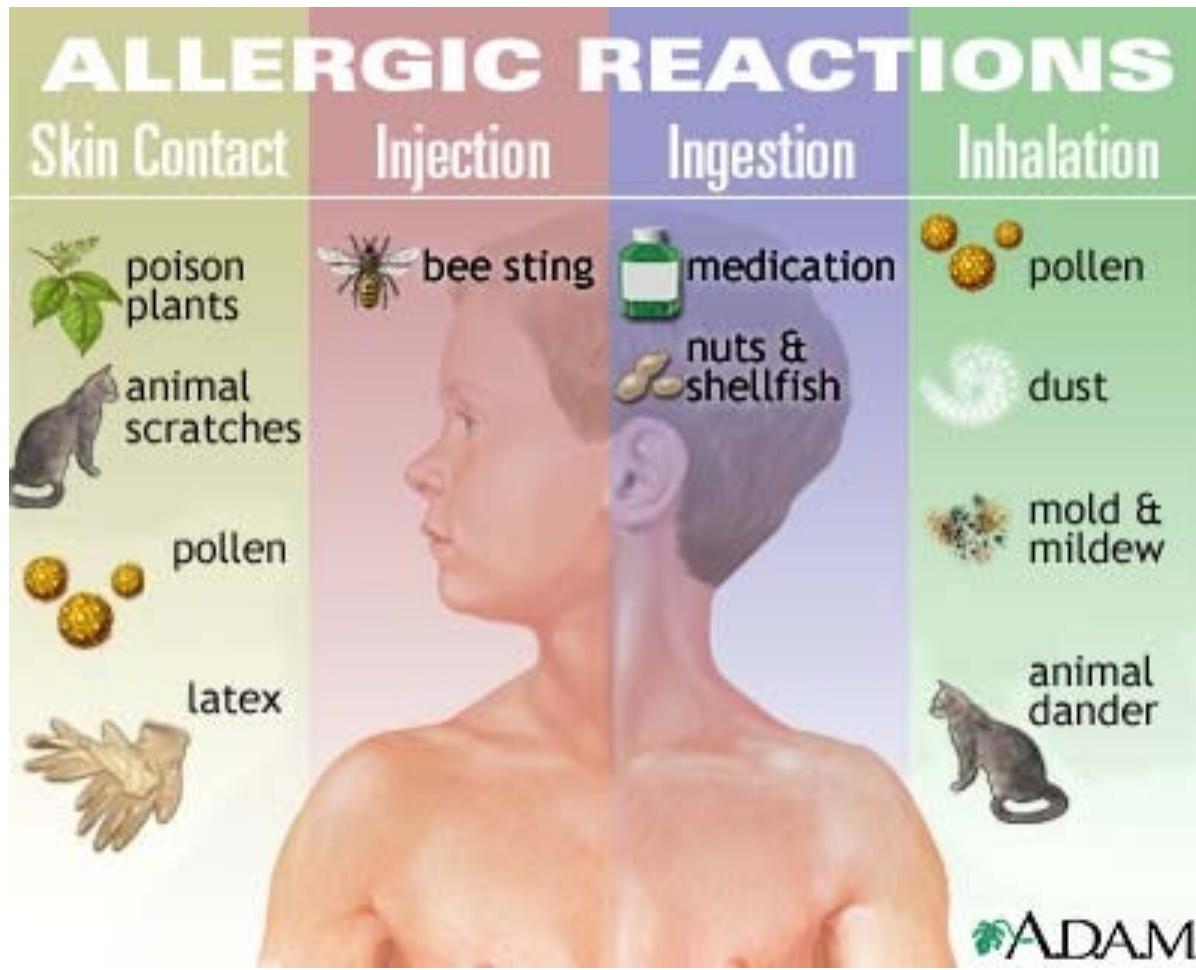
Type I (*Immediate*) Hypersensitivity...

- IgE primarily synthesized in lymphoid tissue of respiratory and GI tract.
- Regulated by T helper cells.
- Specific interleukins are involved in development of eosinophils and promote development of mast cells.
- All act to stimulate overproduction of mucus.
- Basophils and mast cells have highest number of receptors for Fc portion of IgE on surface.

Type I (*Immediate*) Hypersensitivity...

- Reactions range from mild manifestations associated with food allergies to life-threatening anaphylactic shock.
 - *Atopic allergies* include hay fever, asthma, food allergies and eczema.
 - Exposure to allergens can be through inhalation, absorption from the digestive tract or direct skin contact.
 - Extent of allergic response related to port of entry, i.e., bee sting introduces allergen directly into the circulation.
 - *Caused by inappropriate IgE production*
- IgE antibody has an affinity for mast cells or basophils.

Type I (*Immediate*) Hypersensitivity...

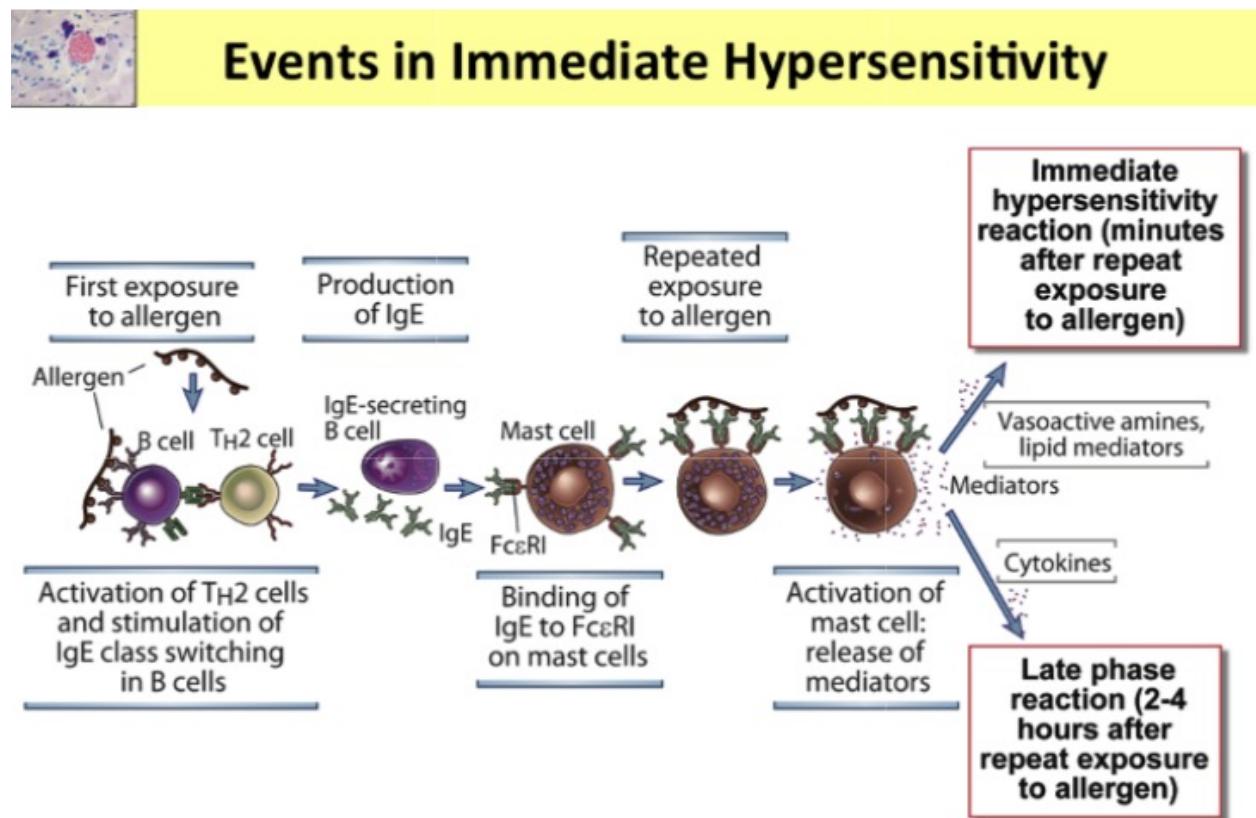


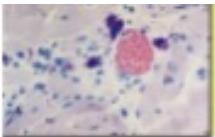
Type I (*Immediate*) Hypersensitivity...

- When IgE meets its specific allergen it causes the mast cell to discharge its contents of vasoactive substances into the circulation.
- This release leads to symptoms of:
 - sneezing,
 - runny noses,
 - red watery eyes and
 - wheezing.
- Symptoms subside when allergen is gone.

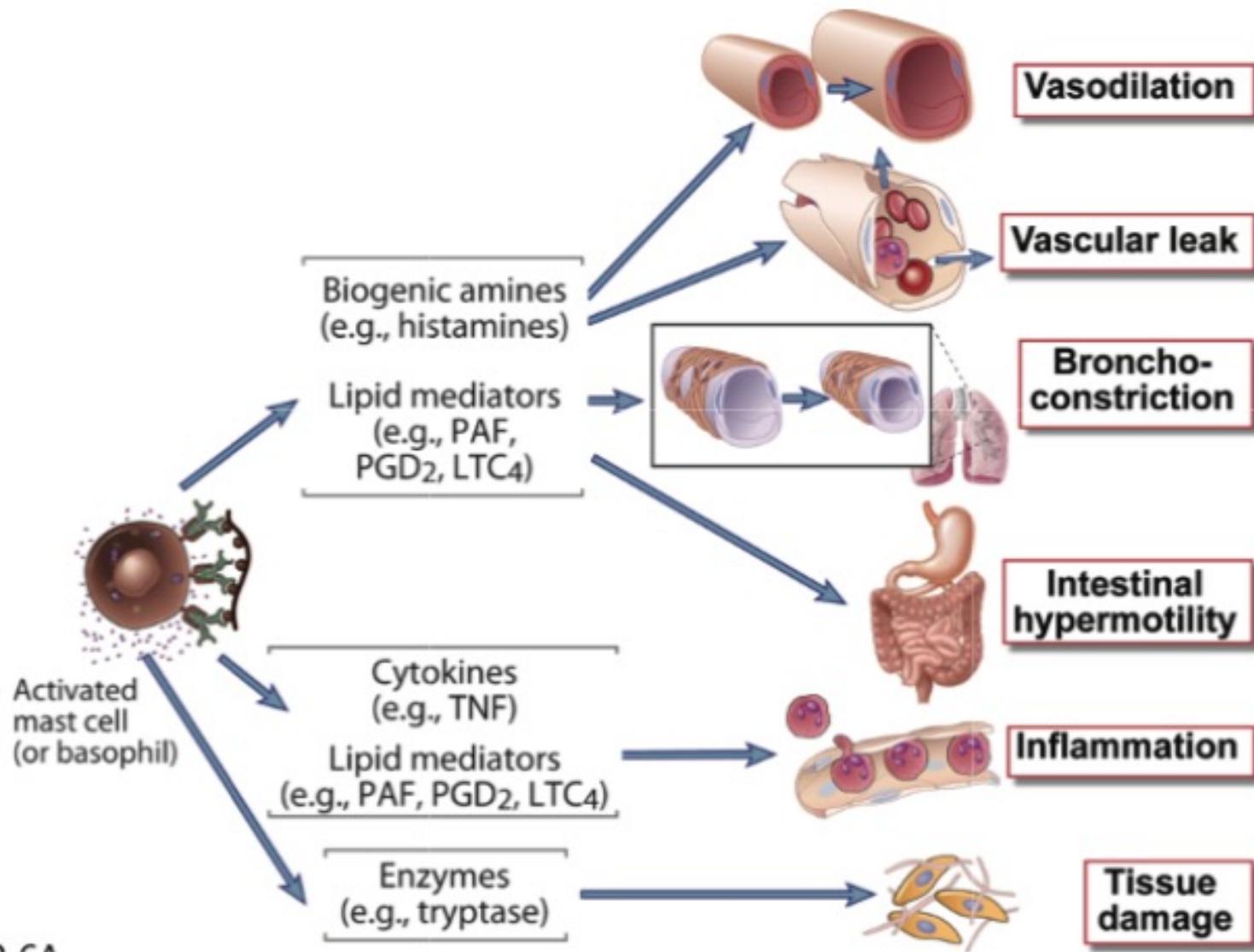
Sequence of events in immediate hypersensitivity reactions.

Immediate hypersensitivity diseases are initiated by the introduction of an allergen, which stimulates TH2 reactions and IgE production. IgE sensitizes mast cells by binding to Fc ϵ RI, and subsequent exposure to the allergen activates the mast cells to secrete the mediators that are responsible for the pathologic reactions of immediate hypersensitivity.





Mediators of Immediate Hypersensitivity



Type I (*Immediate*) Hypersensitivity...

- *Anaphylactic shock* is the most serious and fortunately the rarest form of this Type I hypersensitivity.
- Symptoms are directly related to the massive release of vasoactive substances leading to fall in blood pressure, shock, difficulty in breathing and even death.
- It can be due to the following:
 - Horse gamma globulin given to patients who are sensitized to horse protein.
 - Injection of a drug that is capable of acting as a hapten into a patient who is sensitive, ie, penicillin.
 - Following a wasp or bee sting in highly sensitive individuals.
 - Foods – peanuts, shellfish, etc.

Type II (*Cytotoxic*) Hypersensitivity

- Triggered by antigens found on cell surfaces
 - Altered self antigens
 - Heteroantigens
- Manifested by the production of IgG or IgM antibodies which coat the antigens.
- Mechanisms
 - Antibody coats cell surface promotes phagocytosis – macrophages, neutrophils and eosinophils have Fc receptors to bind to antibody on target cell.
 - Natural Killer cells have Fc receptors, binding, results in cytotoxicity
 - Complement
 - Coats cells which enhances phagocytosis
 - Complement cascade goes to completion results in cell lysis.

Type II (*Cytotoxic*) Hypersensitivity...

- **Transfusion reactions**
 - Hundreds of different antigens expressed on RBCs
 - Antibodies can be produced naturally or through exposure, by transfusion or pregnancy most common
- **Most well-known example due to ABO incompatibility.**
 - Individuals form potent antibodies against ABO antigens not present on their red blood cells.
 - Group O individuals have both anti-A and anti-B antibodies. If this person is transfused with group A blood, it will show an immediate, and possibly fatal, reaction
- Other blood groups may cause delayed reaction or acute reactions.

Fundamentals of ABO blood group antigens

	Group A	Group B	Group AB	Group O
N acetyl-galactosamine	A	B	A B	O
Fucose				
N acetyl-glucosamine				
Galactose				
Red blood cell type	Type A	Type B	Type AB	Type O
Antibodies present	Anti-B	Anti-A	None	Anti-A and Anti-B
Antigens present	A antigen	B antigen	A and B antigen	None

Type II (*Cytotoxic*) Hypersensitivity...

- Hemolytic disease of the fetus and newborn
 - Mother exposed to blood group antigens due to previous pregnancy with antigen positive child or transfusion.
 - Antibody must be IgG
 - Crosses placenta and coats fetal RBCs, destruction of RBCs causes increased bilirubin and anemia.
 - If first pregnancy is first exposure infant usually not affected.
 - Subsequent pregnancies have increased risk and the disease ranges from mild to fatal.
 - All pregnant women are screened for blood group antibodies.

Type II (*Cytotoxic*) Hypersensitivity...

- Autoimmune hemolytic anemia
 - Patients form antibodies to antigens on their RBCs.
- Drug induced hemolysis
 - Some drugs may act as haptens, attach to the RBC membrane causing antibodies to be formed.
 - Antibody reacts with drug on RBC causing hemolysis.

Type II (*Cytotoxic*) Hypersensitivity...

- Some individuals make antibody which cross reacts with self antigens found in both the lung and kidney.
- **Goodpasture syndrome** most well-known example
 - Antibody produced against **basement membrane protein**.
 - This protein present in **lungs and kidneys**.
 - Antibody binding results in inflammation
 - Symptoms are **hemoptysis** and **hematuria**.
- Others like
 - Hashimoto's disease
 - Myasthenia Gravis
 - Diabetes mellitus