RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Immunology 101

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  - Speaker: Lilly, Amgen
  - Speaker, Consultant: Abbvie, Janssen
  - Consultant: Novartis, Sanofi

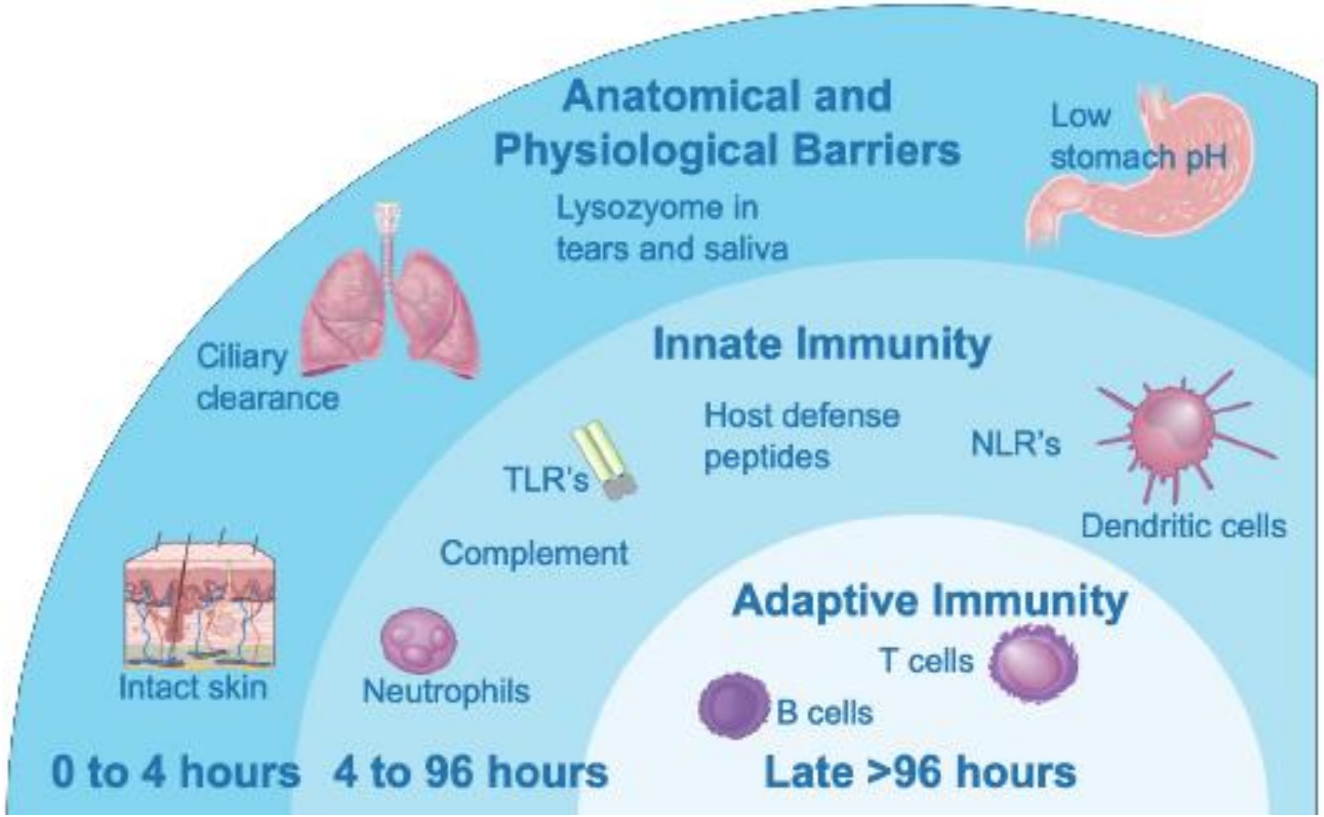
Outline

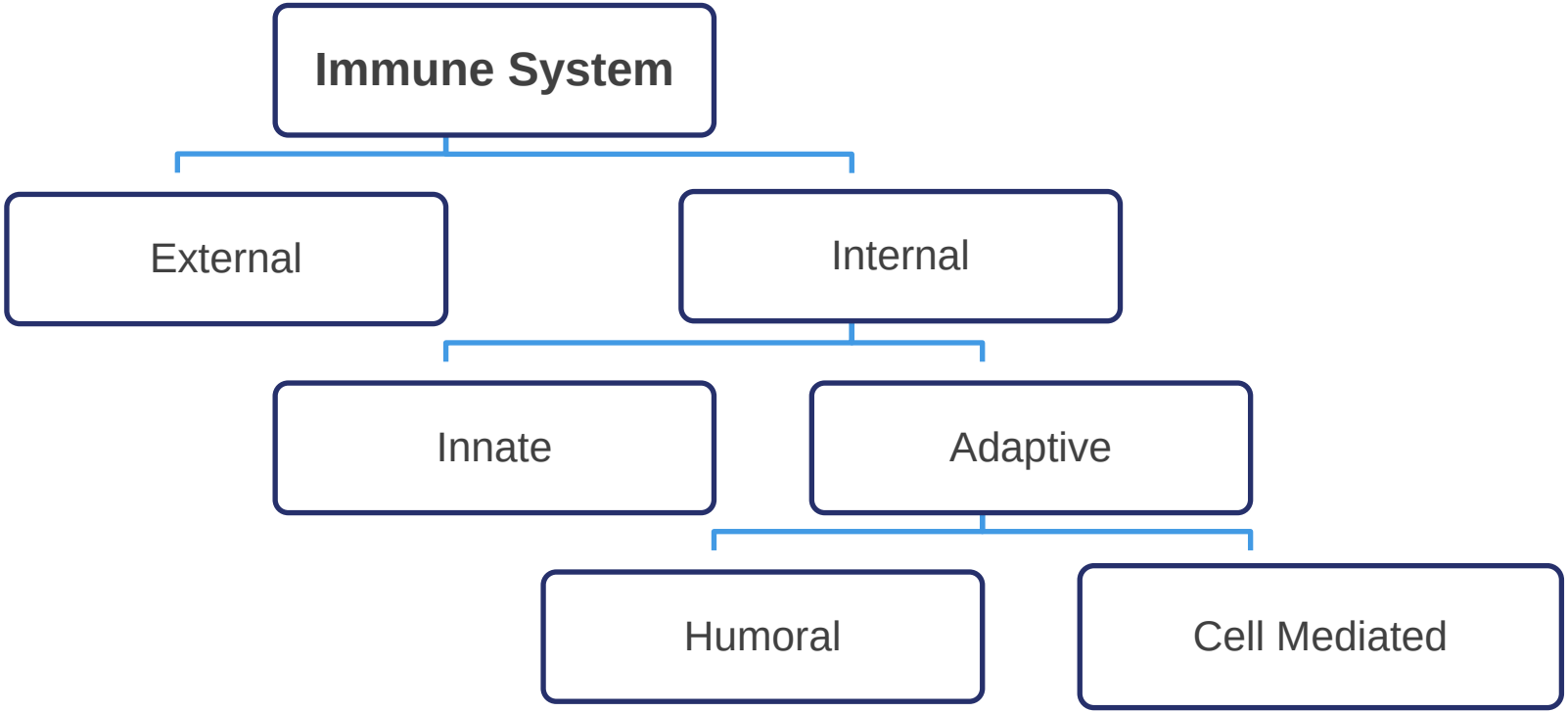
- Organization of the immune system
- The Innate response
  - Lymphocytes
  - Cytokines
  - Complement
- Adaptive Response
  - B cells
  - T cells

The Role of the Immune System

- Prevention
- Identification
- Destruction

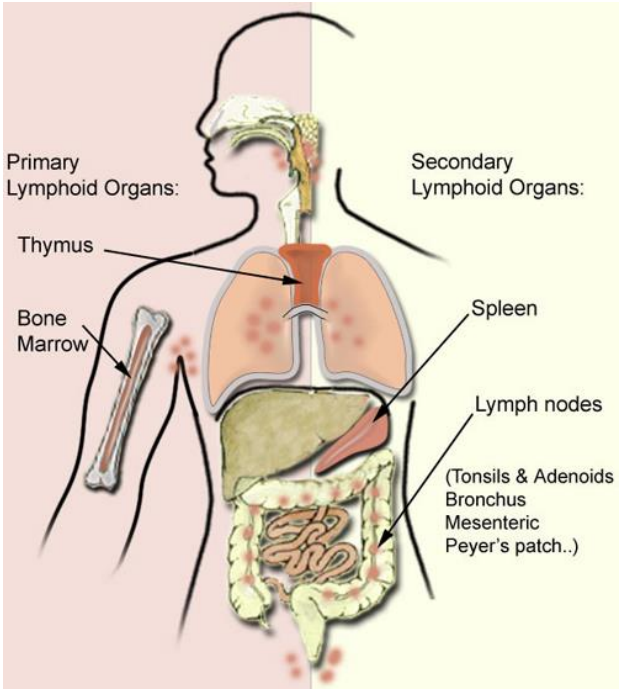
Organization of the Immune System

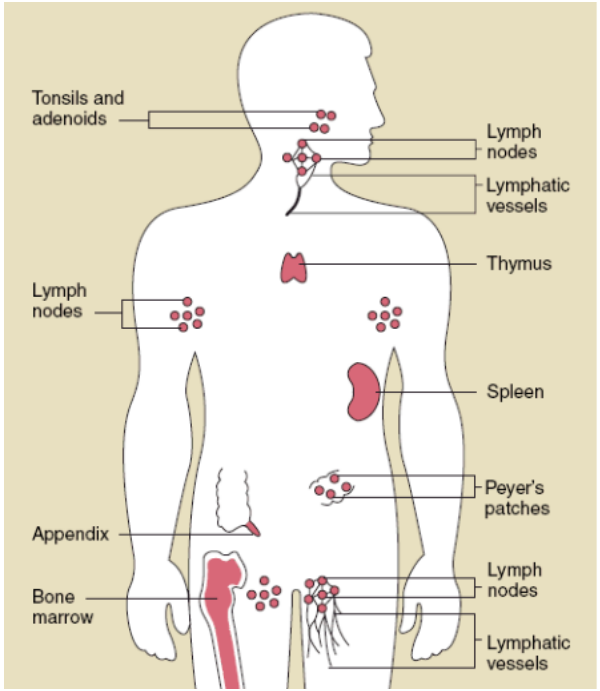



Immune System
External
Internal
Innate
Adaptive
Humoral
Cell Mediated

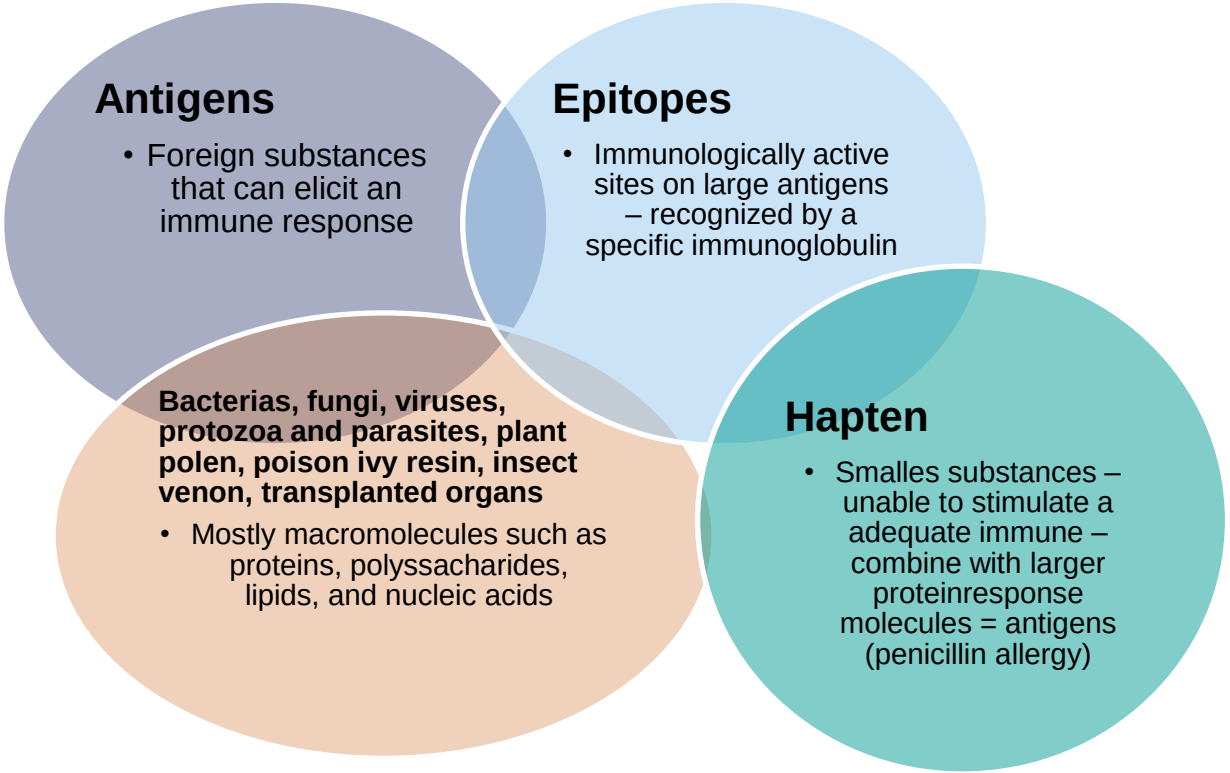
Organs and Tissues

- Spleen
- Lymph Nodes
- Bone marrow
- Blood
- Skin
- Intestines
- Liver
- Lungs

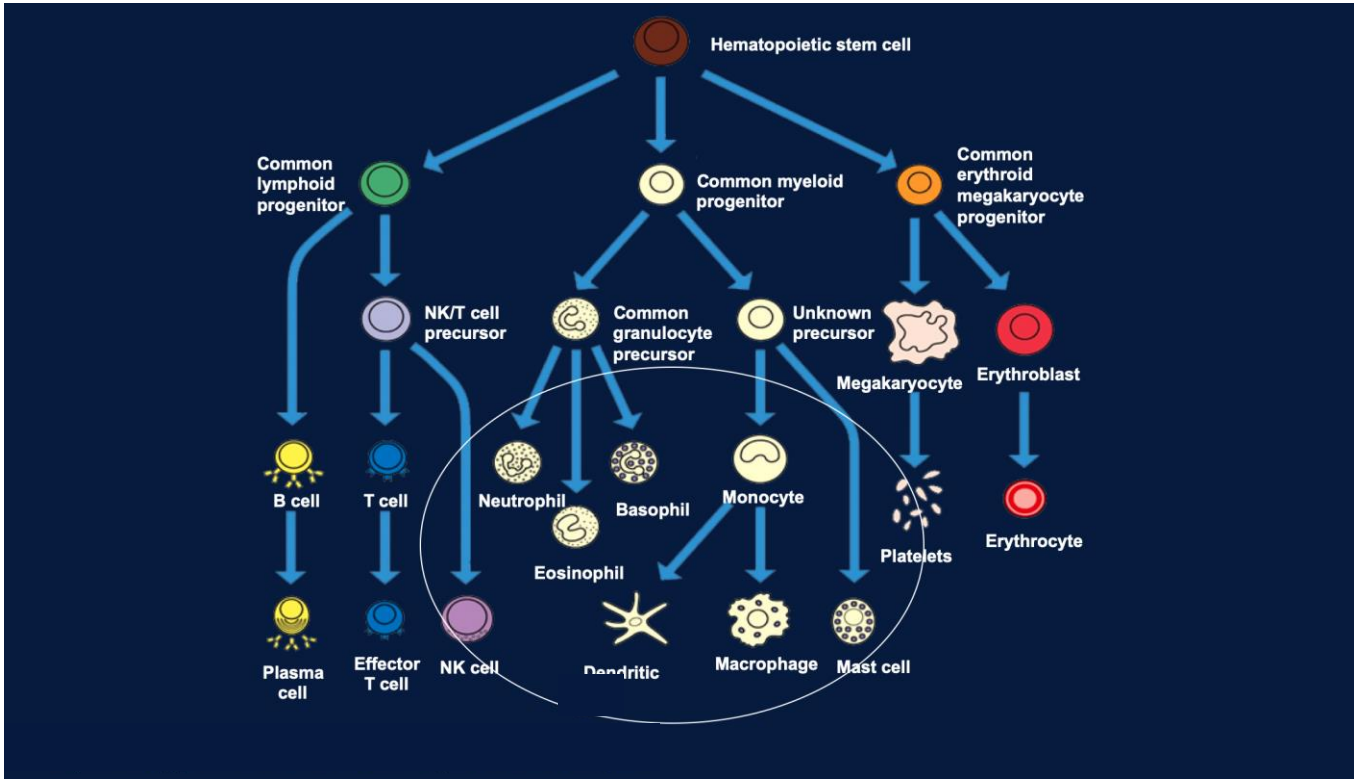




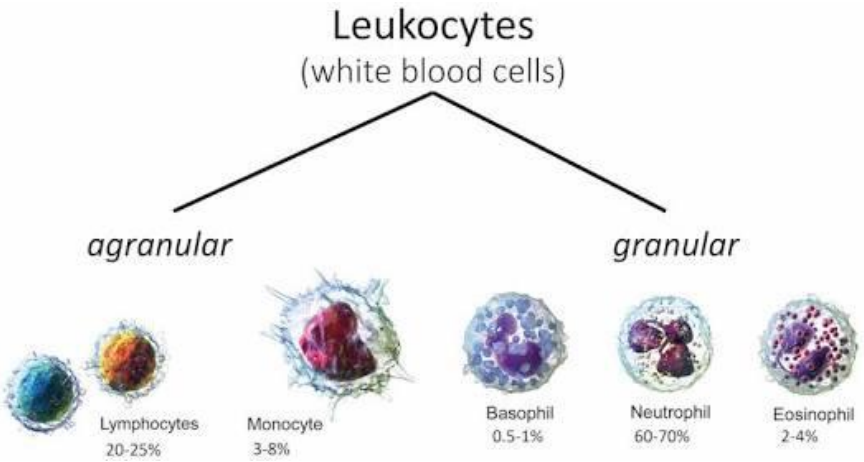
Identifying the Enemy



Cells Involved



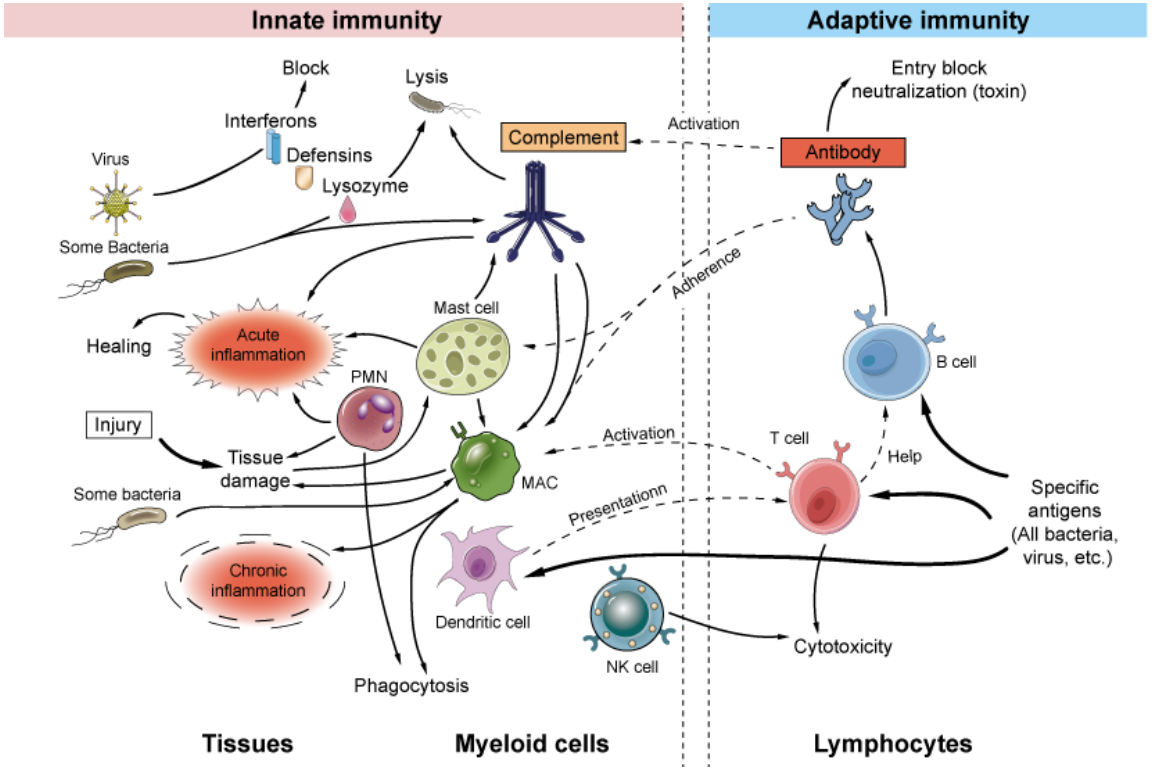
5 Major Cell Types



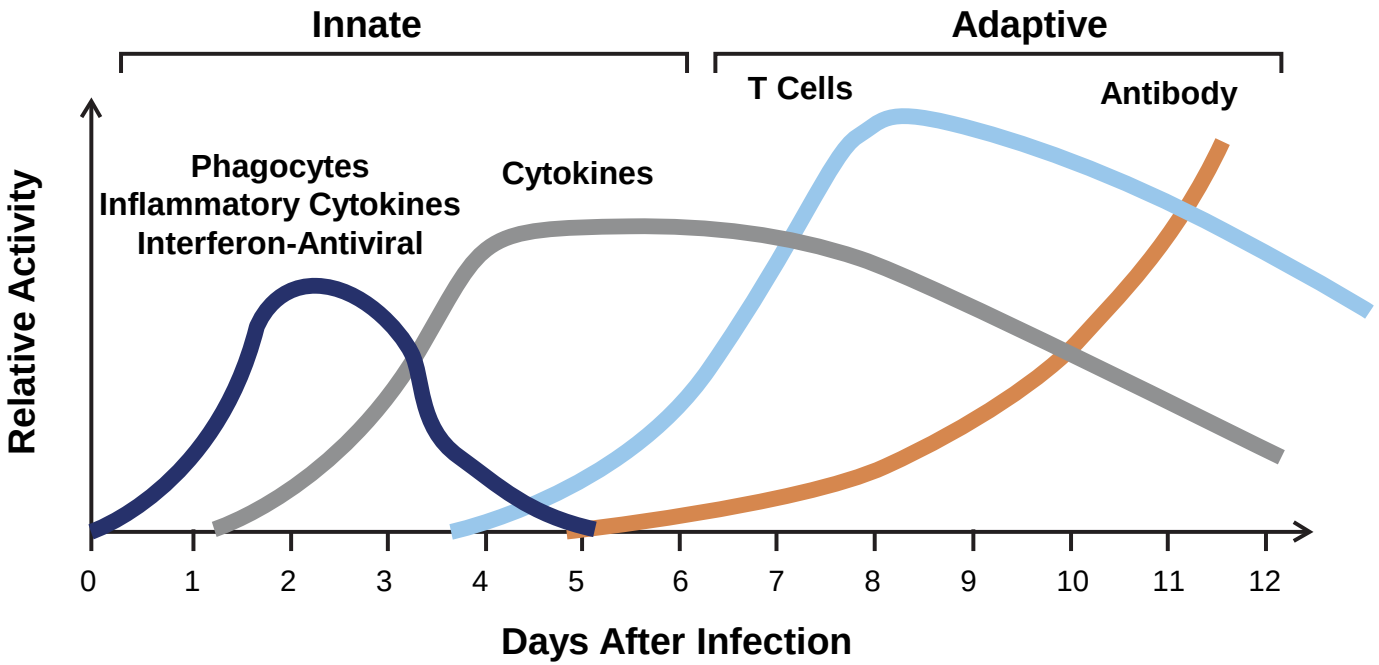
- Neutrophils leave the blood to go to tissues where infection or inflammation is developing
- Eosinophils attack organisms that are too big to be eaten by a single phagocyte
- Basophils do not attack and “swallow” invading cells; they release chemicals that help the body’s allergic response to a pathogen
- Monocytes are cells released into the blood from the bone marrow. When they get to a particular site in an organism, they may change into macrophages that engulf and destroy invading pathogens
- Lymphocytes are the fifth group of white blood cells; divided into three categories:
  NK cells, B cells, T cells

Innate and Adaptive Immunity

- **Innate**: Provides immediate protection against microbial invasion
- **Adaptive**: Develops more slowly and provides more specialized defense against infection



www.creative-diagnostics.com/innate-and-adaptive-immunity.htm.


Innate
Adaptive
T Cells
Antibody
Phagocytes
Inflammatory Cytokines
Interferon-Antiviral
Cytokines
Relative Activity
0
1
2
3
4
5
6
7
8
9
10
11
12
Days After Infection

The Innate Response

- First line of defense
- Present at birth
- Nonspecific immunity
- Prevent the colonization
- Entry and spread of microbes
- Rapid response
- Control or contain and infection while adaptative responses are being produced

- Cytokines, antimicrobial substances, fever, phagocytic activity
- Defenses are anatomic, physiologic, phagocytic, and inflammatory
- Stimulates the adaptative response and influences the nature of the response
- Phagocytes, Complement, natural killers' cells, dendritic cells

Barriers

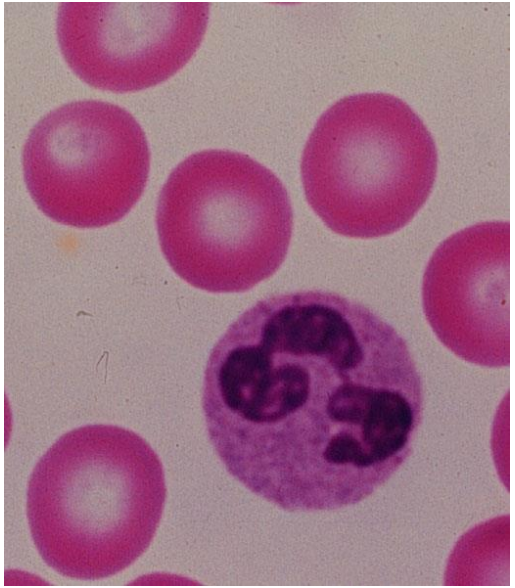
	Skin	Gut	Lungs	Eyes/nose/ oral cavity
Mechanical	Epithelial cells joined by tight junctions			
	Longitudinal flow of air or fluid		Movement of mucus by cilia	Tears Nasal cilia
Chemical	Fatty Acids	Low pH Enzymes (pepsin)	Pulmonary surfactant	Enzymes in tears and saliva (lysozyme)
	ß-defensins Lamellar bodies Cathelicidin	α-defensins (cryptdins) RegIII (lecticidins) Cathelicidin	α-defensins Cathelicidin	Histatins ß-defensins
Microbiological	Normal microbiota			

Key Players of the Innate Response

- Phagocytes
- Complement proteins
- Natural Killer Cells
- Dendritic Cells

Phagocytes

- Phagocytes : Neutrophils
  - “Foot soldiers”
    - Short-lived (~5 days)
    - Summoned by chemicals released by macrophages (cytokines: IL-1 and TNF)
    - Fight bacterial, fungi, cell remains and a variety of foreign substances
    - Granules contain degrading enzymes (lyosomes)
    - Epinephrine, exercise, stress and corticosteroid therapy – cause rapid increase (pulls from the marginating pool)
    - Endotoxins or microbes – cause transient decrease in circulating neutrophils (pulled into the tissues)
    - Stopped and “instructed” to leave the blood by 2 more systems
    - Multiple steps/receptors are safety measure
    - Powerful
    - Fun fact: pus is mainly dead neutrophils

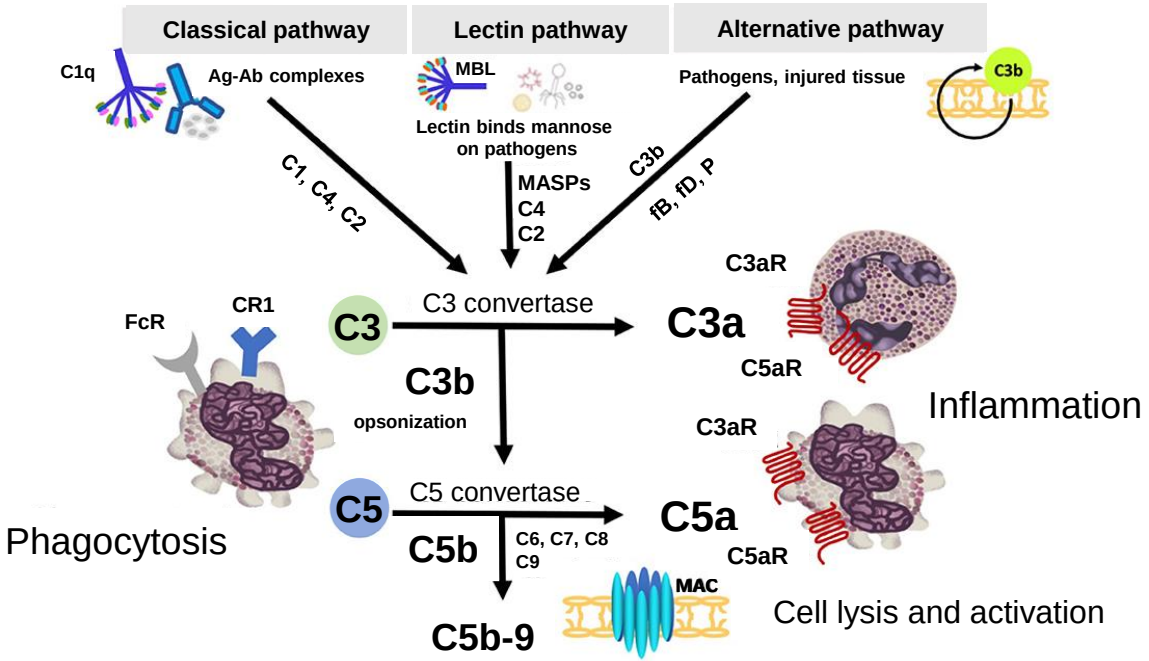


Complement System

- Ancient – protects against bacterial infections
- Contains about 50 serum and membrane components
- Three traditional activation pathways:
  - Antibody-mediated classical pathway
  - The lectin pathway,
  - Alternative (or tick over) pathway which also amplifies the classical and lectin pathways
  - All three pathways converge to cleave and activate C3 and C5 leading to a common terminal pathway and formation of the membrane attack complex
  - Complement system – Jack of all trades
    - Complement deficiency impairs both B and T cell responses
    - Involved in inflammation, hemostasis, embryogenesis, and organ repair and development
    - Alterations in the system are involved in thrombotic disorders, autoimmune disorders, schizophrenia, pre-eclampsia, alloimmune responses including allograft rejection and graft-versus-host disease, and cancer

Regal JF, Burwick RM, Fleming SD, et al. The complement system and preeclampsia. *Current hypertension reports. 2017;19*(11), 1-12.

Complement system



Girardi G, Lingo JJ, Fleming SD, Regal JF, et al. Essential Role of Complement in Pregnancy: From Implantation to Parturition and Beyond. *Front. Immunol.* 2020;11:1681. doi: 10.3389/fimmu.2020.01681.

Natural Killer Cells

- Natural Killer Cells
  - Short-lived (~7 days)
  - “On-call” (like neutrophils)
  - Once they get to target area, 2 roles:
    - Cytokine production
    - Kill via induction of apoptosis in target
      - “Kill” and “Don’t Kill” switches

Dendritic Cells

- Link between innate and adaptive immune system
- Antigen presenting cells
- Main role is to process antigen material and present it on the cell surface to T Cells

- Phagocytes: Macrophages
  - "Border Patrol"
    - Largest, Long-lived, Survive from months years to months in the tissues
    - Can sense invaders, grab, eat, destroy (Phagocytosis), digest, release cytokines
    - Responsible for
      - Chronic inflammation
      - Granulomatous inflammation – capsule around insoluble materials that cannot be digested
      - Foreign body granulomas – inert foreign bodies (talc, sutures)
      - Immune granulomas – insoluble particles that are capable of inciting a cell-mediated immune response. (tuberculosis)
    - Other names depending where
      - Antigen Presenting Cell
      - Histiocytes/loose connective tissue, microglial cells/brain, kupfer cells/liver
    - Link the innate to the adaptive

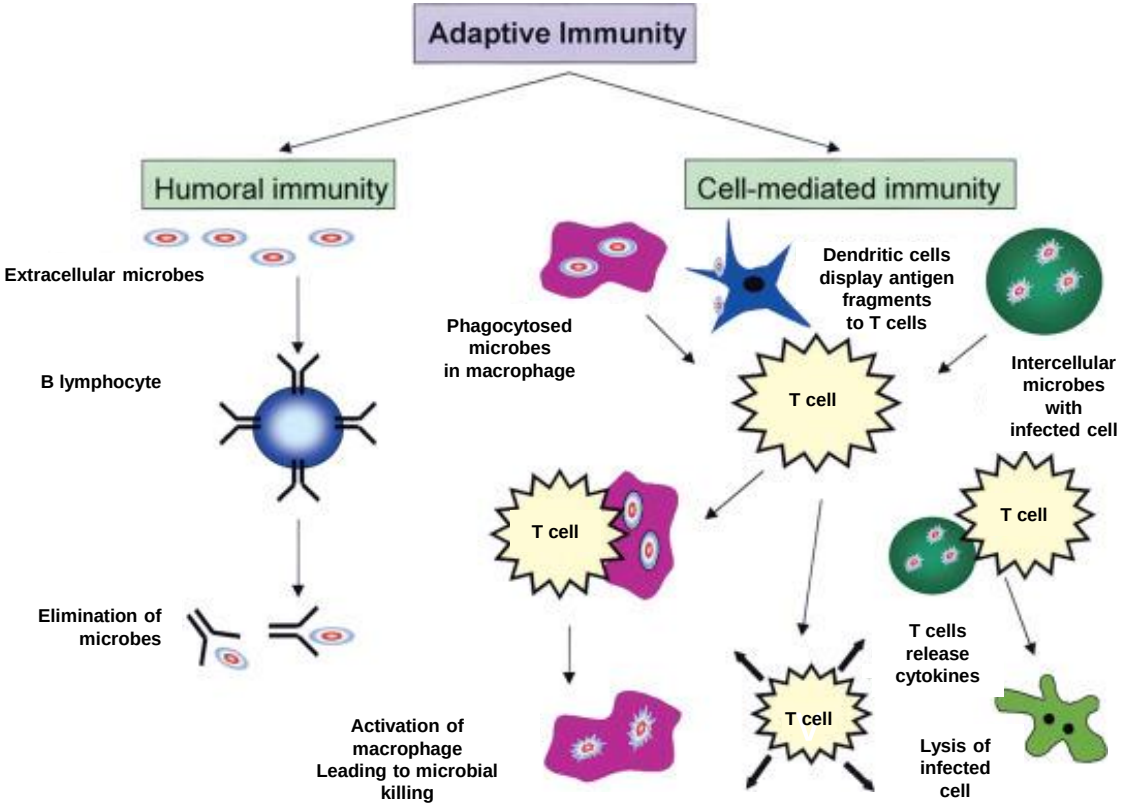
Adaptive Immunity

- Secreted antibodies bind to microbes, block their ability to infect host cells, and promote infection and destruction
- Very specific
- Develops in steps

Adaptive Immunity

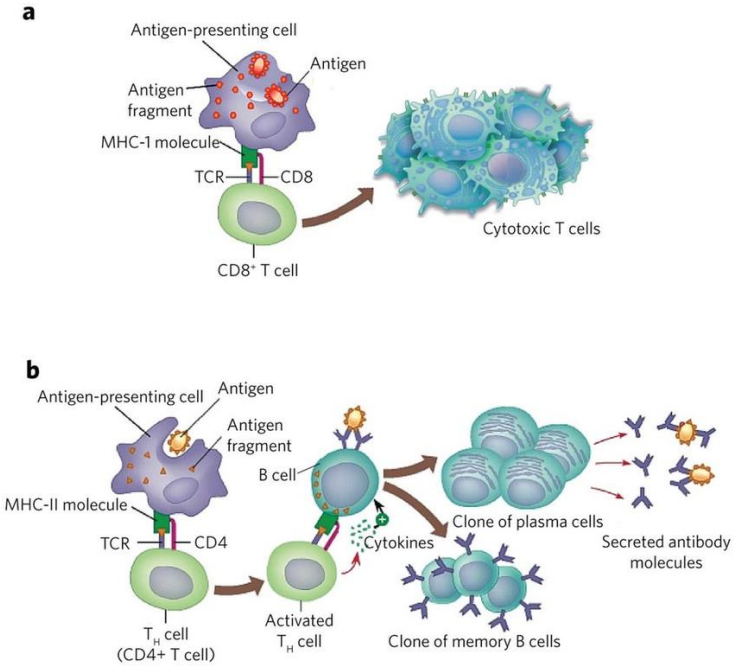
- Antigen-specific immune response
- More complex than the innate immune system
  - An antigen first must be processed and recognized.
  - Once an antigen has been recognized, the adaptive immune system creates an army of immune cells specifically designed to attack that antigen.
  - Adaptive immunity also includes a "memory" that makes future responses against a specific antigen more efficient.
- The adaptive immune system is divided into two parts:
  - Humoral (antibody-mediated) → B cells
  - Cellular → T cells
  - Both B and T cells recognize the antigen, proliferate in response to it, and migrate back to the site of injury. There they release cytokines that attract effector cells
  - The important difference between B cells and T cells is how they recognize antigens

Abbas, A. & Lichtman, A. & Pillai, S. 2014.


Adaptive Immunity
Humoral immunity
Cell-mediated immunity
Extracellular microbes
B lymphocyte
Elimination of microbes
Phagocytosed microbes in macrophage
Dendritic cells display antigen fragments to T cells
Intercellular microbes with infected cell
T cell
T cell
T cell
T cell
T cells release cytokines
Lysis of infected cell
Activation of macrophage Leading to microbial killing

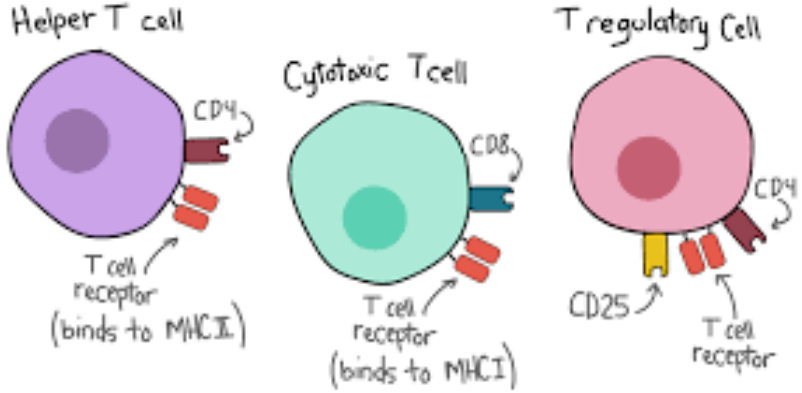
T-Cells

- When activated by APC, naïve T Cells secrete cytokines that stimulates the proliferation of T Cells and their differentiation into effector T Cells
- Helper T cells recruit neutrophils to the site, activate macrophages to kill ingested microbes, and some stay and help B lymphocytes to produce antibodies
- Cytotoxic T Cells directly kill cells harboring microbes

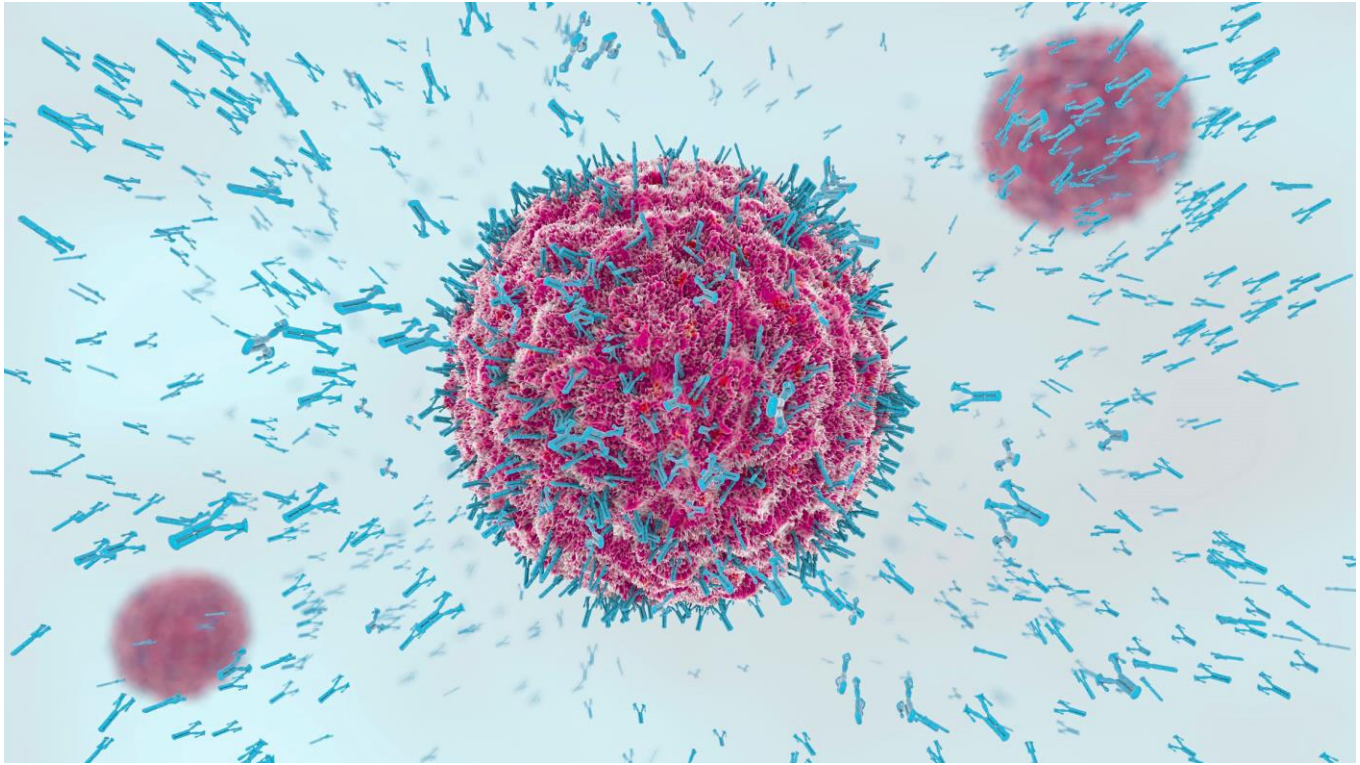


T-Cells – Different Cells With Different Functions

- 3 types of T Cells
  - Helper T cells (presenters)
    - Secrete cytokines (e.g., IL-6, IFN-g)
  - Cytotoxic lymphocytes (CTLs, “killer”)
    - Contact target and triggers it to commit suicide
  - Regulatory T cells
    - In charge of suppressing helper T cells if necessary



Humoral Immunity (B Cells)

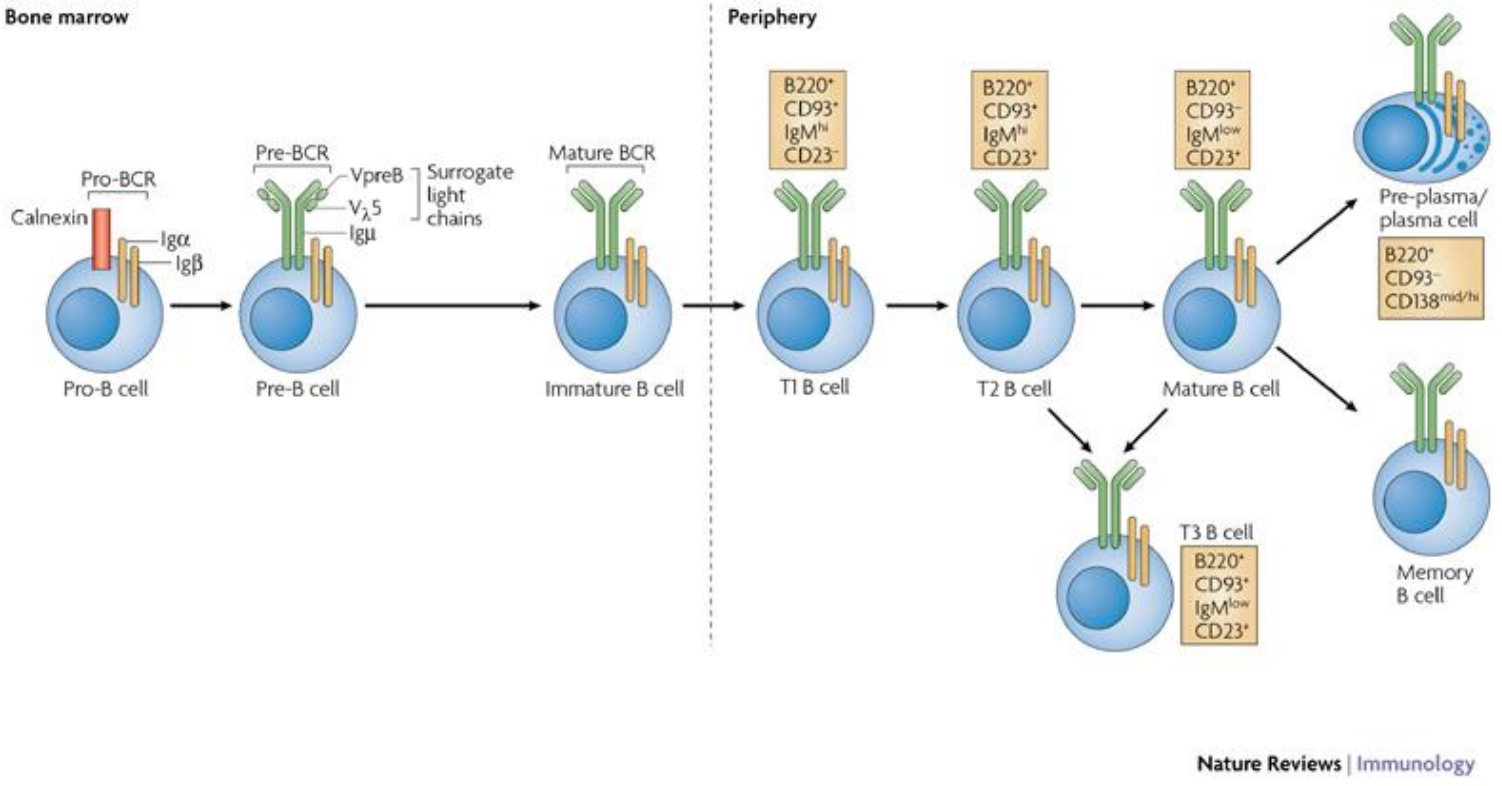


Humoral Immunity (B Cells)

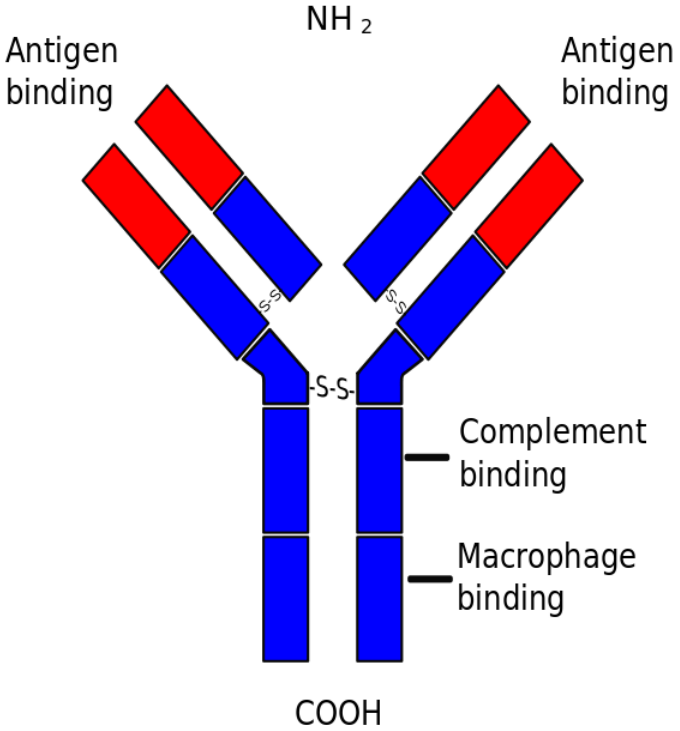
- On activation, B lymphocytes proliferate and then differentiate into plasma cells that secrete different classes of antibodies with distinct functions
  - Bind to microbes and prevent infection of the cells
  - Coat microbes to target them for phagocytosis
  - Activate the complement system

Abbas, A. & Lichtman, A. & Pillai, S. 2014.

B Cell Differentiation



More About Antibodies



Immunoglobulins

CLASS	GENERAL STRUCTURE		LOCATION	FUNCTION
IgG	Monomer		Free in blood plasma; about 80 percent of circulating antibodies	Most abundant antibody in primary and secondary immune responses; crosses placenta and provides passive immunizationto fetus
IgM	Pentamer		Surface of B cell; free in blood plasma	Antigen receptor on B cell membrane; first class of antibodies released by B cells during primary response
IgD	Monomer		Surface of B cell	Cell surface receptor of mature B cell; important in B cell activation
IgA	Dimer		Saliva, tears, milk, and other body secretions	Protects mucosal surfaces; prevents attachment of pathogens to epithelial cells
IgE	Monomer		Secreted by plasma cells in skin and tissues lining gastrointestinal and respiratory tracts	When bound to antigens, binds to mast cells and basophils to trigger release of histamine that contributes to inflammation and some allergic responses

LIFE 8e. Table 18.3. LIFE: THE SCIENCE OF BIOLOGY. Eighth Edition. © 2007 Sinauer Associates, Inc. and W. H. Freeman & Co.

Now to Put It All Together…..

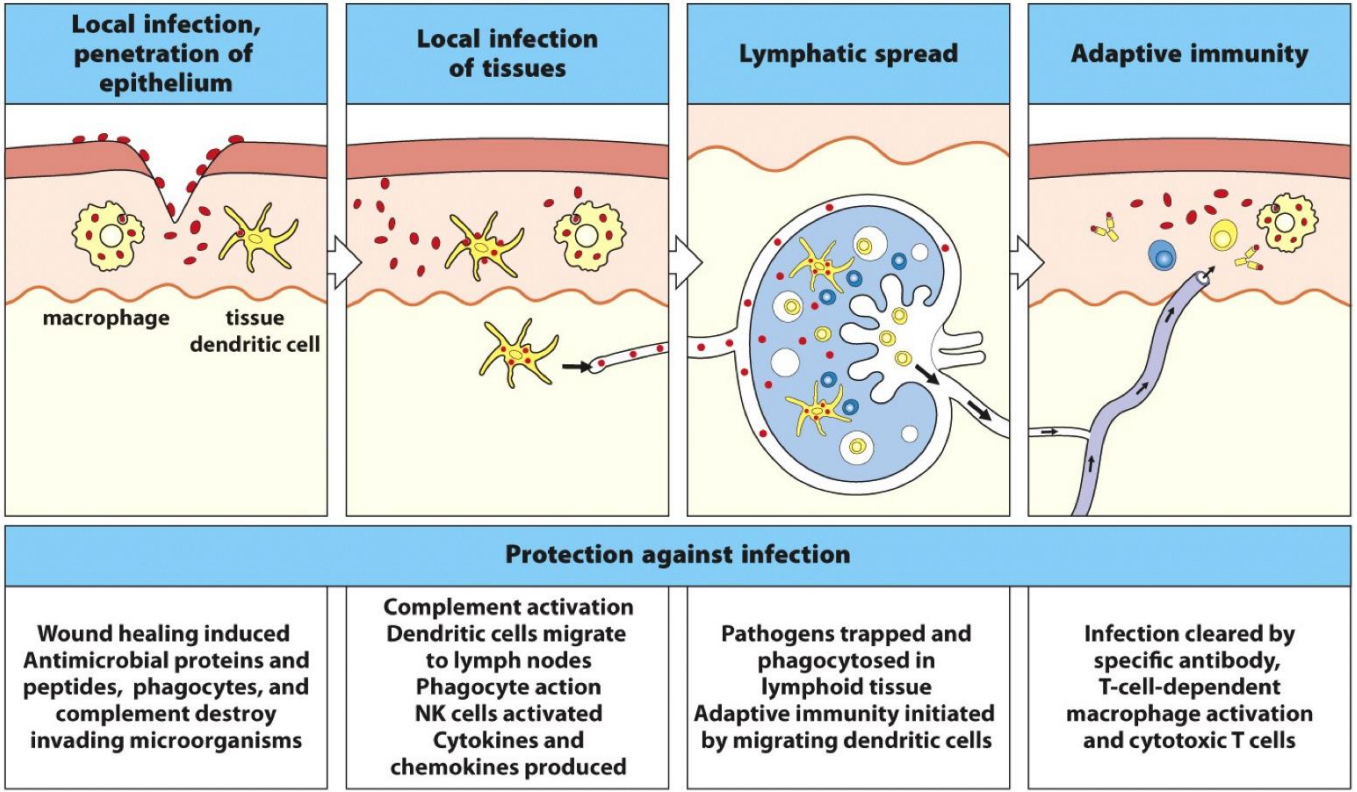
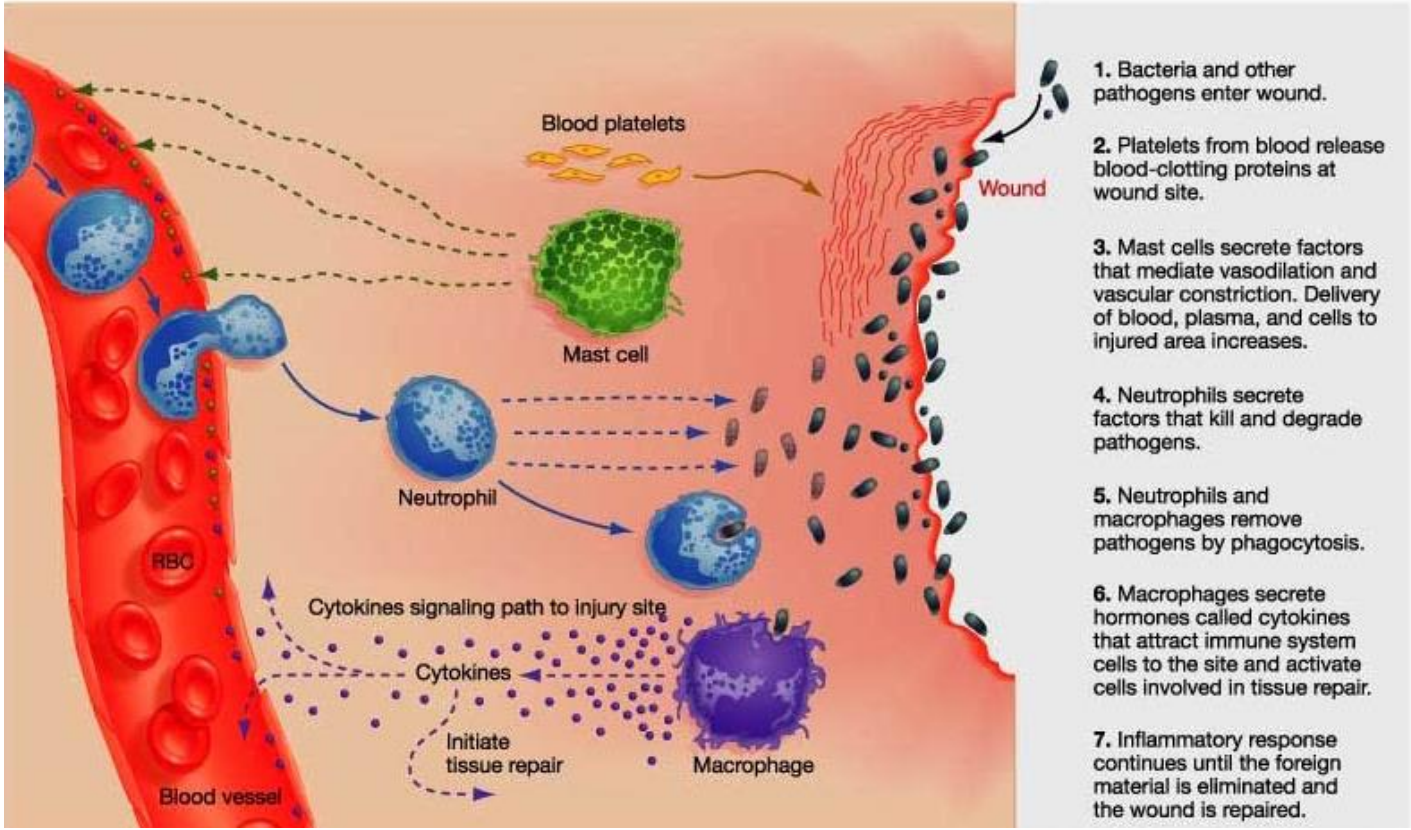


Figure 11.2 *Janeway's Immunobiology*. 8ed. (© Garland Science 2012).


Blood platelets
Wound
Mast cell
Neutrophil
RBC
Cytokines signaling path to injury site
Cytokines
Initiate tissue repair
Macrophage
Blood vessel
1. Bacteria and other pathogens enter wound.
2. Platelets from blood release blood-clotting proteins at wound site.
3. Mast cells secrete factors that mediate vasodilation and vascular constriction. Delivery of blood, plasma, and cells to injured area increases.
4. Neutrophils secrete factors that kill and degrade pathogens.
5. Neutrophils and macrophages remove pathogens by phagocytosis.
6. Macrophages secrete hormones called cytokines that attract immune system cells to the site and activate cells involved in tissue repair.
7. Inflammatory response continues until the foreign material is eliminated and the wound is repaired.

Summary

- The role of the immune system is multifactorial; prevention, identification, and destruction
- The immune system includes innate immunity which is non-specific and quick and adaptive immunity which is specific and initially slow
- The immune system has many cells and tissues
- Inflammation is an important defense mechanism to protect us but too much of anything is not good –
  i.e., autoimmune diseases

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