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Immune system.

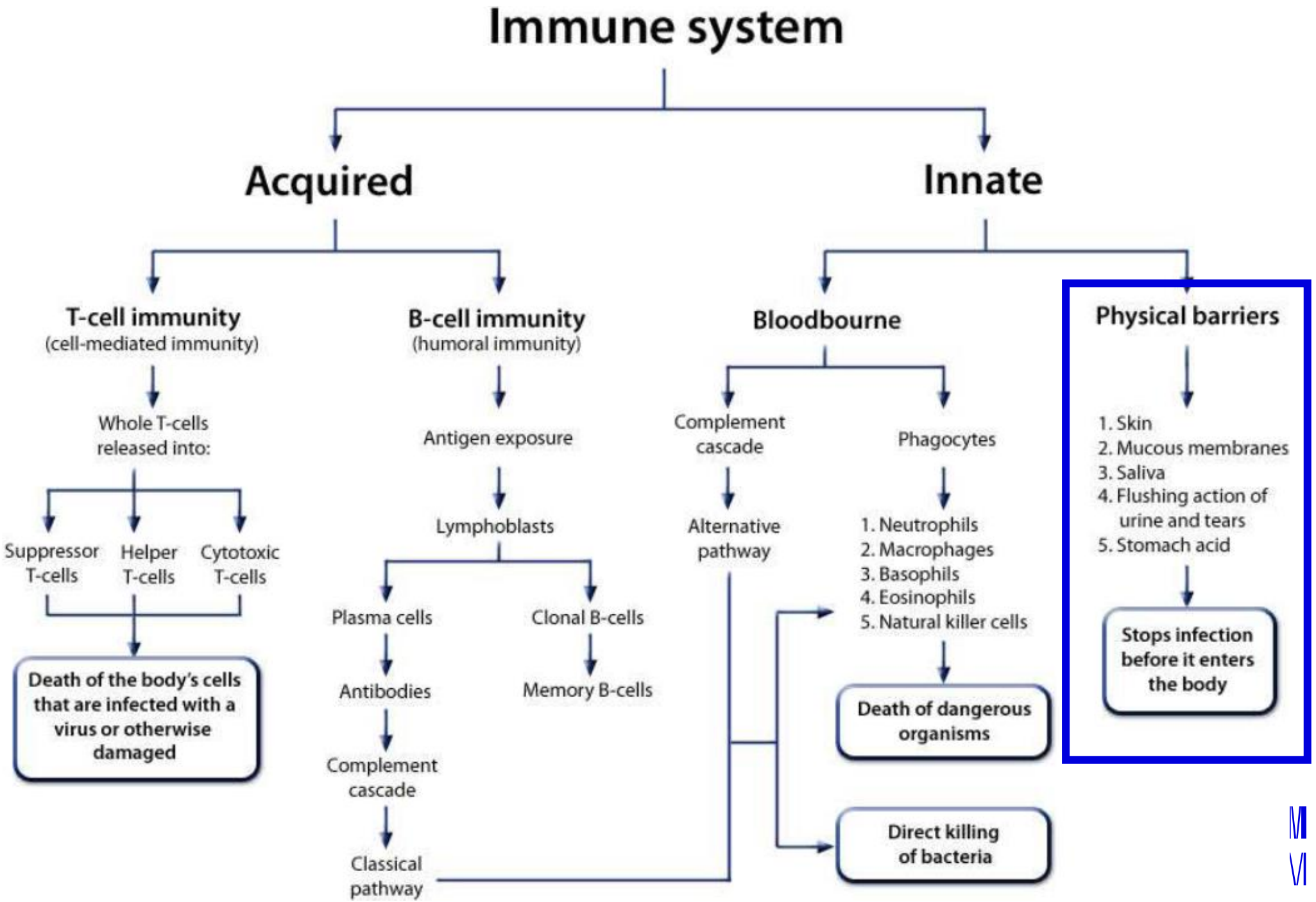
Budínská Xenie

Final exame questions

- 80. Mechanism of innate immunity
- 81. Acquired immunity

Immune system

- **Basic concepts**:
- protection of the organism against pathogenic microorganisms and their toxins;
- auto-tolerance: recognizes its own tissue and cells;
- immune surveillance (recognizes internal pollutants; removes old, damaged, mutated cells);
- antigens: substances that the IS recognizes and reacts to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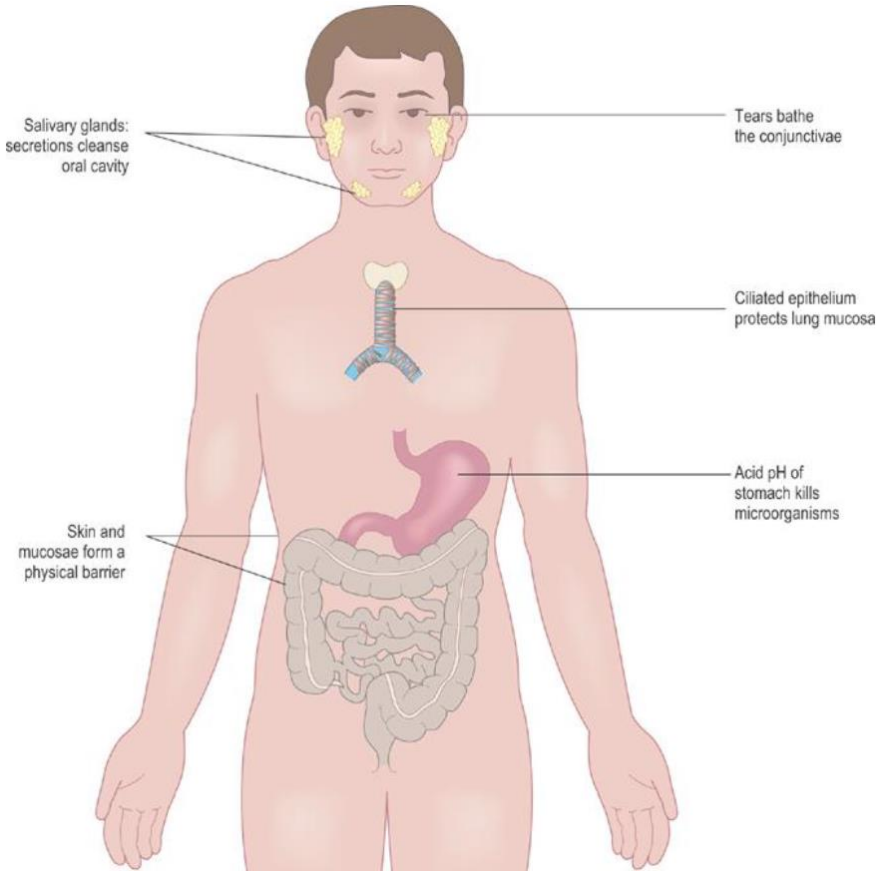
Acquired
Innate
T-cell immunity
(cell-mediated immunity)
B-cell immunity
(humoral immunity)
Bloodbourne
Physical barriers
Whole T-cells released into:
Antigen exposure
Complement cascade
Phagocytes
1. Skin
2. Mucous membranes
3. Saliva
4. Flushing action of urine and tears
5. Stomach acid
Suppressor T-cells
Helper T-cells
Cytotoxic T-cells
Lymphoblasts
Alternative pathway
1. Neutrophils
2. Macrophages
3. Basophils
4. Eosinophils
5. Natural killer cells
Stops infection before it enters the body
Death of the body's cells that are infected with a virus or otherwise damaged
Plasma cells
Clonal B-cells
Antibodies
Memory B-cells
Death of dangerous organisms
Complement cascade
Direct killing of bacteria
Classical pathway

Physical barriers



Barrier Defenses:

- include the skin and mucous membranes of the respiratory, urinary, and reproductive tracts;
- mucus traps and allows for the removal of microbes;
- many body fluids including saliva, mucus, and tears are hostile to many microbes;
- the low pH of skin and the digestive system prevents growth of many bacteria.

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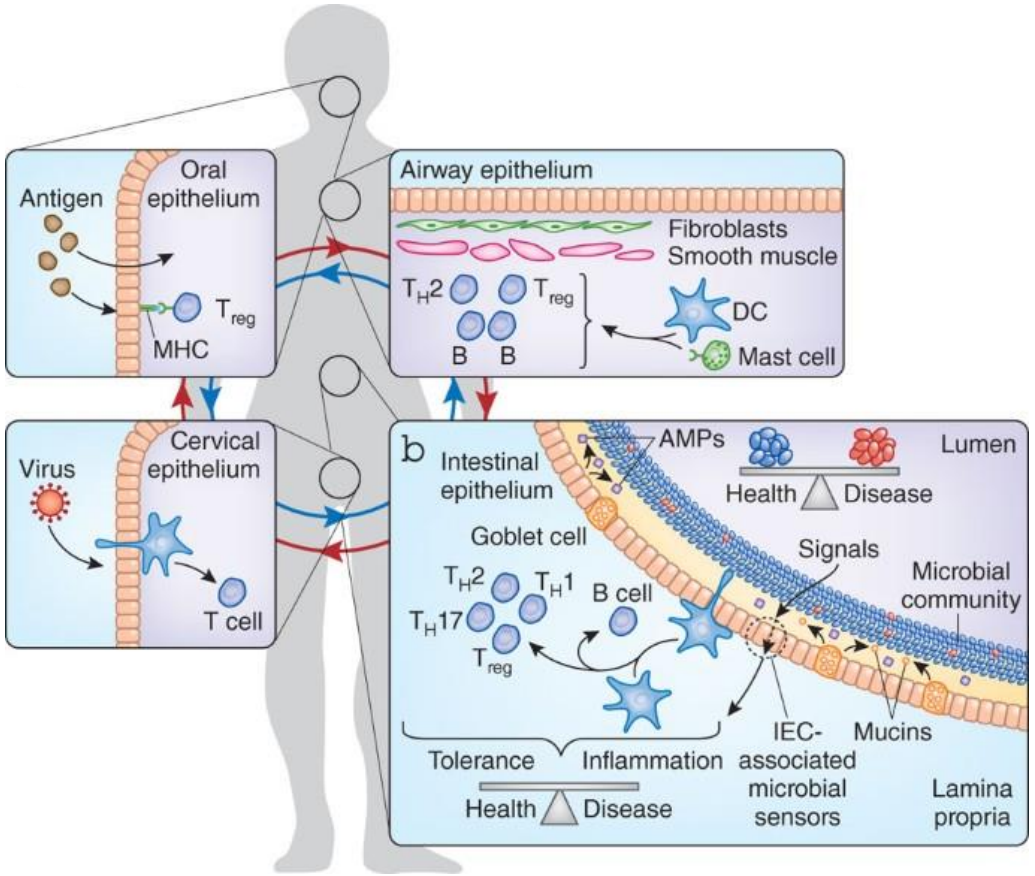
Mucosal immune system



MALT mucosa associated lymphoid tissue:

- GALT (GIT);
- BALT (bronchus);
- Peyer's plaques in the distal section of the ilea, histological specimen;
- d-MALT - diffuse lymphatic tissue (cells are dispersed in the mucosa or submucosa);
- o-MALT - organized lymphatic tissue (cells are arranged in lymphatic follicles that can be isolated or associated with so-called follicular lymphatic aggregates.

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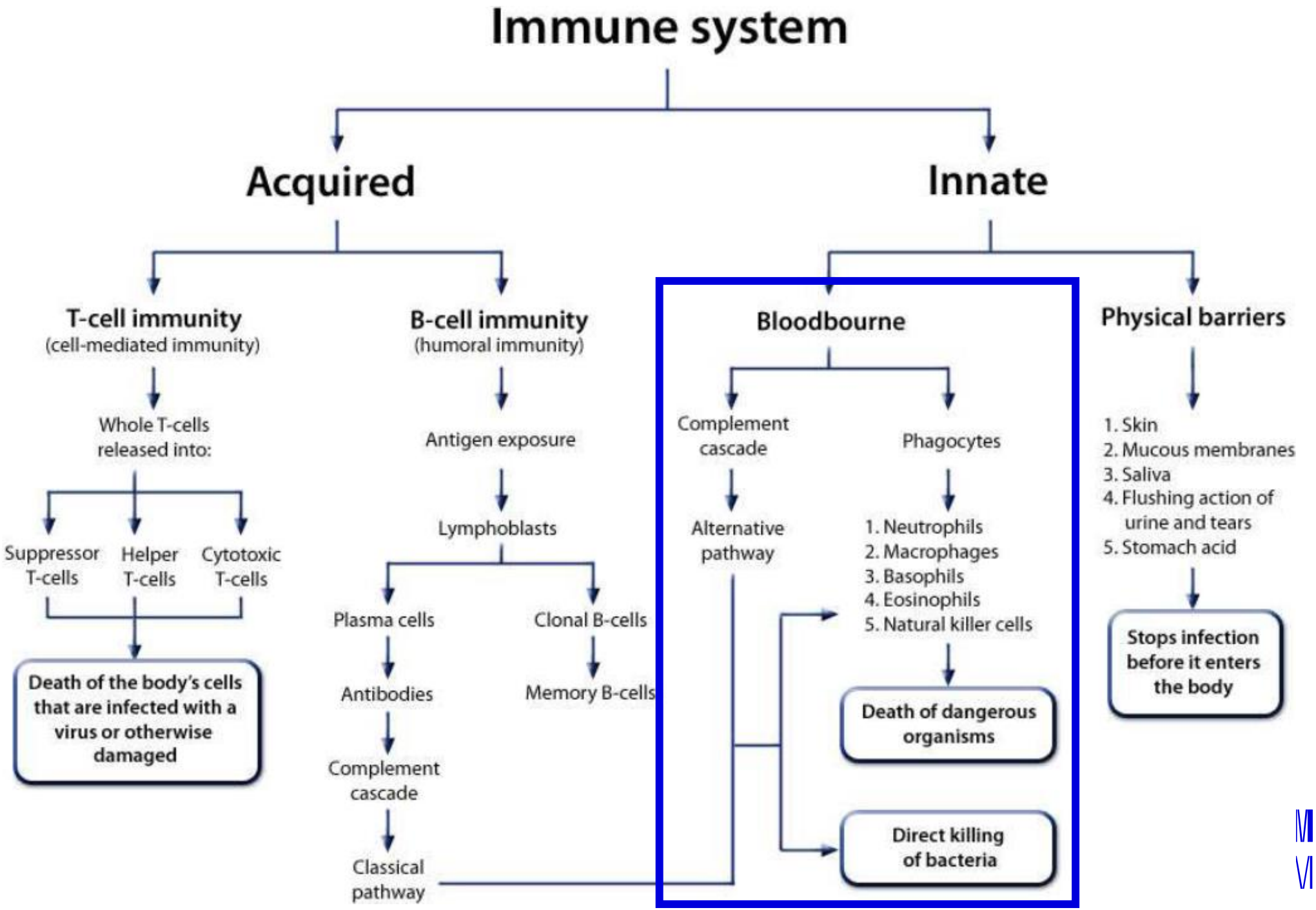
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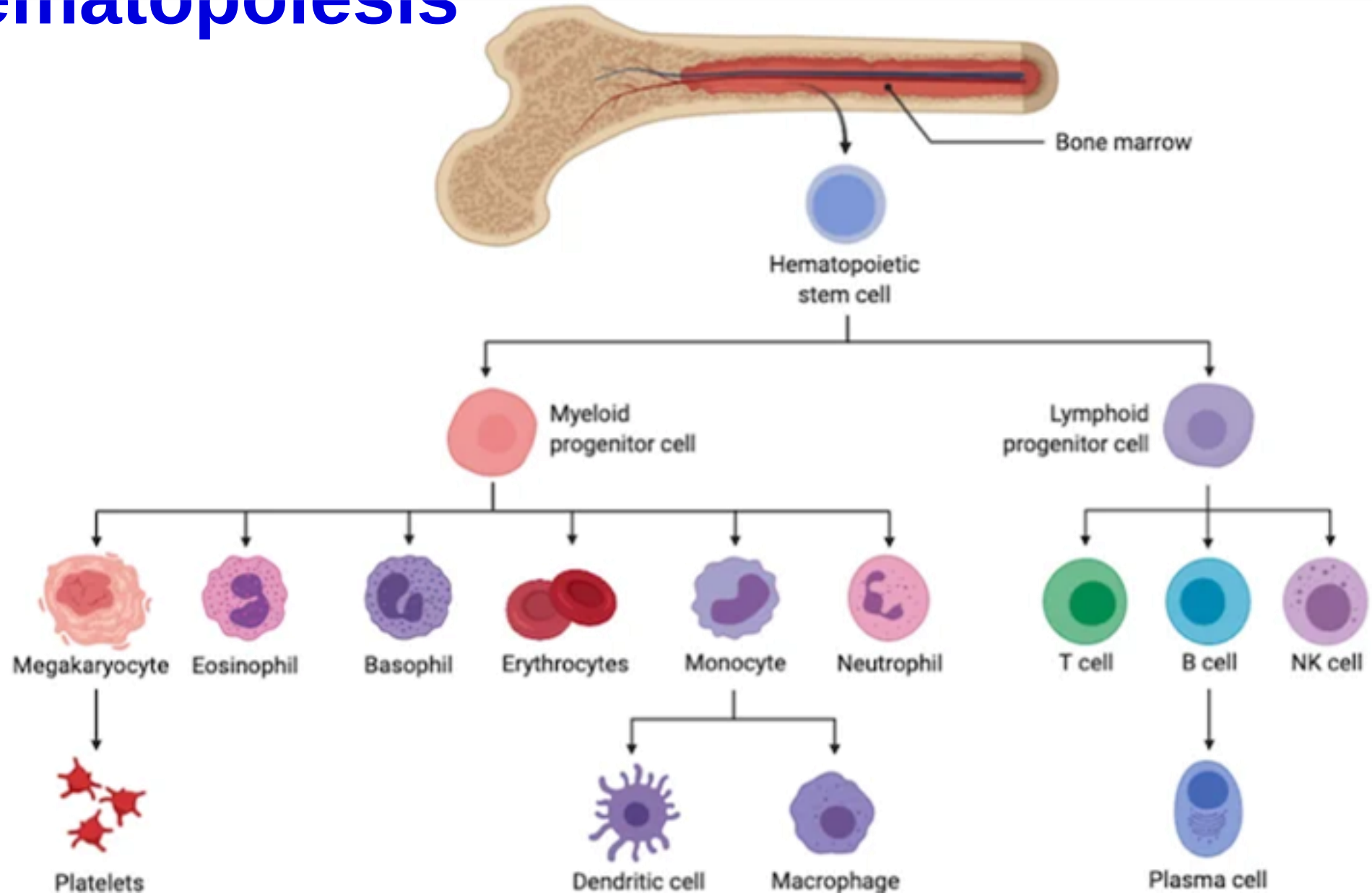
Haematopoiesis



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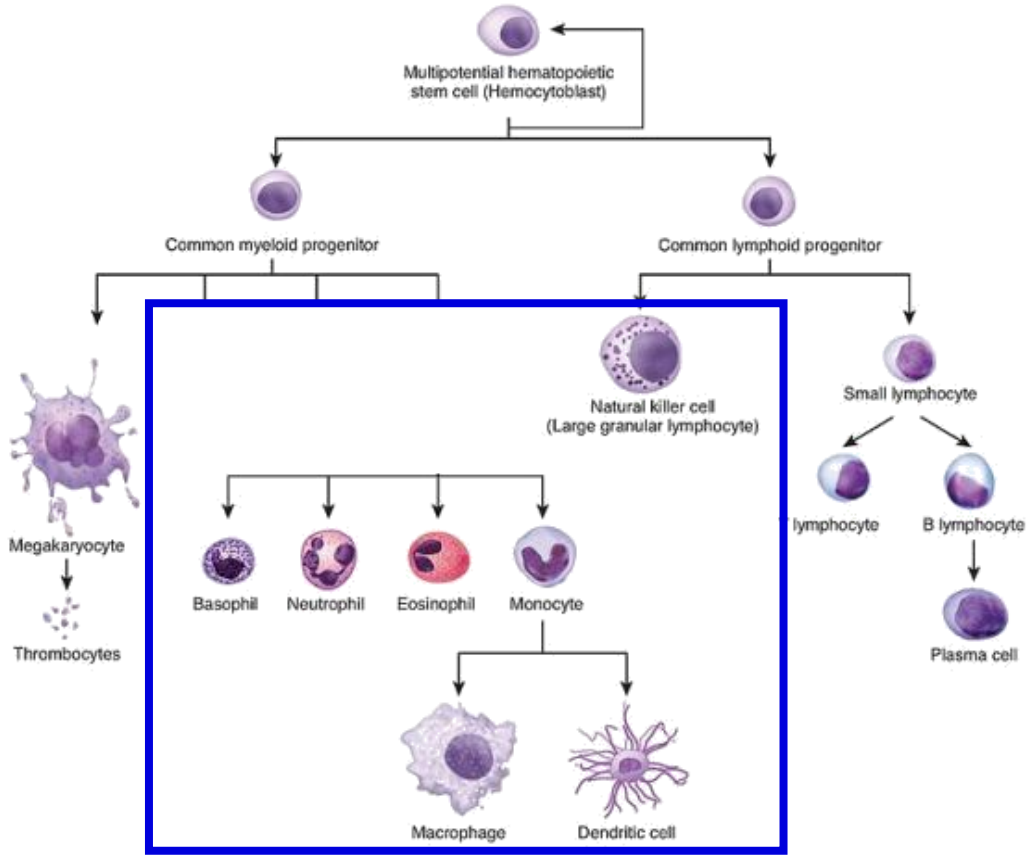
Innate immune system

- already in place
- rapid response
- non-specific pattern response
- functions:
  - physical barriers
  - leukocyte recruitment (inflammation)
  - antiviral defenses
- Parts:
  - physical/chemical barriers
  - phagocytes (neutrophils, macrophages, dendritic cells, mast cells, NKCs)
  - complement



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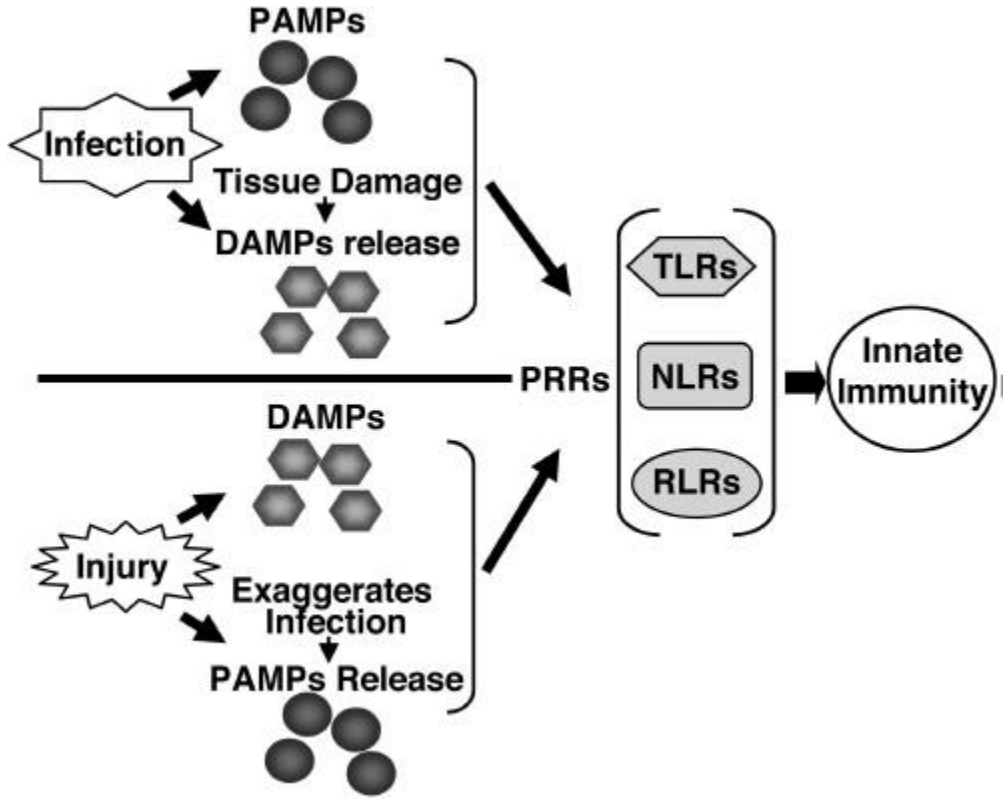
Recognizing invaders

- Pathogen-associated molecular patterns (**PAMPs**):
  - common molecular patterns typically found on pathogens (ex. Bacterial lipopolysaccharides, mannose, viral nucleic acids)
- Damage-associated molecular proteins (**DAMPs**):
  - common molecular patterns found on the surface of injured or dead host cells (ex. Heat shock proteins)

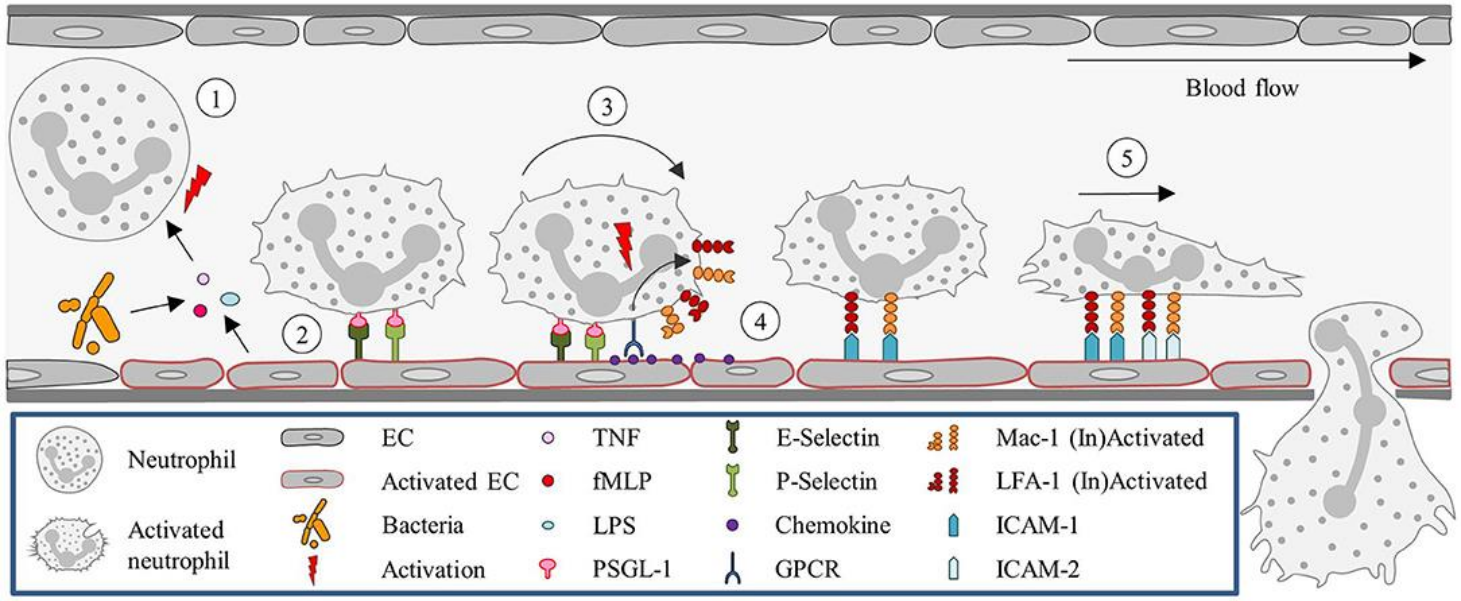


- Pattern recognition receptors:
  - receptors on cells of the immune system that recognize *PAMPs* and *DAMPs*
  - when the pattern recognition receptor binds a ligand (PAMP or DAMP) this triggers signal pathway activation → transcription factors → gene expression of inflammatory and antiviral products → recruitment/activation of immune cells

Macrophages

- phagocytic cell of the innate immune system;
- monocyte-derived macrophages:
  - monocyte in blood
  - mature to macrophage in tissue, are CD14+
- non-monocyte-derived macrophages:
  - arise/reside within tissues, derived from embryological structures (ex. Kupffer cells in liver, alveolar macrophages)
- functions:
  - phagocytose cells targeted for destruction, clean up debris of dead cells;
  - APCs (express more MHCII): IFN-γ (secreted by Th-cells and NKCs) activates macrophages;
  - direct killing of pathogen (recognizes PAMP → phagocytosis);
  - secrete TNF-α, ROS and NO (directly kill pathogens);
  - aid in angiogenesis and fibrosis.

Neutrophils



- phagocytic leukocyte
- rapid first-responders
- short lifespan
- Inciting injury:
  - macrophage recognizes invader and secretes IL-1 and TNF=>endothelial cells express **selectin**
- Rolling:
  - Selectin+selectin ligand =>slow-down of neutrophi+rolling =>detect LPS and express **integrin**
- Adhesion/Crawling:
  - integrin+ICAM =>stops neutrophil migration
- Transmigration:
  - PMNs squeeze out of vascular space using PECAM-1
- Migrate to infection:
  - IL-8 triggers PMNs to migrate to site of infection and signals for increased phagocytosis

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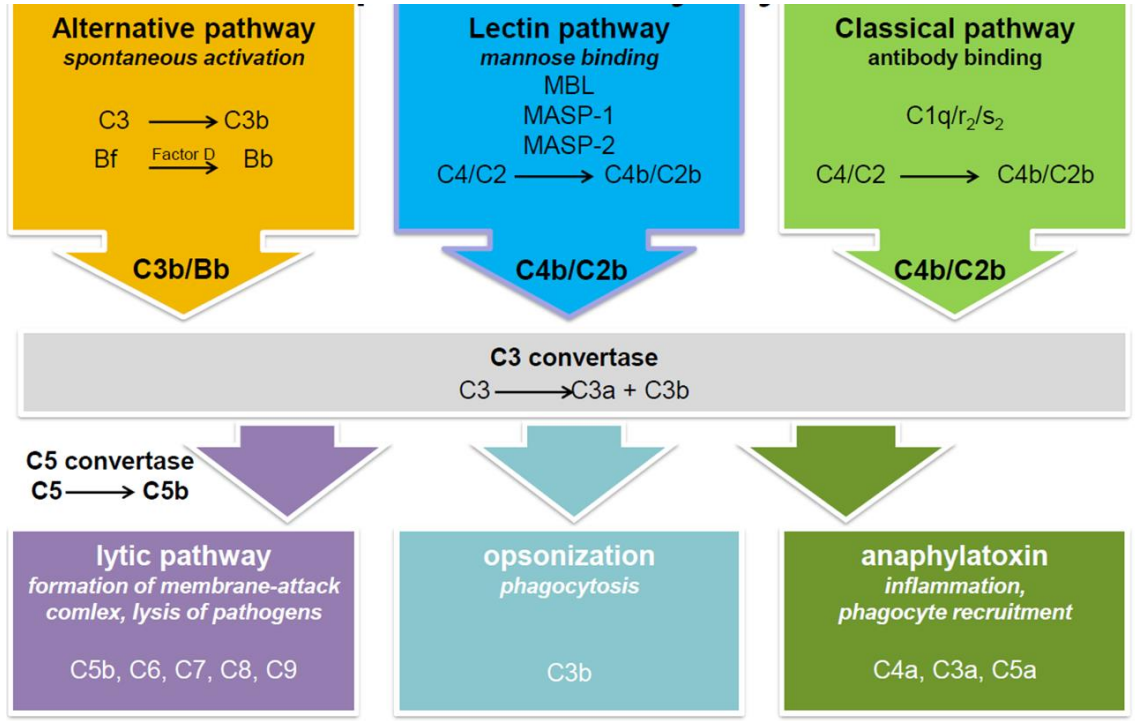
Complement cascade

- system of proteins; part of the innate immune system
- functions:
  - cell lysis (membrane attack complex – MAC)
  - opsonize
  - attract other immunological cells
- complement activation pathways:
  - classical activation pathway
  - alternative activation pathway
  - lectin activation pathway



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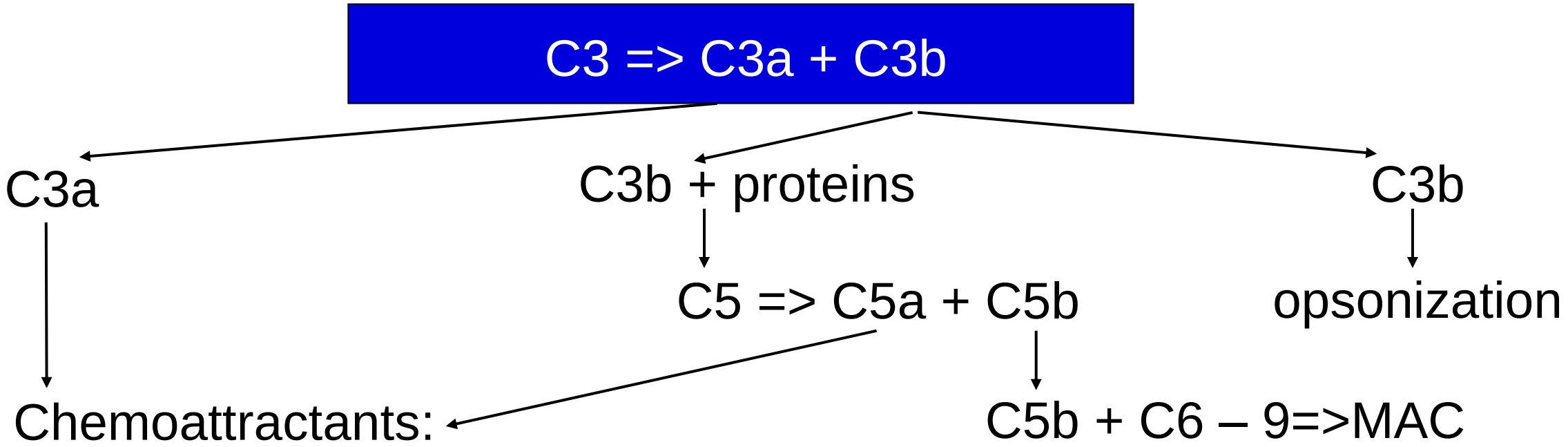
Complement activation pathways

- classical (Ab dependent) complement activation pathway:
  - IgM/IgG brings together multiple C1 complexes
  - inhibitor falls off C1
  - C1 starts cascade that cleaves C3
- alternative (Ab INdependent) complement activation pathway:
  - spontaneous cleavage of C3
- lectin complement activation pathway:
  - mannose binding lectin (MBL) binds mannose on pathogen surface
  - activates MASP
  - MASP cleaves C3

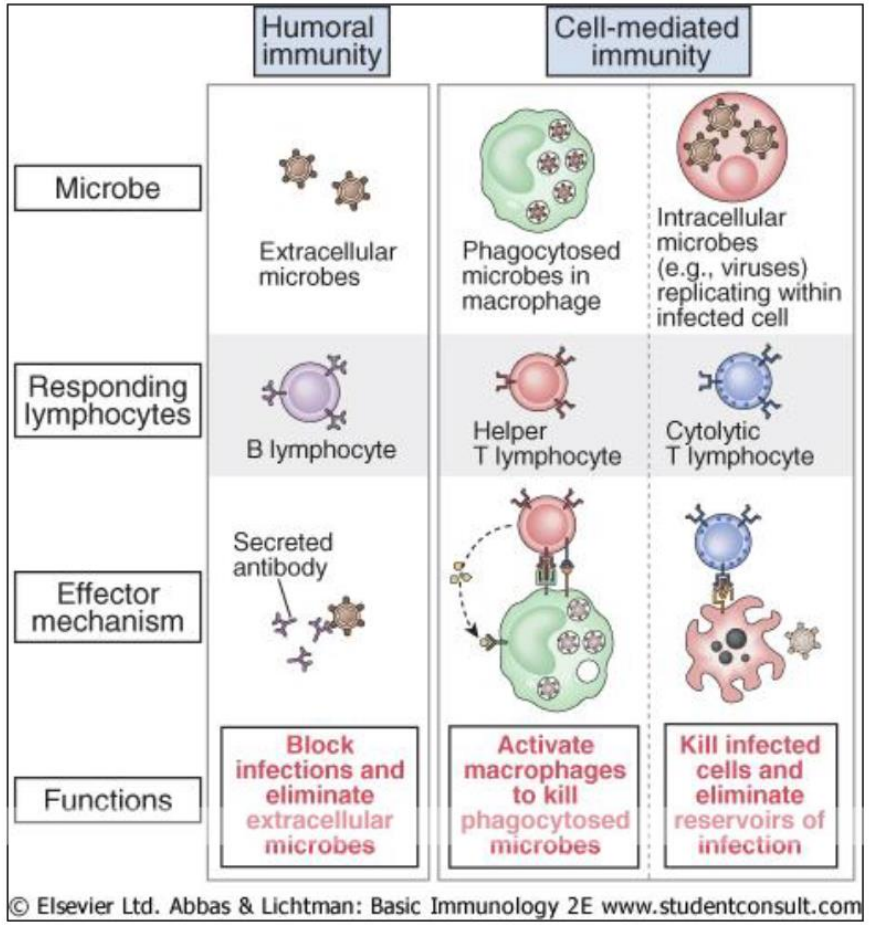
Common pathway



The membrane attack complex (**MAC**) is a complex of proteins typically formed on the surface of pathogen cell. Assembly of the MAC leads to pores that disrupt the cell membrane of target cells, leading to cell lysis and death.

Adaptive immune system

- develops in response to pathogen (antigen)
- specific (responds to Ag)
- diverse (recognizes a lot of Ags)
- immunological memory
- humoral immunity:
  - targets extracellular pathogens in blood + mucosal secretions
  - B-cells → make Ab
- cell-mediated immunity:
  - targets intracellular pathogens
  - T-cells (Cytotoxic T-cells (CD8+), Helper T-cells (CD4+)



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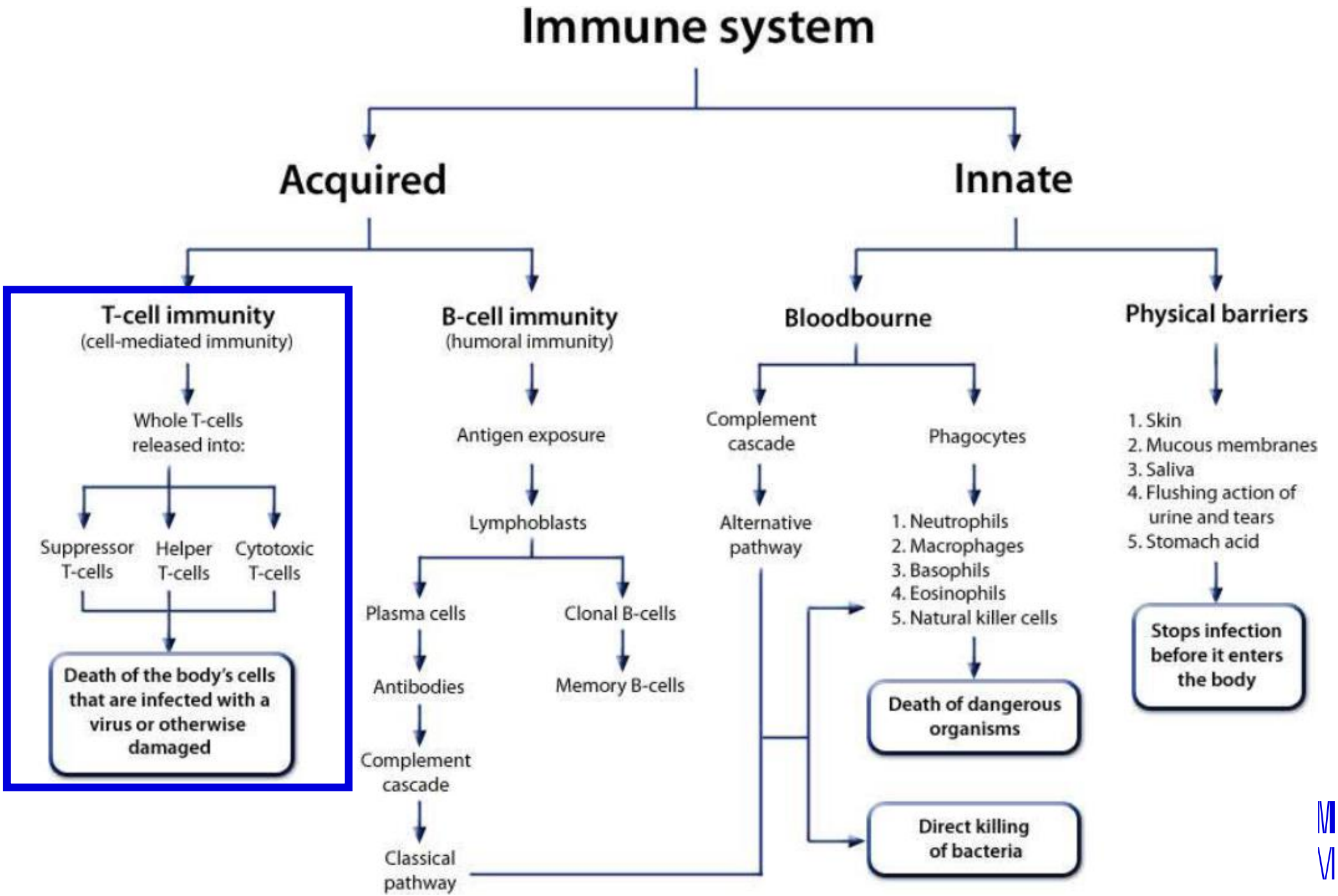
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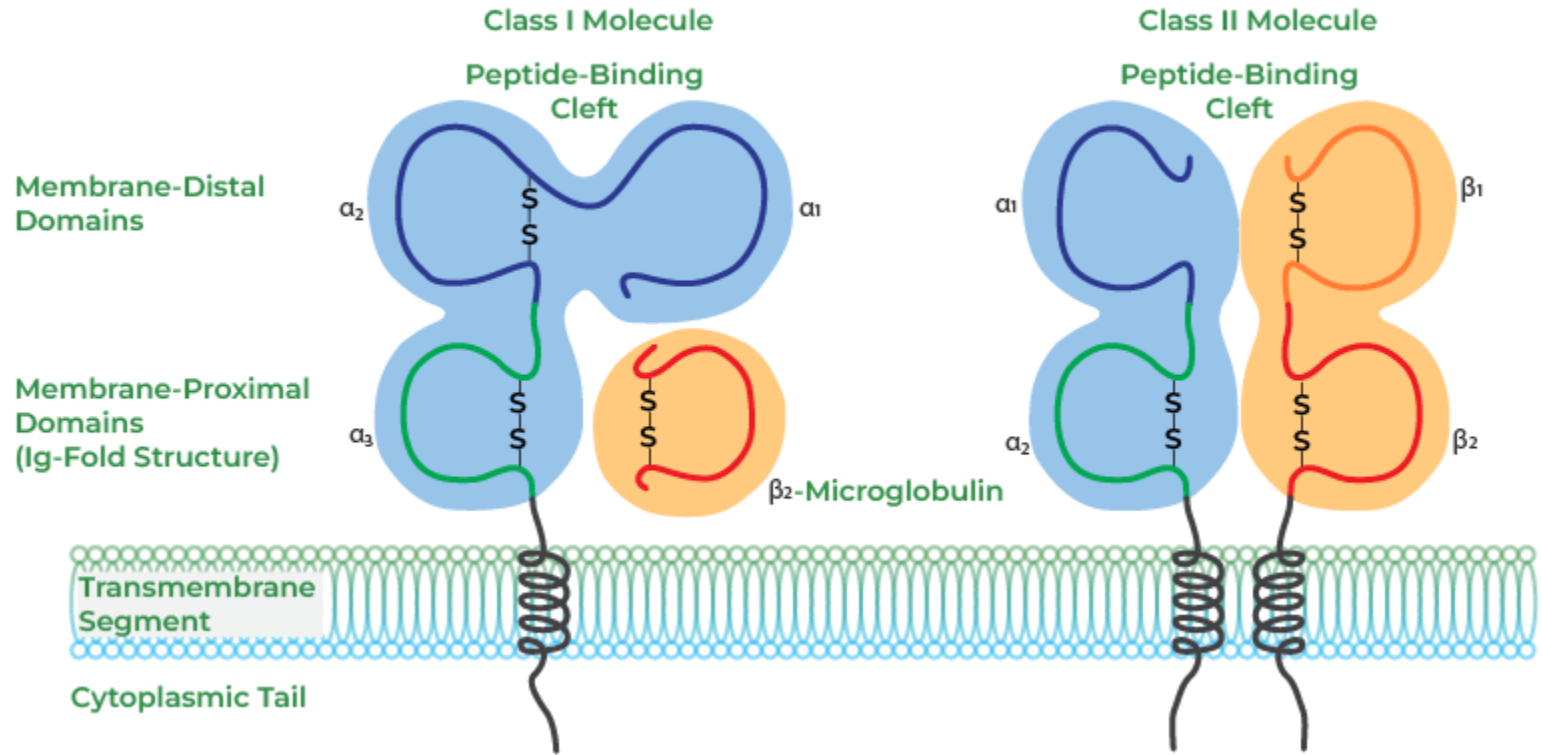
Major histocompatibility complex

- **MHC I:**
- expressed on all nucleated cells
- endogenous peptides
- recognized by CD8+ T cells

- **MHC II:**
- expressed on APCs
- exogenous peptides
- recognized by CD4+ T cells



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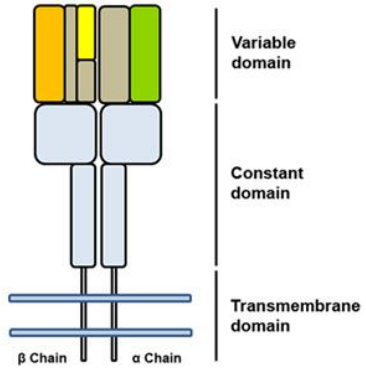
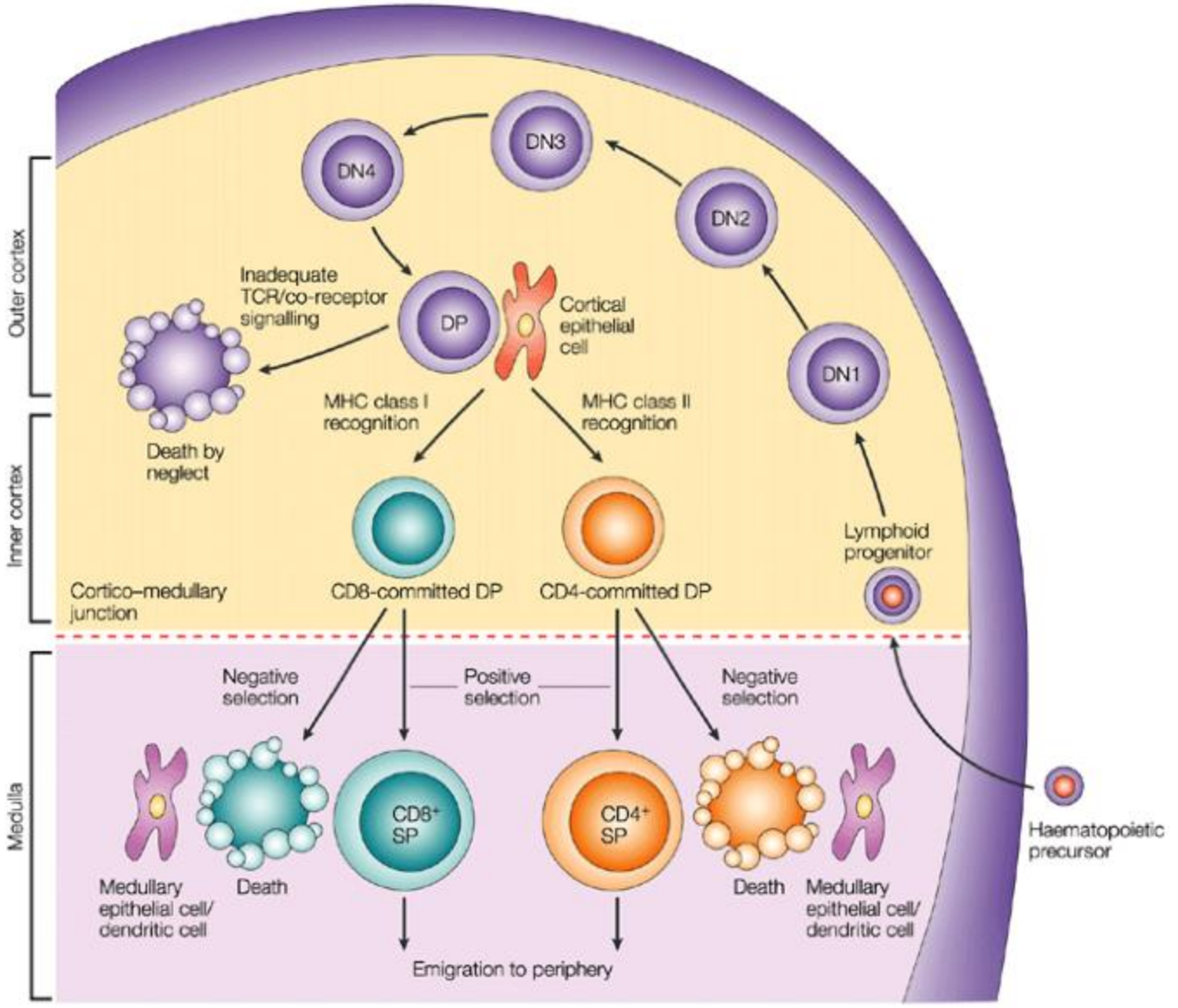
T-Lymphocyte maturation and selection

- Stem cells migrate from **bone marrow** to **thymus**
- Double negative T-cells (without CD4/CD8 stage)
- TCR gene rearrangement (of β chain) via VDJ recombination
- Double positive T cells (CD4+CD8+ stage)
- TCR gene rearrangement (of α chain) via VDJ recombination

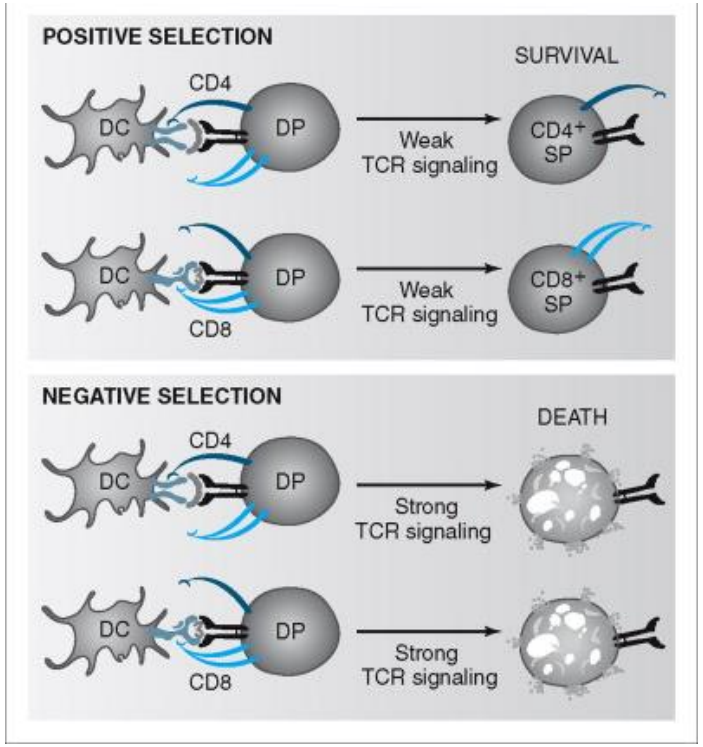




** V(D)J Recombination is a process that occurs in developing B and T cells to create unique antigen-binding regions of antibodies and T-cell receptors*

T-Lymphocyte maturation and selection

- Positive selection:
- ensures MHC restriction
- allows maturation of TCRs that can recognize self MHC-peptide complexes;
  - recognizing MHC I → CD8+
  - MHC class II → CD4+
  - no recognition → apoptosis
- Central tolerance (negative selection):
- ensures the TCR doesn't interact too strongly with self MHC-peptide complexes
  - if too strong → apoptosis



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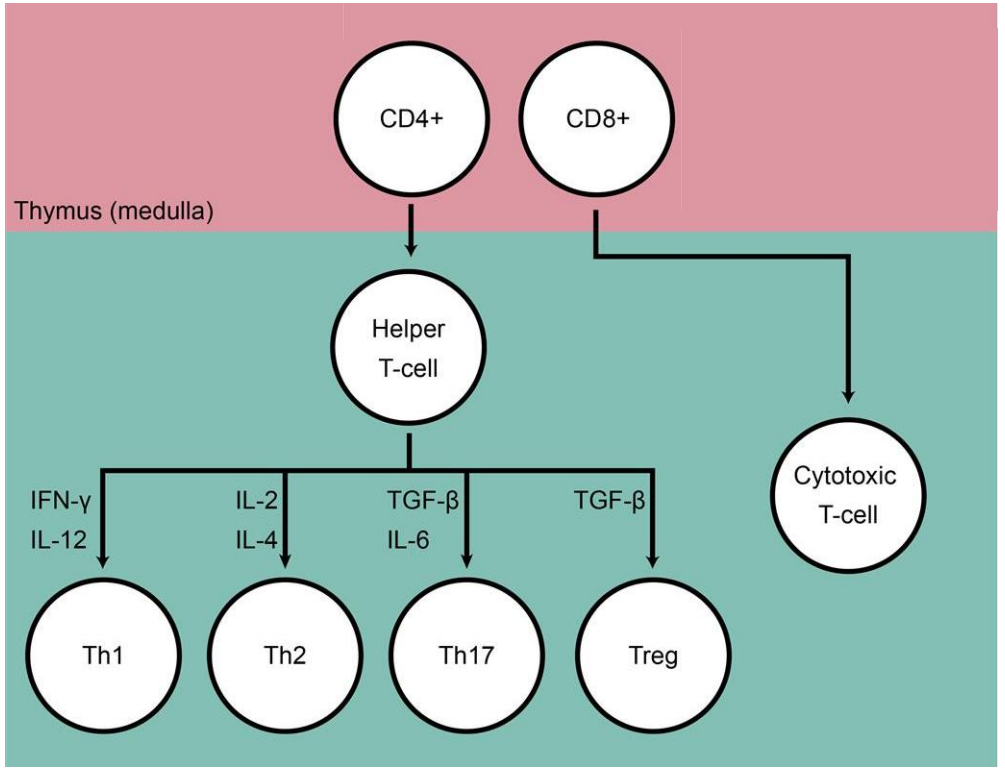
Helper T-cells

- Naive helper T cells (CD4+):
- Th1
- Th2
- Th17
- regulatory T-cells
- Activate phagocytes and IgE



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Th1

APC → IL-12 and IFN-γ → Th1

↓

IL-2 and IFN-γ

↓

Macrophages

+

T killer cells

- against **intracellular** pathogens
- Th1 cells are linked to:
- autoimmune diseases
- chronic inflammatory conditions

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Th2

APC → IL-4 → Th2

↓

IL-4 and IL-5

↓

eosinophils

+

mast cells

+

IgE

+

macrophages

- against helminths
- Th2 cells are linked to:
- allergic reactions

Macrophage

Mast cell

Eosinophil

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Th17

Th17
↓
IL-17 and IL-22
↓
neutrophil

- against extracellular pathogens
- Th17 cells are linked to:
- psoriasis
- rheumatoid arthritis
- autoimmune diseases

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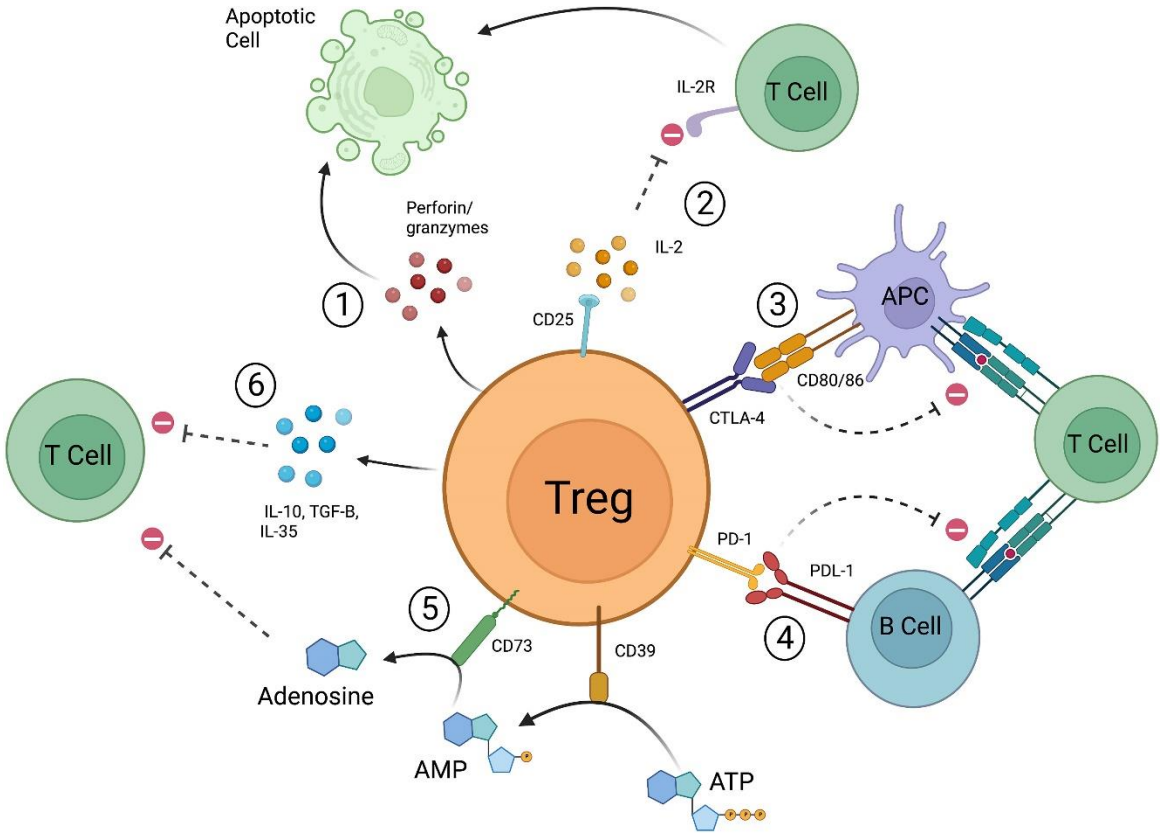
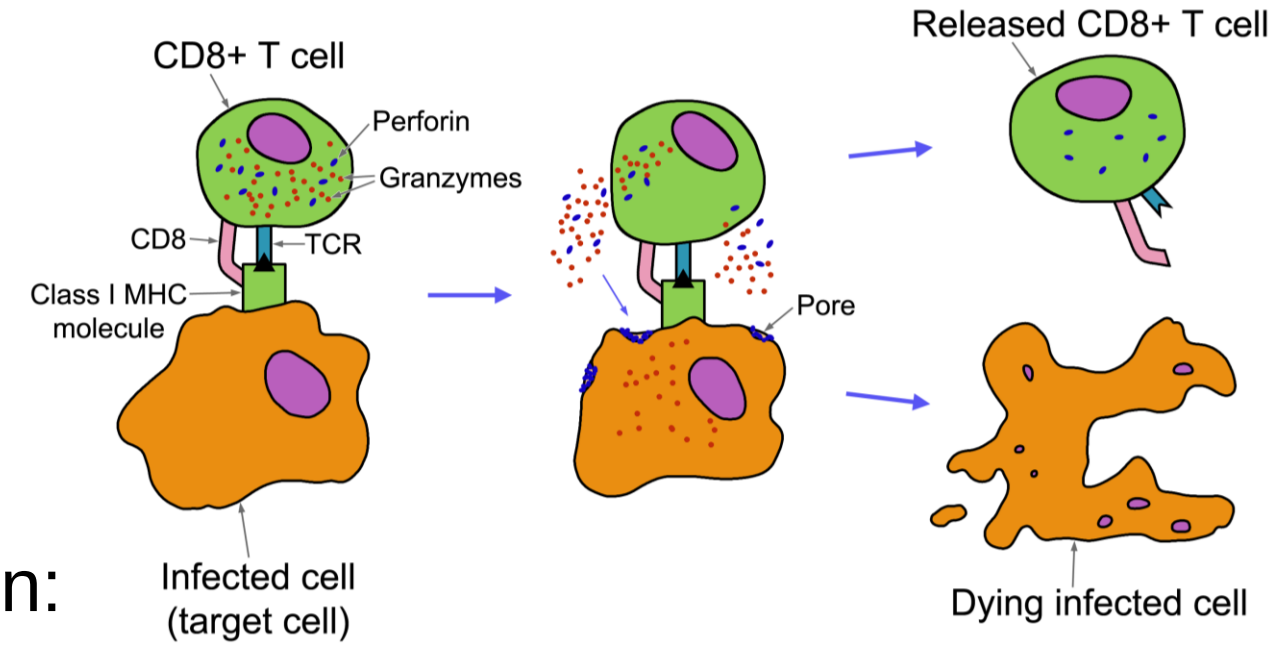
Regulatory T-cells

- express the cell surface proteins CD4 and CD25
- regulate the immune system by suppressing the immune response:
  - eliminate self-reactive T-cells (important for maintaining self-tolerance)
  - inhibit B-cell activation and proliferation
  - inhibit dendritic cell activation and proliferation
  - inhibit macrophage activation and proliferation
- **IL-2**:
  - ↑ Tregs
  - IL-10 → ↓ macrophages, dendritic cells, MHC class II expression, Th1 cytokine production
  - IL-35 → ↑ Tregs, ↓ macrophages + pro-inflammatory T-cells
- **IL-6**:
  - ↓ Tregs

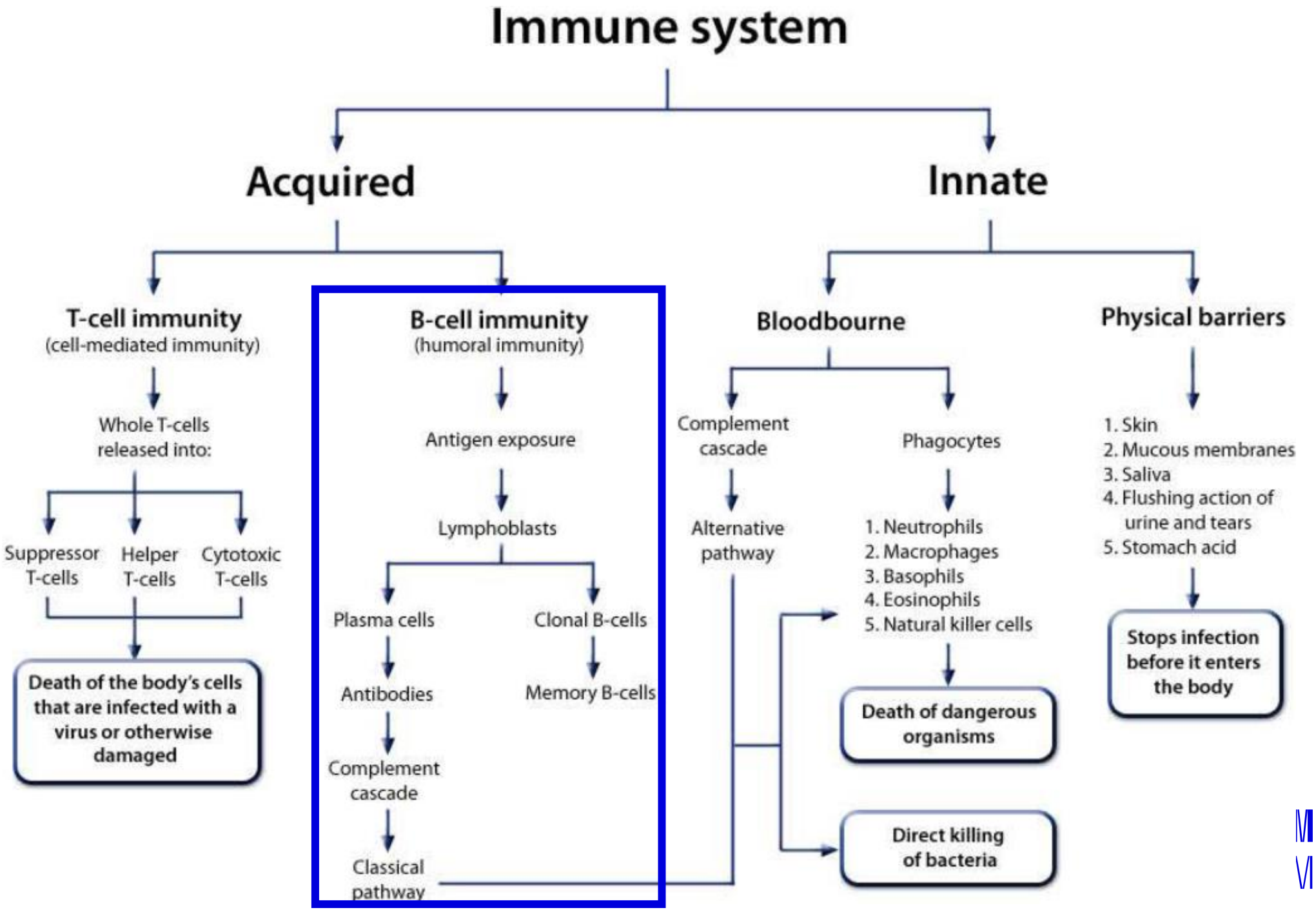


Cytotoxic T-cells

- Cytotoxic T-cells (CD8+)
- virus-infected cells
- tumor cells
- donor graft cells



- Steps of cytotoxic T-cell activation:
  - Antigen presented on MHC class I of infected cell
  - T-cell receptor (TCR) of cytotoxic T-cell binds to antigen presented by MHC class I of infected cell
  - CD28 on cytotoxic T-cell binds to B7 (CD80/86) on APC
  - Th1 (subset of helper T-cells) release IL-2 → ↑ cytotoxic T-cells
- Perforin forms pores in the target cell → granzyme B enters through channel → triggers intracellular signaling cascade → induces apoptosis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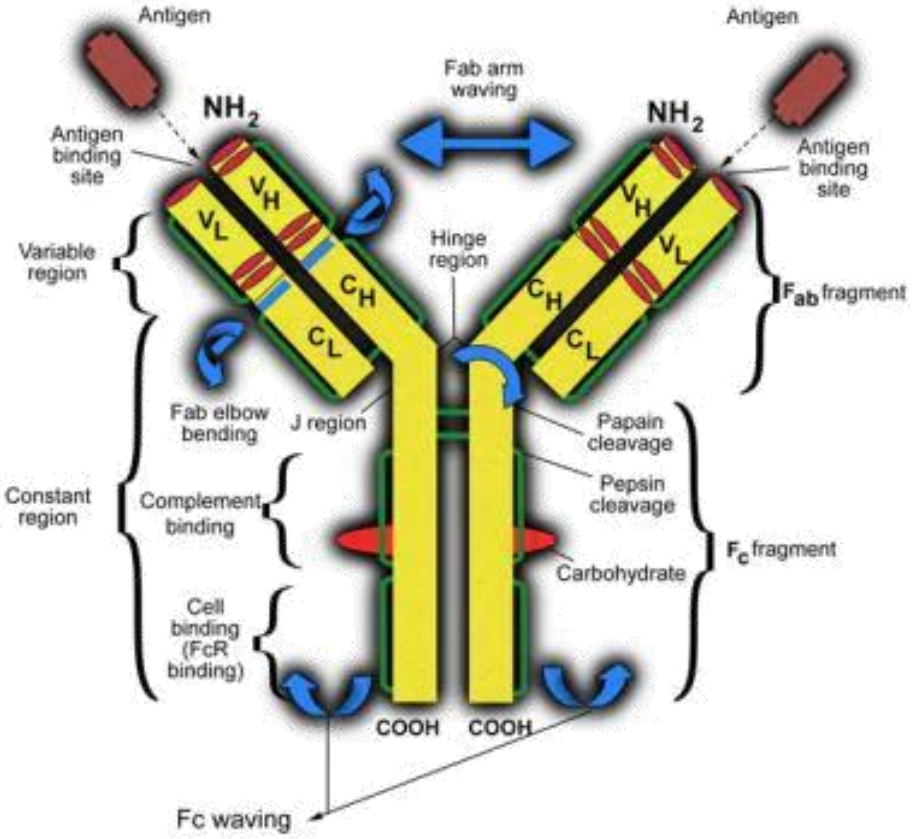
B-cell maturation

- B-cell development takes place in the bone marrow
- Steps of B-cell development:
  - hematopoietic stem cell →common lymphoid progenitor cell →early pro-B-cell →late pro-B-cell →large pre-B-cell →small pre-B-cell →immature B-cell →mature (naive) B-cell
- Positive selection
  - allowing proliferation of B-cells that have strong affinity to MHC molecules
- Negative selection:
  - removing self-reactive B-cells
- immature B-cells migrate to secondary lymphoid tissues (lymph nodes, spleen)
- follicular B-cells reside in follicles of germinal centers of secondary lymphoid tissues
- marginal zone B-cells target blood-borne antigens trapped in the spleen

Somatic hypermutation and affinity maturation

- B-cells undergo random point mutations in the B-cell receptor, resulting in the creation of new B-cells with increased antigen affinity and specificity (affinity maturation)
- Activation-induced cytidine deaminase (AID):
  - adds point mutations (cytosine → uracil) to the variable regions of the heavy and light chains (somatic hypermutation);
  - also involved in modifying constant regions of the BCR (isotype class switching)
- Immunoglobulins produced by B-cell → IgD, IgA, IgM, IgG, IgE

Immunoglobulin structure



- 2 identical heavy chains
- 2 identical light chains
- constant region (**Fc**) remains the same among all antibodies in a class
- **Fab** fragments (fragment antigen-binding region) are responsible for antigen recognition and binding; form the "arms" of the Y;
- The variable region (**Fv**) is the top part of the Fab fragment; this area varies between antibodies; contains the paratope (antigen binding site)

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- IgM:
  - is the first antibody produced by activated naive B-cells
  - first response to early infection
  - can be attached to cell surface or secreted into blood & lymph
  - can activate classical complement pathway
- IgG
  - is the most abundant ab in blood
  - can pass from parent to fetus via the placenta
  - tags antigens so phagocytes can eat them (opsonization)
  - capable of antibody-dependent cellular cytotoxicity
- IgA:
  - is responsible for mucosal immunity
  - secreted in GI, respiratory, and genitourinary tracts and found in saliva, tears, & milk
- IgE:
  - provides helminth protection
  - is responsible for mast cell degranulation
- IgD
  - co-expressed with IgM
  - least understood