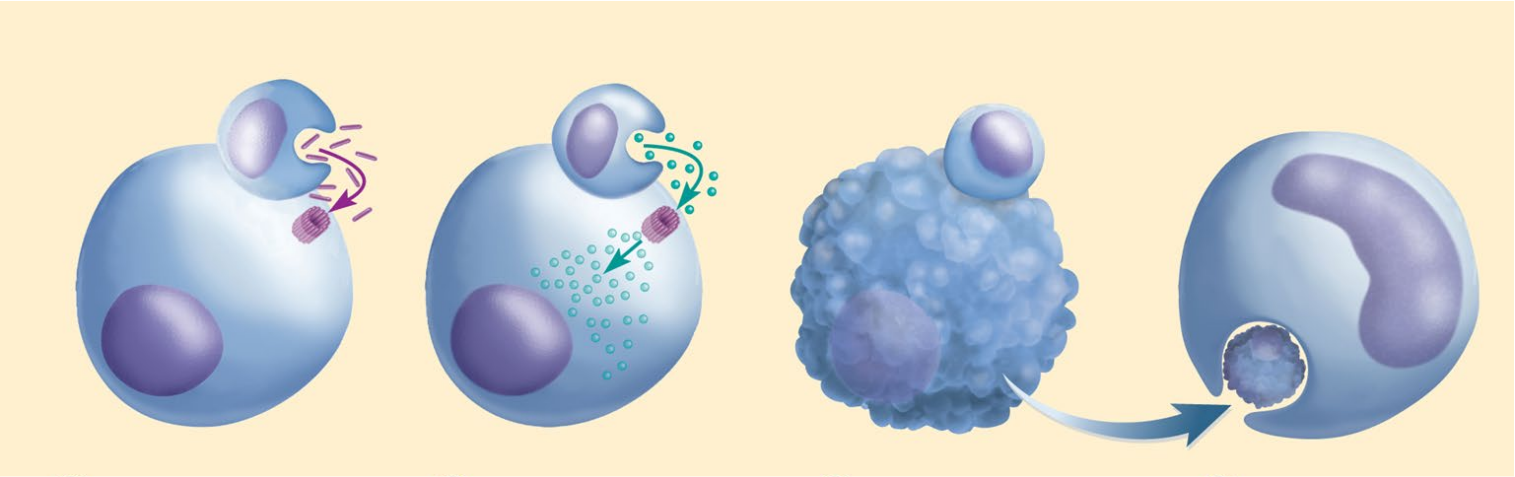
Chapter 21.4

The Immune System's Three Lines of Defense

- The First Line of Defense
- The Second Lines of Defense
- The Intro to the Third Line of Defense



The Immune System Defends Us Against Pathogens

What is a pathogen? (*microorganisms capable of producing disease in a healthy person)*

What may damage our tissues? *infections (by bacteria, virus, parasites), toxins, chemicals, physical trauma, and radiation*

Human host cells must defend themselves against internal and external threats that may harm us.

Immune system use three separate "lines of defenses"

–First Line – physical barriers
–Second Line – nonspecific resistance
–Third Line – adaptive immunity

Innate

Not innate

The Immune System's Three Lines of Defense

First line of defense = external barriers = Skin + mucous membranes // innate defense – because present at birth // include secretions by barriers

Second line of defense – provides non-specific resistance to pathogens

Innate defense - because present at birth

Uses different methods /// leukocytes and macrophages, molecules, immune surveillance cells, inflammation, and fever

Effective against a broad range of pathogens / but not specific to any one pathogen!

The Immune System's Three Lines of Defense

Third line of defense (acquired immunity – requires activation // not innate

This defense develops after birth

Defeats "specific" pathogens // key idea is specificity

Leaves body with 'memory cells' – allows for more rapid secondary response to pathogen

Cellular and humoral response (able to attack pathogen inside or outside of our cells!)

First Line of Defense - “Physical Barriers”

Physical Factors	Chemical Factors on Surfaces of Physical Barriers
Epidermis of skin	Sebum
Mucous membranes	Lysozyme
Mucus	Gastric juice
Hairs	Vaginal secretions
Cilia	Defensin
Lacrimal apparatus	
Saliva	
Urine	
Defecation and vomiting	

First Line of Defense - “Physical Barriers”

Skin

makes it mechanically difficult for microorganisms to enter the body

toughness of keratin

too dry and nutrient-poor to support microbial growth

defensin – peptides that kill microbes by creating holes in their membranes

acid mantle – thin film of lactic acid from sweat which inhibits bacterial growth

First Line of Defense - “Physical Barriers”

Mucous membranes

digestive, respiratory, urinary, and reproductive tracts are open to the exterior and protected by mucous membranes

mucus physically traps microbes

lysozyme - enzyme destroys bacterial cell walls

Sub-epithelial areolar tissue

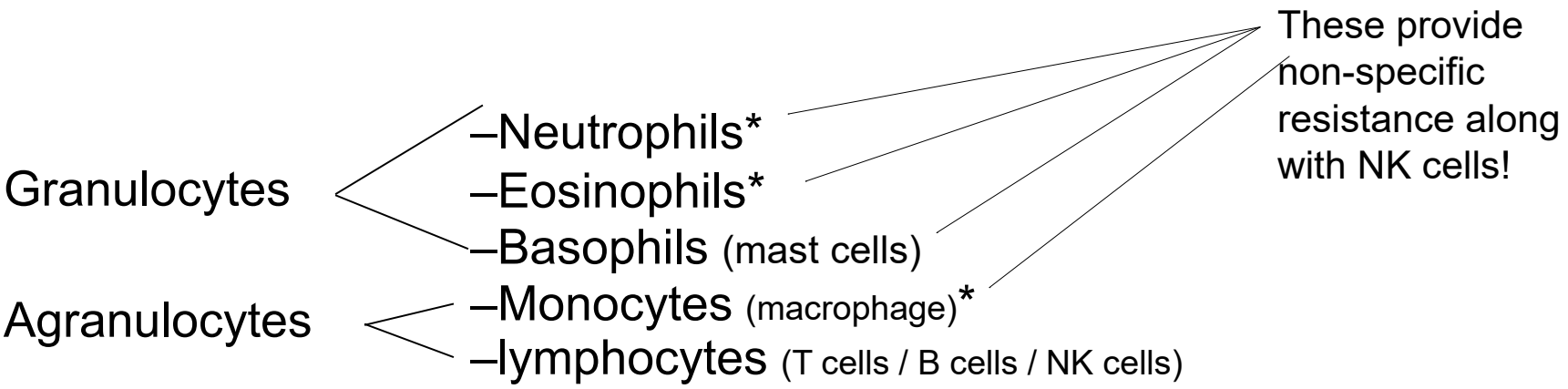
- viscous barrier of hyaluronic acid (nickname = glue that holds cells together / stuff in interstitial spaces / hydrated protein)

- hyaluronidase - enzyme used by pathogens to make hyaluronic acid less viscous

Second Line of Defense
Non-Specific Resistance

Antimicrobial Substances	Cellular
Interferon	Natural killer cells
Complement system	Phagocytes
Iron-binding proteins	Physiologic
Antimicrobial proteins	Inflammation
	Fever
	TOLL Like Receptors / PAMP

Second Line of Defense Cellular Effectors Non-Specific Resistance



Phagocytes provide the cellular component

–Able to engulf bacteria, endo-cytocytosis

–Dead infected cells, and fragments of cells

–Internalized as phagosome / fuse with lysosomes

Neutrophils kill bacteria and eosinophils kill parasites with respiratory bursts

What are the three lymphocyte types?

Circulating blood contains

–80% **T cells (cellular immunity)**
–15% **B cells (humoral immunity)**

Primary role 3rd line of defense

– 5% **NK cells (immune surveillance)**

Primary role in 2nd line of defense

Many diverse functions

T and B lymphocytes play key role in Acquired Immunity

NK Cells key role in 2nd line - because they perform general surveillance for cells infected with cancer or virus

NK Cells recognize and attack infected cells – this is why we refer to NK cells as “immune surveillance”

NK cells also play a role in the 3rd line of defense.

NK Cells Provide Immune Surveillance

Immune surveillance –natural (NK) killer cells continually patrol tissue looking for pathogens inside our cells (bacteria and virus).

Natural killer (NK) cells attack and kill infected cells. Macrophage come to area and "clean up the mess"

Primary role to kill cells infected with virus and cancer cells

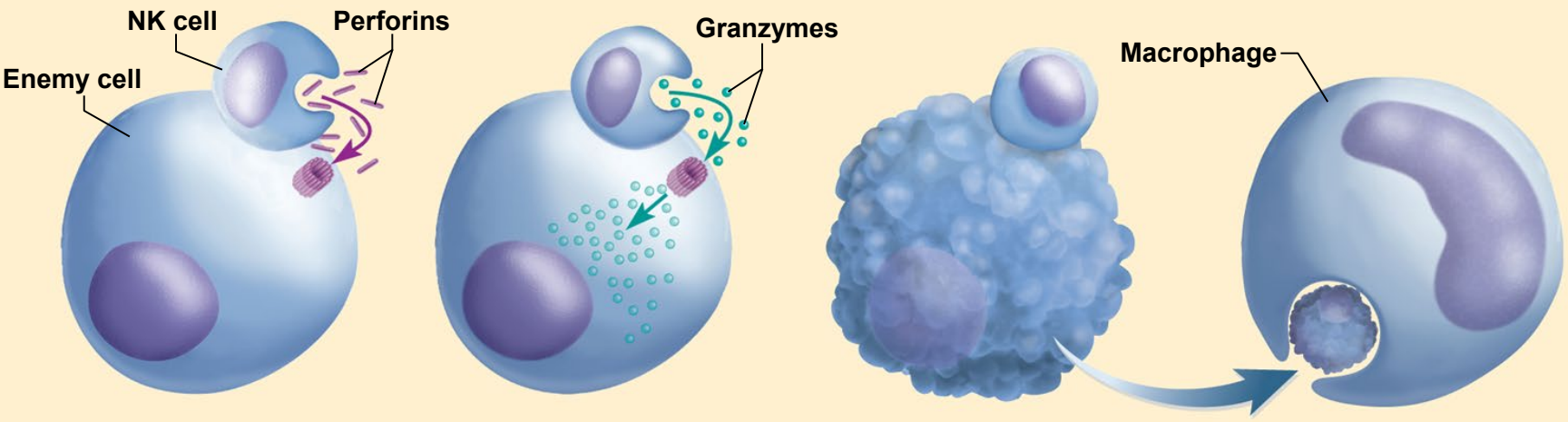
Recognizes host cells infected with cancer or virus // NK cells bind to host cell then release proteins called perforins // cause the kiss of death!

– polymerize a ring and create a hole in its plasma membrane

– secrete a group of protein degrading enzymes – granzymes

– enter pore and degrade cellular enzymes and induce apoptosis

Action of NK cell



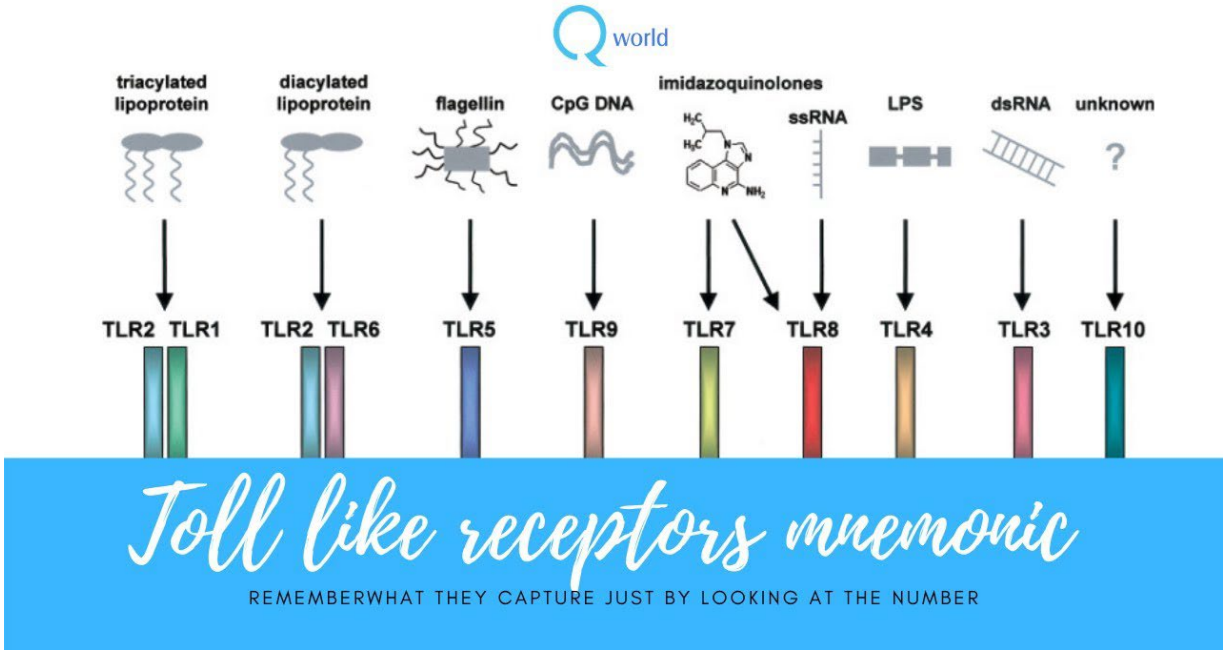
Note: same mechanism used by cytotoxic T cells to kill infected cells in acquired immunity! This mechanism is called the “kiss of death”.

Toll Like Receptors and Pathogen Associated Molecular Patterns

Type of “non-specific resistance” // 2nd line of defense.

The toll like receptors are on the WBC plasma membrane. The receptors are matched to pathogen associated molecular pattern molecules common to and on many different types of bacteria surface.

Toll Like Receptors (TLR) are on plasma membranes of macrophage, neutrophils, and epithelial cells lining mucous membranes (e.g. respiratory and GI tracts).

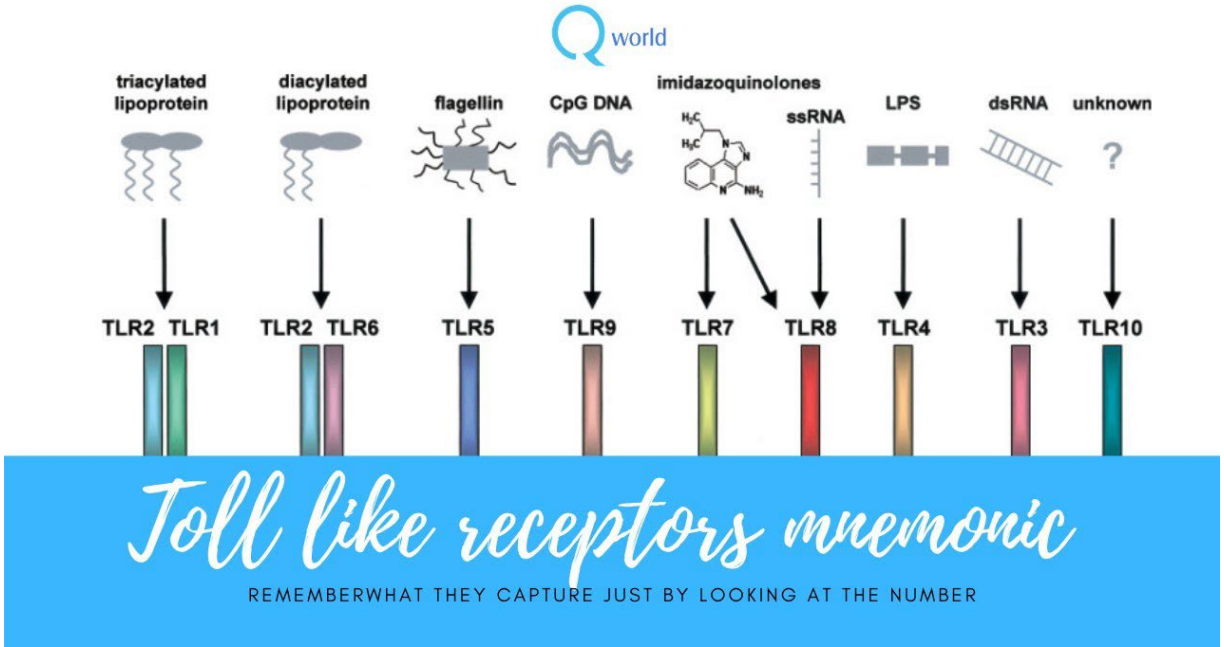


Toll Like Receptors and Pathogen Associated Molecular Patterns

TLR are docking stations for "pathogen associated molecular patterns" (PAMP) located on bacteria and virus /// 11 different types of human TLR

Each one recognizes a different "class" of microbe (e.g. gram negative bacterial like salmonella but same receptor would also bind to all gram-negative bacteria)

Once bound to a PAMP the TLR activates the release of inflammatory chemicals called "cytokines" from monocyte



Non-Cellular Antimicrobial Proteins
Part of the Second Line of Defense

Two families of antimicrobial proteins on internal tissues of body

Interferons *// proteins that inhibit viral reproduction – secreted by cells infected by virus // an "alarm signal" for other cells in area to initiate anti viral mechanisms within their cells*

Complement system // proteins made by liver and circulate in blood // when activated these proteins kill pathogens by forming tubes that make holes in pathogen's cell membranes // different activation methods // *provide short-term, nonspecific resistance to pathogenic bacteria and viruses /// complement functions in both in the 2nd and 3rd line of defense*

Interferon

Secreted by cells infected by a viruse

Provide no benefit to the cell infected by the virus but the cell secretes interferon // lymphocytes, macrophage, fibroblasts all may secrete interferon

Interferon is a signal molecule and alerts neighboring cells so they may initiate anti-viral resistance mechanisms // less likely to be infected by the virus

Interferon bind to surface receptors on neighboring cells /// activate second-messenger systems

Mechanism of actions:

Alerted host cell metabolism to synthesizes various proteins that defend it from infection // breaks down viral genes // helps prevent replication of virus by “host cell”

Signal NK cells and macrophages to migrate to area of infection /// goal is to destroy infected cell before they can liberate a swarm of newly replicated viruses /// activated NK cells to destroy malignant cells

Complement System

A group of 30 or more globular proteins that make powerful contributions to both to the second line of defense and to third line of defense. / nonspecific resistance and specific immunity

–Proteins synthesized mainly by the liver

–Circulate in the blood as inactive proteins

–Activated by the presence of the pathogen

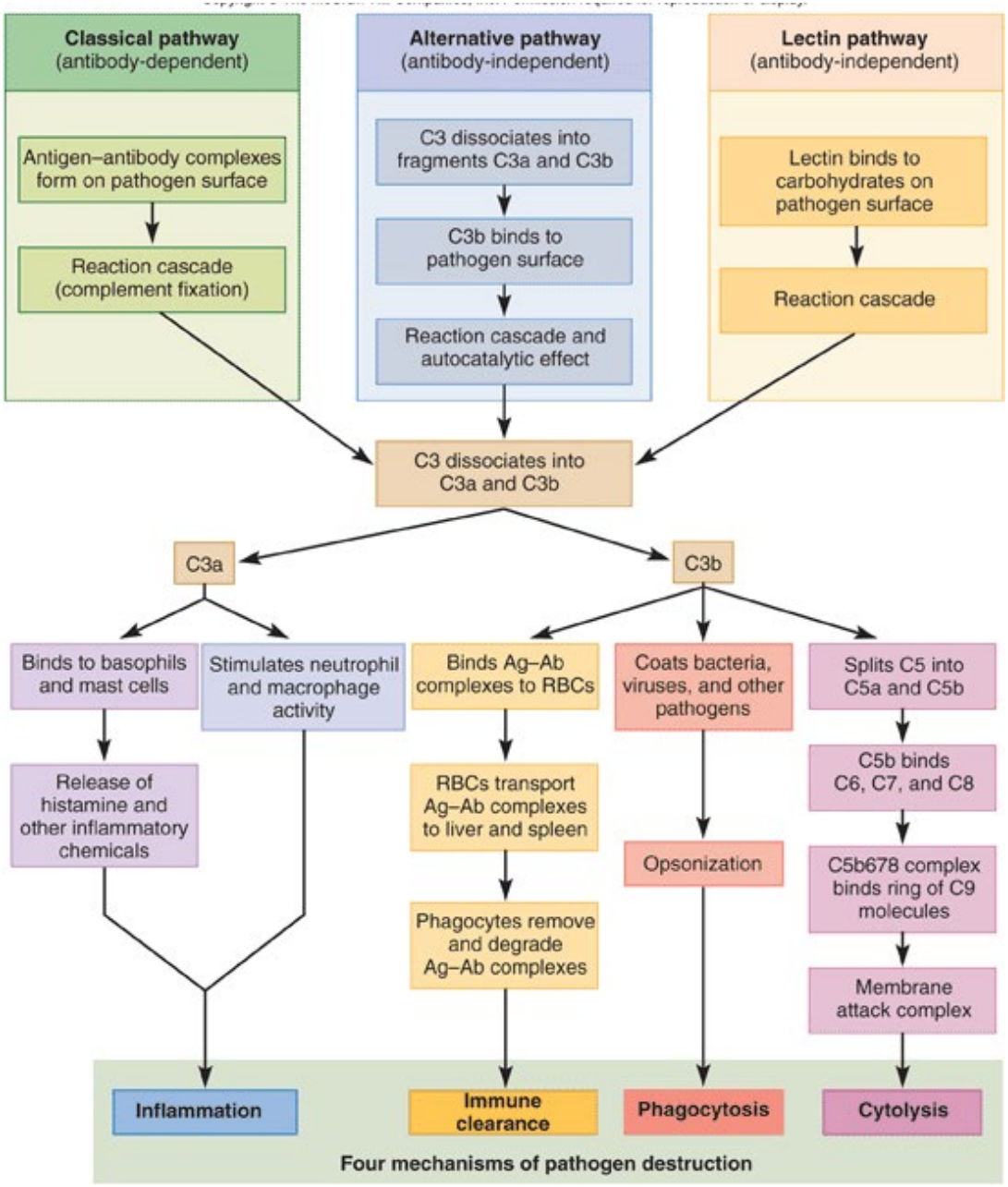
–C3 is the "key" starter protein in the complement system

•C3 must be split into C3a and C3b to activate system

•C3a and C3b then activate separate "mechanisms"

•three different "mechanisms" may become active when C3 splits into C3a and C3b.

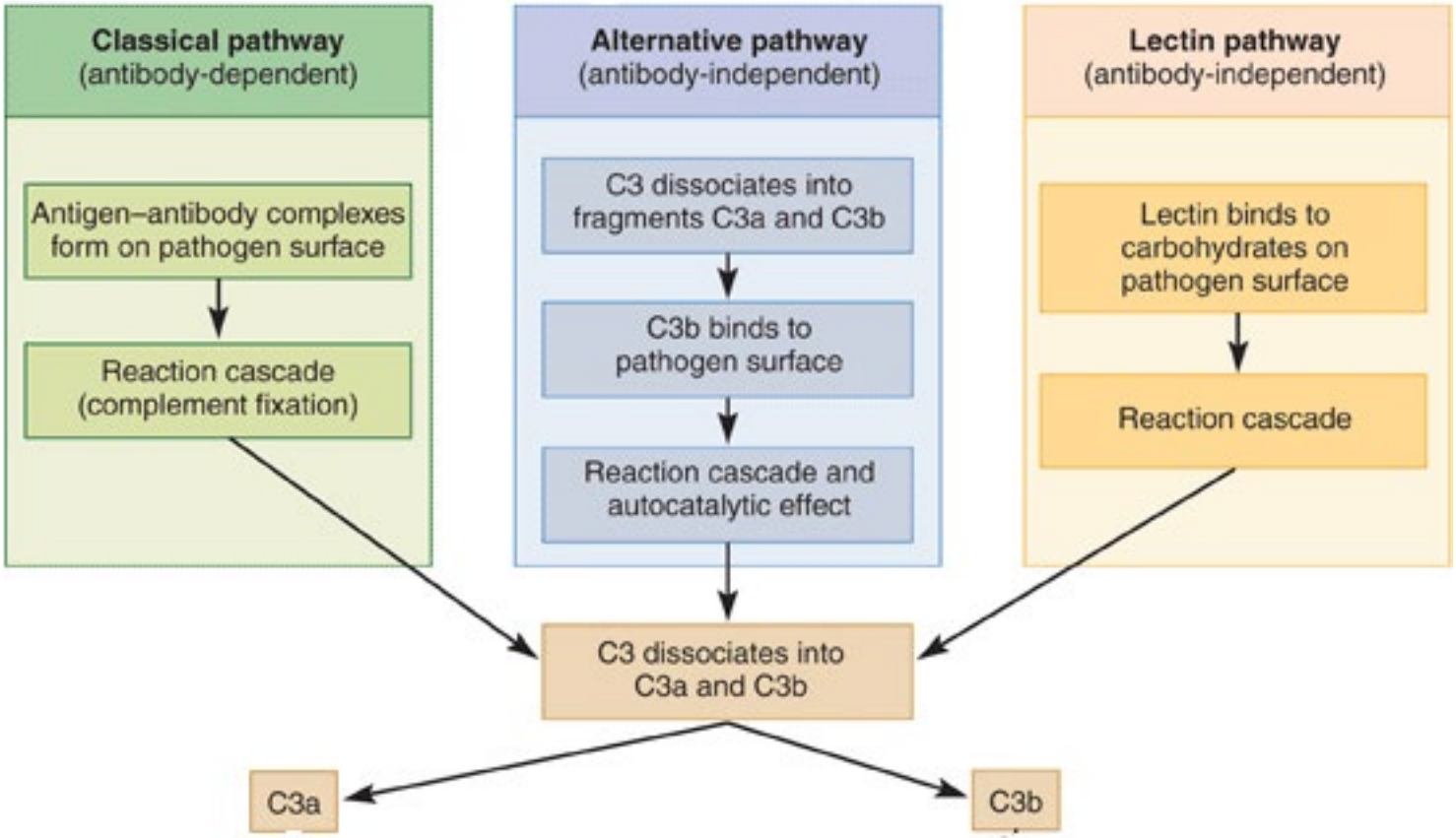
Complement Activation



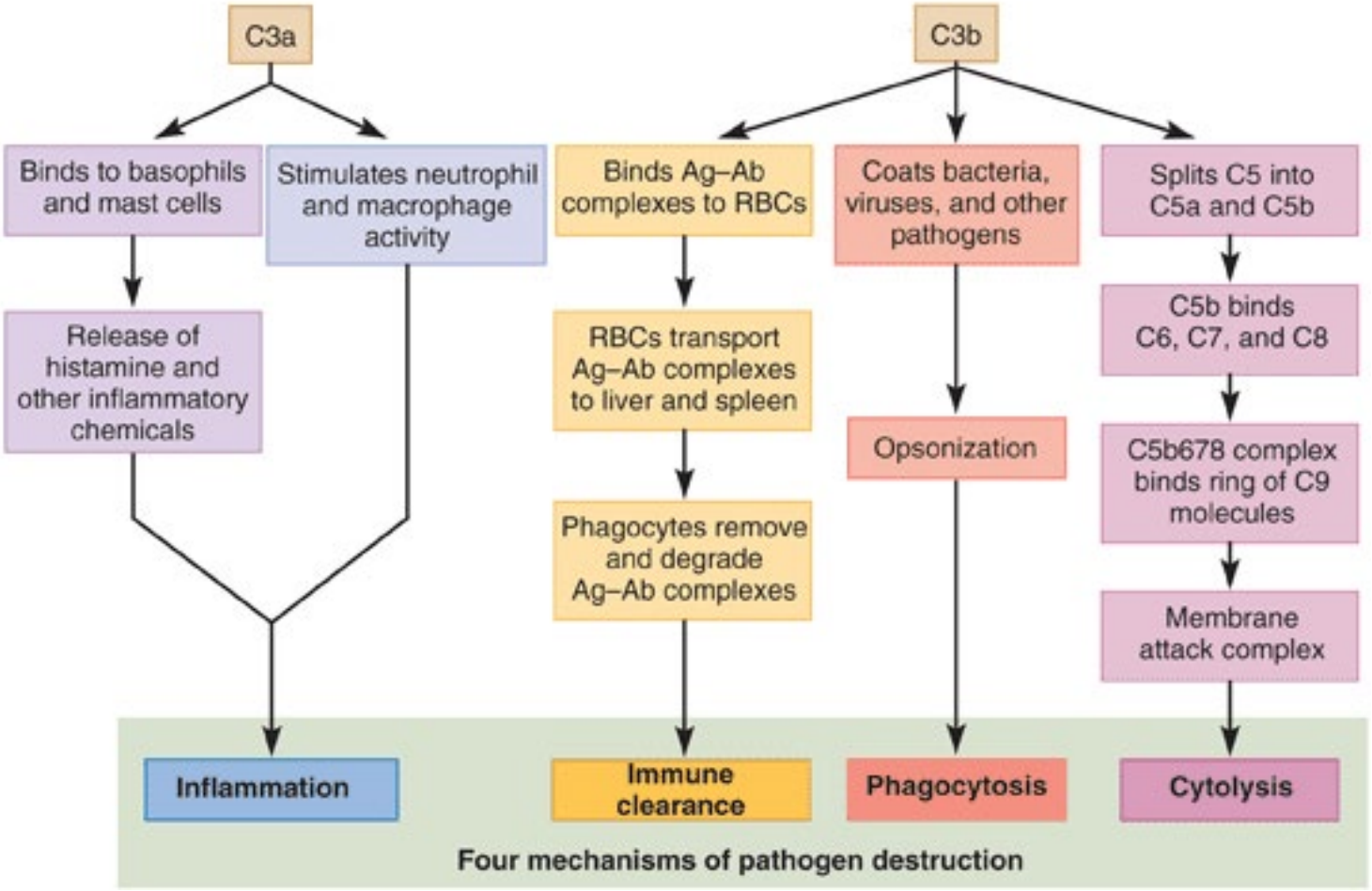
This is how complement is activated. (Three Options)

This pathway is part of specific immunity because it depends on the B Cells / plasma cells antibodies.

These pathways are part of the non specific resistance because they function independent of the B and T cells.



Complement's outcomes are a mixture of non-specific resistance and immunity:



What are the four outcomes of complement?

First of Complement's Four Outcomes
Immune Clearance

C3b binds together antigen-antibody complexes with red blood cells

These RBCs (with attached antigen-antibody) circulate through the liver and spleen

Macrophages strip off and destroy the Ag-Ab complexes leaving RBCs unharmed

<u>Principal means of clearing foreign antigens from the bloodstream</u>

Second of Complement's Four Outcomes
Phagocytosis

Neutrophils and macrophages **cannot phagocytize "naked"** bacteria, viruses, or other pathogens

C3b assist them by **opsonization**

Opsonization coats microbial cells with C3b and serves as binding sites for phagocyte attachment

Said to makes the foreign cell more appetizing to the macrophage and neutrophils!

Third of Four Complement's Outcomes
Cytolysis

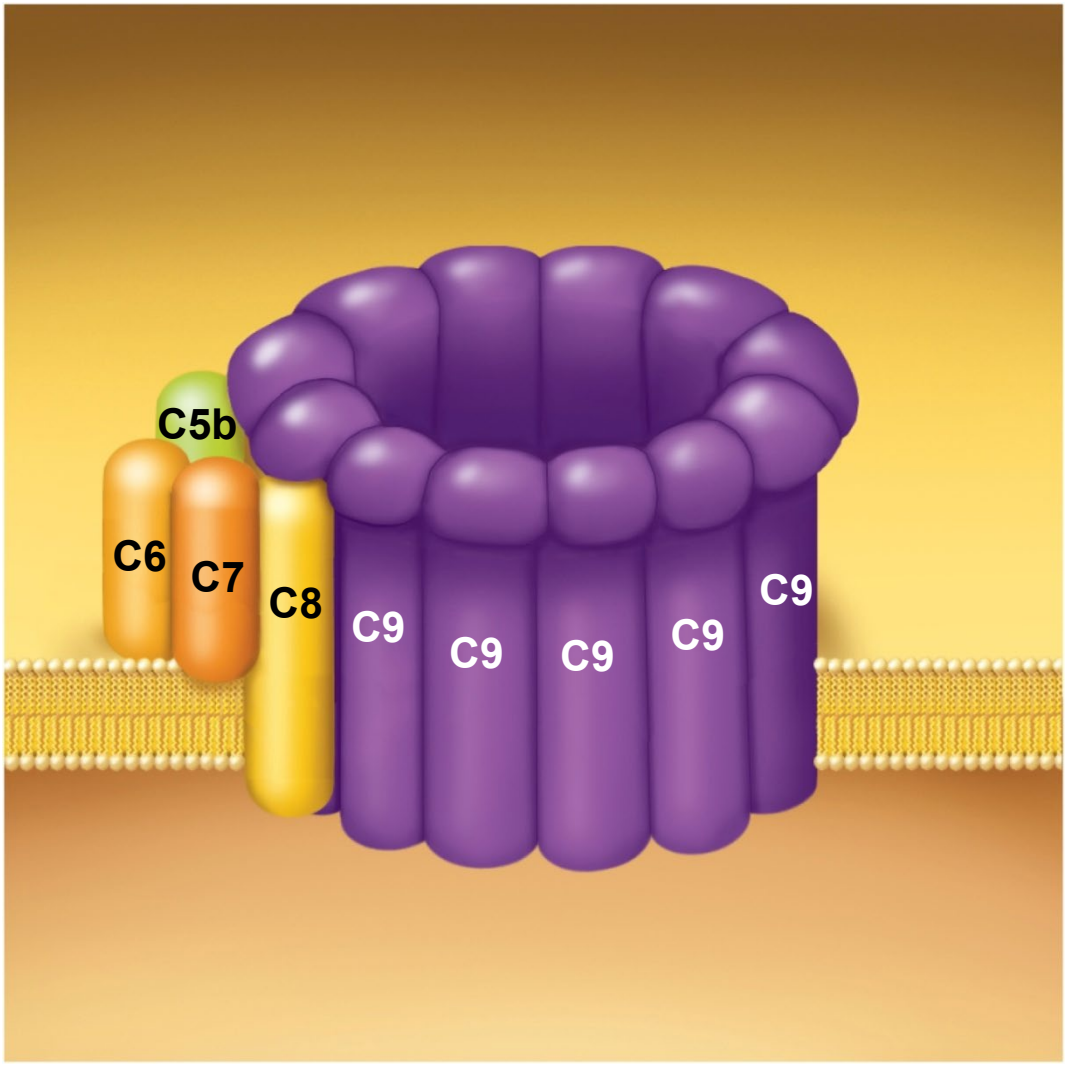
C3b splits other complement proteins

Bind to pathogen or non-host cells

Attract more plasma complement proteins (results in formation of the **membrane attack complex**)

Forms a hole in the target cell // electrolytes leak out, water flows in rapidly, and **cell ruptures**

Membrane Attack Complex



Fourth of Complement's Outcomes
Inflammation

C3a stimulates mast cells and basophils to secrete histamine and other inflammatory chemicals / this "initiates" inflammation

Activates and attracts neutrophils and macrophages

Speed pathogen destruction in inflammation

Inflammation

Part of the 2nd Line of Defense
(non-specific resistance)

Local defensive response to tissue injury of any kind, including trauma and/or infections

General purposes of inflammation

- limit spread of pathogens
- destroy pathogens
- remove debris from damaged tissue
- initiate tissue repair (i.e. remember regeneration vs fibrosis)

Four cardinal signs of inflammation

- **redness**
- **swelling**
- **heat**
- **pain**

More About the Four Cardinal Signs

heat – results from hyperemia

redness – due to hyperemia, and extravasated RBCs in the tissue

swelling (edema) – due to increased fluid filtration from the capillaries

pain – from direct injury to the nerves, pressure on the nerves from edema, stimulation of pain receptors by prostaglandins, bacterial toxins, and a kinin called **bradykinin**

Note: immobilization of sore area like a joint is sometimes referred to as a "fifth event" but not a "cardinal sign"

What are the four steps of Inflammation?

Mobilization of body defenses

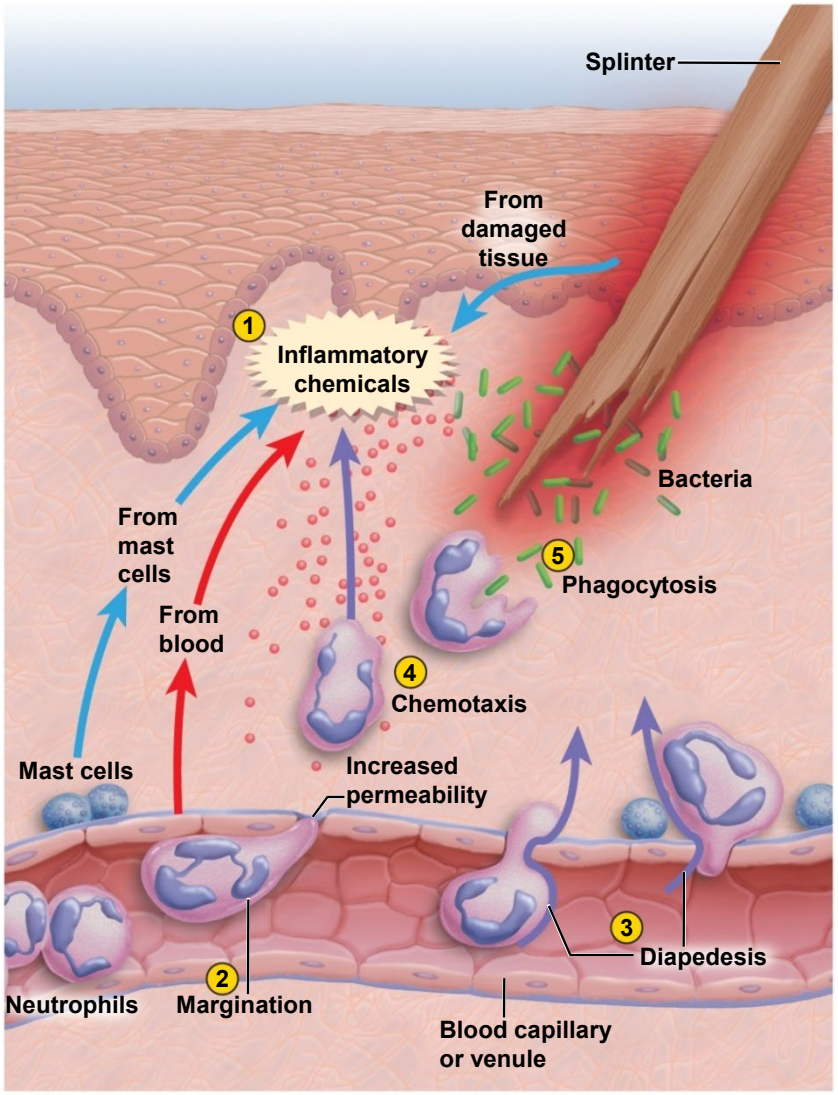
Containment and destruction of pathogen

Tissue cleanup

Tissue repair

Inflammation in a tissue causes fibroblast to migrate into the damaged area. Fibroblast secrete extracellular collagen fibers into the interstitial space (scar tissue). What is the clinical significance for someone with a chronic inflammatory response to asthma? Asthma becomes what?

Inflammation - Mobilization of Defenses



Leukocyte behavior

Margination

selectins cause leukocytes to adhere to blood vessel walls

Diapedesis (emigration)

leukocytes squeeze between endothelial cells into tissue space

Inflammation - Mobilization of Defenses

Selectins – cell-adhesion molecules made by endothelial cells that aid in the recruitment of leukocytes /// make membranes sticky and snag leukocytes

Integrins – on neurtrophils' plasma membrane and interact with selectins to stop neutrophils near location of inflammation.

Margination – adhesion of the leukocytes to the vessel wall

Diapedesis (also called emigration) - leukocytes crawl through developing gaps between endothelial cells so they can enter tissue fluid

Extravasation is the leakage of fluid, such as blood, lymph, or medication, from a blood vessel or other container into the surrounding tissues

Inflammation
Containment and Destruction of Pathogens

A priority of inflammation is to prevent the pathogens from spreading throughout the body

Fibrinogen that filters into tissue fluid converted to fibrin and clots /// forms a sticky mesh that walls off microbes

Heparin prevents clotting at site of injury

Pathogens are in a fluid pocket surrounded by clot

Attacked by antibodies, phagocytes, and other defenses

Neutrophils, the chief enemy of bacteria, accumulate at the injury site within an hour

After leaving the bloodstream, move to site of infection by chemotaxis – respiratory burst!

Inflammation - Containment and Destruction of Pathogens

Chemotaxis – attraction to chemicals such as bradykinin and leukotrienes that guide them to the injury site

Neutrophils are the "first responders" to arrive at site of infection

Kill bacteria by phagocytosis & respiratory burst (main killing force)

Secrete cytokines for recruitment of macrophages, NK cells, and additional neutrophils

Macrophages and T cells secrete colony-stimulating factor to stimulate leukopoiesis

Neutrophilia – 5000 cells/μL to 25,000 cells/μL in bacterial infection

Eosinophilia – elevated eosinophil count in allergy or parasitic infection

Inflammation
Macrophage are the tissue's cleanup crew!

Macrophage are the primary agents of tissue cleanup // after respiratory burst // arrive in 8 to 12 hours

As monocytes in blood emigrate into tissue spaces they become macrophage

- engulf and destroy bacteria
- engulf damaged host cells
- engulf dead and dying neutrophils

Remember, macrophage are also APC

Fibroblast come into area after macrophage to make new extracellular fibers.

Inflammation
Why do we have edema during inflammation?

Edema contributes to tissue cleanup mechanism

Swelling compresses veins and reduces venous drainage

Interstitial fluid now directed into the lymphatic capillaries

Lymphatic vessels collect and move lymph into lymph nodes where there is a high concentration of microphage /// in nodes macrophage remove bacteria, dead cells, tissue debris, and antigen presentation occur here

Pus is the accumulation of dead neutrophils, bacteria, other cellular debris, and tissue fluid forms a pool of yellowish green fluid

Abscess – accumulation of pus in tissue surrounded by fibrin

Inflammation
Tissue Repair

Platelet-derived growth factor secreted by blood platelets and endothelial cells in injured area

- stimulates fibroblasts to multiply
- synthesize new collagen fibers

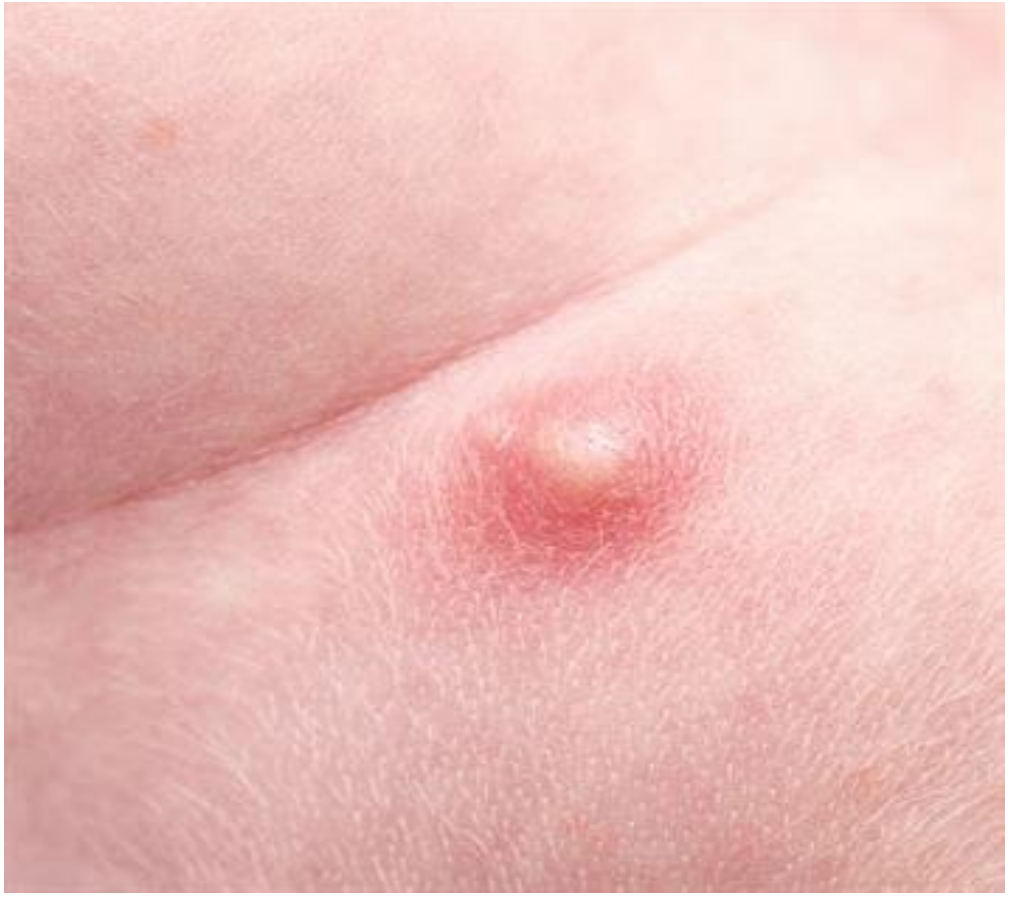
Hyperemia delivers oxygen, amino acids, and other necessities for protein synthesis

Increased **heat** increases metabolic rate, speeds mitosis, and tissue repair

Fibrin clot forms a scaffold for tissue reconstruction

Pain makes us limit the use of a body part so it has a chance to rest and heal.

What are the four cardinal signs of inflammation?



Four Cardinal Signs = Redness, Edema, Pain, Heat

(What often occurs with inflammation but is not considered a cardinal sign?)

What is fever?

An abnormally elevation of body temperature // normal 37 Celsius or 98.6 F

Also called pyrexia /// febrile refers to pyrexia // results from trauma, infections, drug reactions, brain tumors, and other causes // e.g. inflammation

Fever is an adaptive defense mechanism /// a moderate fever inhibits bacterial infection /// therefore, fever does more good than harm

- –promotes interferon activity
- –elevates metabolic rate and accelerates tissue repair
- –inhibits reproduction of bacteria and viruses
- –limiting access of iron // fever stimulates liver to store iron

Antipyretic – fever-reducing medications by inhibiting PGE_2

What causes fever?

Initiation of fever by exogenous pyrogens

- fever producing agents
- glycolipids on bacterial and viral surfaces

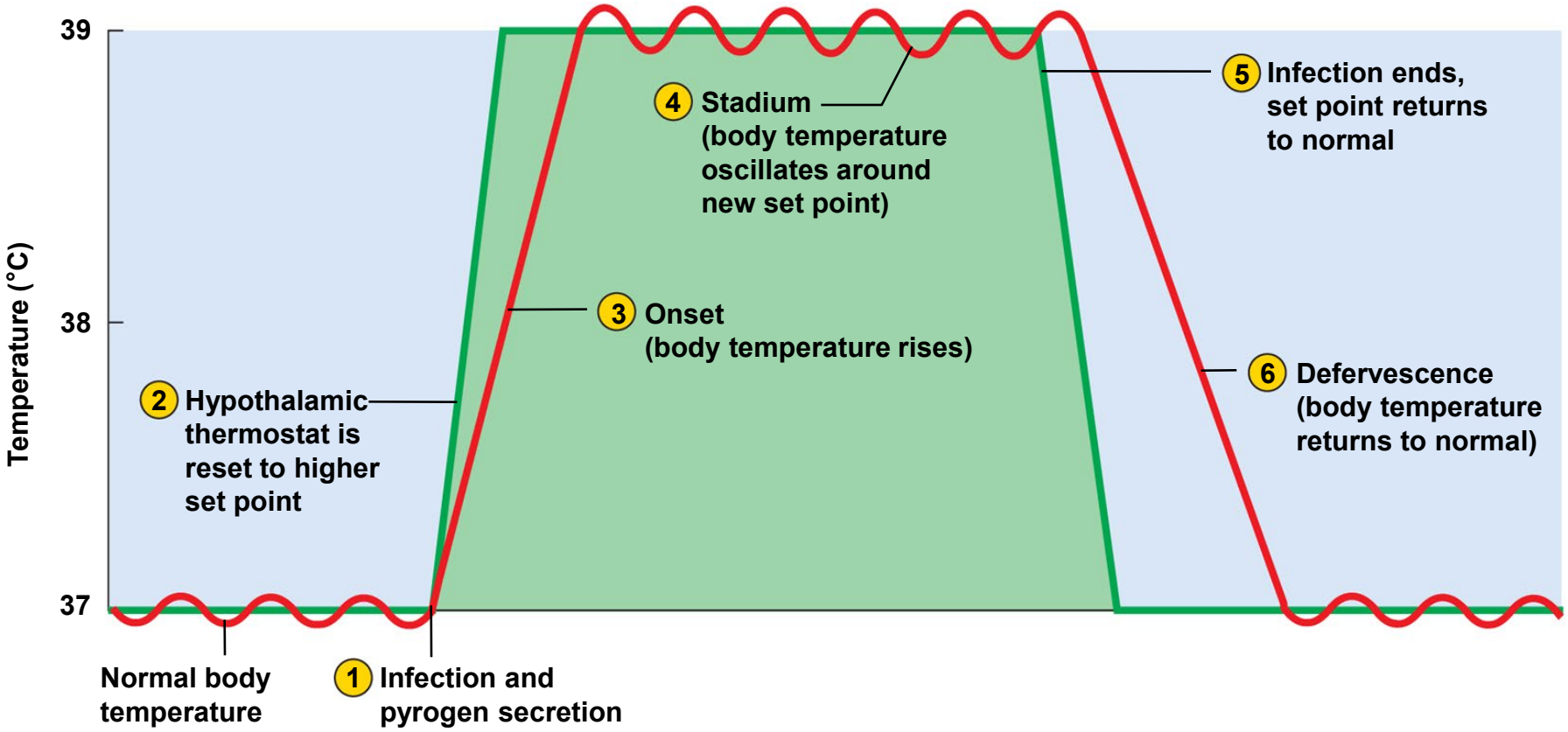
Attacking neutrophils and macrophages secrete chemicals like interleukins, interferons, and other cytokines that act as endogenous pyrogens

Stimulate neurons in the anterior hypothalamus to secrete prostaglandin E_2

PGE_2 raises hypothalamic set point for body temperature

Three stages of fever = onset, stadium, defervescence

Inflammation – Course of Fever



The Third Line of Defense

What makes acquired immunity special?

Specificity - able to recognize specific species of pathogen // recognize foreign antigen // after pathogen enters our body the immune system “captures then identifies the pathogen and activates B cells to neutralize pathogens outside of our cells and cytotoxic T cells to kill pathogen inside of our cells. (Note: the same pathogen may be in either location!) The response takes several days to a week.

Memory – stores record of the type of pathogen after the first exposure // if the same pathogen enters our body then there is a veru rapid response to eliminate the pathogen (minutes not days!)

What is the difference between a cellular and humoral responses?

The Third Line of Defense is Adaptive (also called Acquired)

Cytotoxic T cells and helper T cells provide the cellular response // eliminate host cells infected with bacteria

B cells and helper T cells provide the humoral response // render bacteria in body fluids harmless and tag bacteria for destruction

Review function
of the formed elements.

Neutrophils

Wander about within the fluids and through the connective tissues of the body to seek and kill bacteria

–Able to use phagocytosis, kill, and digestion the bacteria

–Also able to create a killing zone when they identify pathogen in tissue

•produces a cloud of anti-bacterial chemicals

•Degranulation // lysosomes discharge into tissue fluid

•respiratory burst – neutrophils rapidly absorb oxygen

•toxic chemicals are created ($O_2^{\cdot -}$, H_2O_2, HClO) /// Free radical of oxygen, hydrogen peroxide, hypochlorite

•kill more bacteria with these toxic chemicals than by phagocytosis

Eosinophils

High concentration in the mucous membranes

•Stand guard against parasites, allergens (allergy causing agents), and other pathogens

•Kill tapeworms and roundworms by producing superoxide, hydrogen peroxide, and toxic proteins

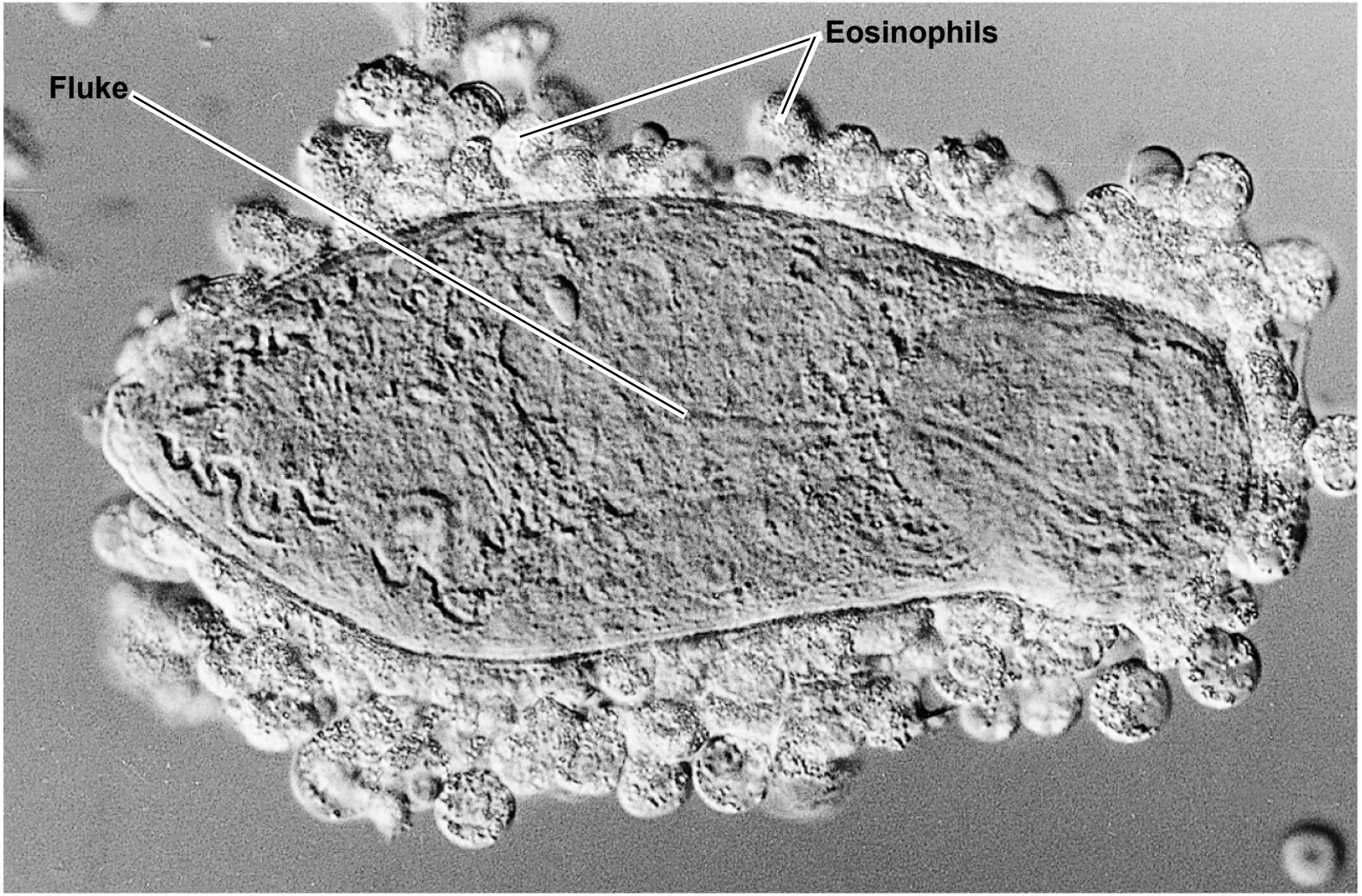
•Promote action of basophils and mast cells

•Use phagocytosis to capture antigen-antibody complexes

•Limit action of histamine and other inflammatory chemicals

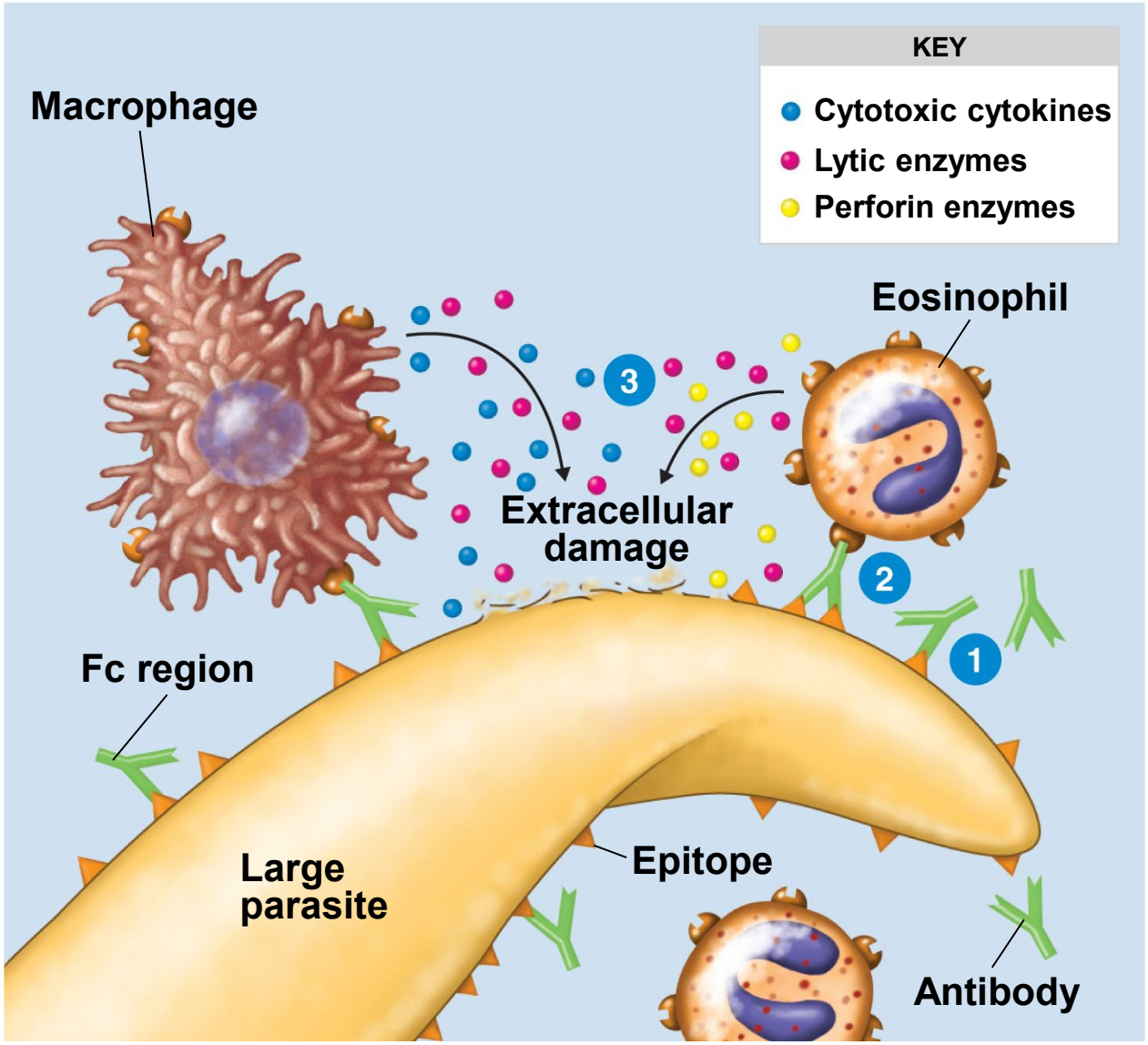
•Create a "respiratory burst" like neutrophils but to kill parasites

Antibody-dependent cell-mediated cytotoxicity (ADCC).



(b) **Eosinophils adhering to the larval stage of a parasitic fluke.**

Antibody-dependent cell-mediated cytotoxicity (ADCC).



Organisms, like some parasites to large to be ingestion by phagocytic cells, must be attacked and eliminated by extracellular molecules.

Basophils Change into Mast Cells

Secrete chemicals that aid mobility and directs the action of other leukocytes // initiates inflammation

–leukotrienes – activate and attract neutrophils and eosinophils

–histamine – a vasodilator which increases blood flow // peeds delivery of leukocytes to the area

–heparin – inhibits the formation of clots // would impede leukocyte mobility

–basophils become mast cells //// after basophil leave blood and lodge themselves into the CT throughout body

–secrete similar substances

–IgE become mast cell membrane receptors / antigen binding results in degranulation of mast cell.

Monocytes to Macrophage

Emigrate from the blood into the connective tissue

- change from monocyte to macrophage

- monocytes secrete many different types of cytokines which regulate inflammation and immunity while they are in blood

- macrophage system – this includes all the body's phagocytic cells, include not only the "macrophage" (Note: neutrophils , B cells, and eosinophils)

- wandering macrophages – actively seeking pathogens // widely distributed in loose connective tissue

- resident "fixed macrophages" = phagocytize only pathogens that come to them

    - microglia – in central nervous system
    - alveolar macrophages – in lungs
    - hepatic macrophages – in liver
    - nodal macrophage – lymph nodes
    - splenic macrophage - spleen