

Chapter 16:

Innate Immunity

- 1. Overview of Innate Immunity**
- 2. Inflammation & Phagocytosis**
- 3. Antimicrobial Substances**

1. Overview of Innate Immunity

The Body's Defenses

Innate (Nonspecific) Immunity		Adaptive (Acquired) Immunity (Chapter 17)
First line of defense	Second line of defense	Third line of defense
<ul style="list-style-type: none">• Intact skin• Mucous membranes and their secretions• Normal microbiota	<ul style="list-style-type: none">• Natural killer cells and phagocytic white blood cells• Inflammation• Fever• Antimicrobial substances	<ul style="list-style-type: none">• Specialized lymphocytes: T cells and B cells• Antibodies

The body has 2 types of defense against infection

Innate Immunity

- physical barriers (the skin & mucous membranes)
- immediate, non-specific responses to pathogens, injuries

Adaptive Immunity (covered in ch. 17)

- delayed, highly specific responses to foreign material

Innate Immunity

The innate immune response is the body's 1st line of defense and includes:

1) physical barriers between inside & outside

- the skin and the mucous membranes of the digestive, respiratory and genito-urinary tracts**
- all substances secreted at these barriers and all of the normal microbiota that live on these surfaces**

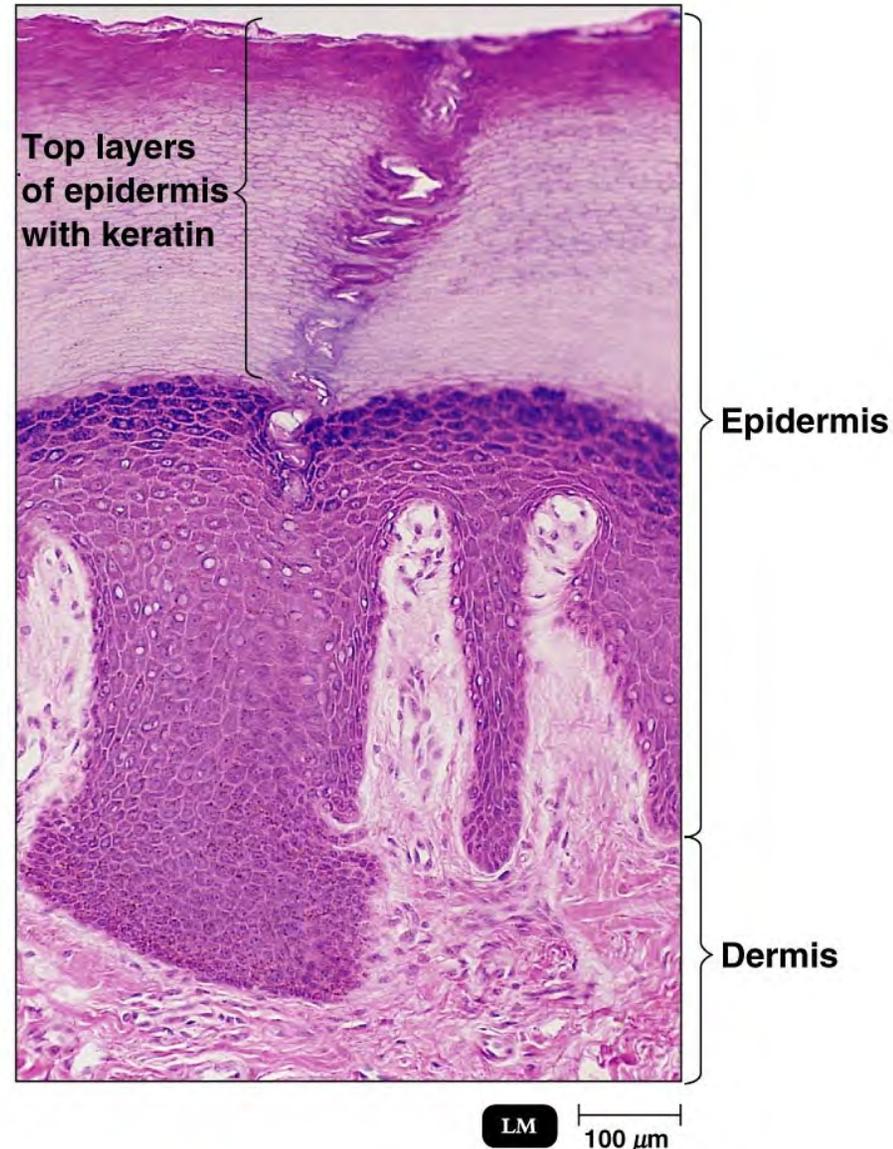
2) non-specific cellular & physiological responses

- i.e., inborn (innate) general responses to the presence of pathogens that breach the body's physical barriers**
- independent of prior exposure, response is immediate**
- eliminates the vast majority of pathogens that gain entry**

Physical Defenses

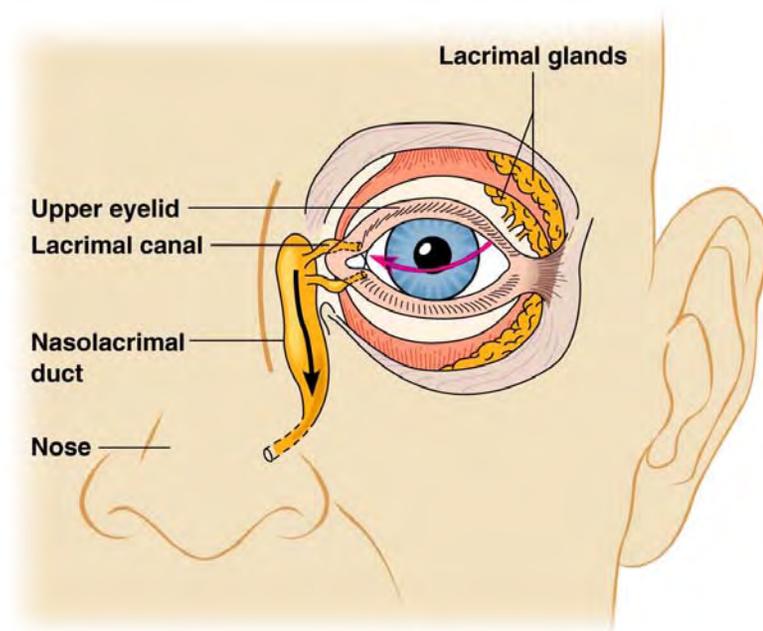
Key features of the Skin:

- **dry, acidic surface (resists microbial growth)**
- **multiple layers of tough yet dead keratinized cells**
- **continual loss of outer dead skin layers removes potential pathogens**
- **sebum from hair follicles (lowers pH) & lysozyme from sweat resist microbial growth**



Key features of the Eyes:

- tears continually released by lacrimal ducts
- contain antimicrobial substances (e.g. lysozyme), wash away any microbes, debris on the eye surface



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Key features of the Mucous Membranes:

- includes the linings of the respiratory, digestive & genitourinary tracts
- vulnerable due to very thin epithelial layer, moist surface
- continually produce mucus, a viscous glycoprotein that traps microbes and debris
- acidic environment of stomach kills most microbes

Summary of Physical Defenses

TABLE 16.3

Summary of Innate Immunity Defenses

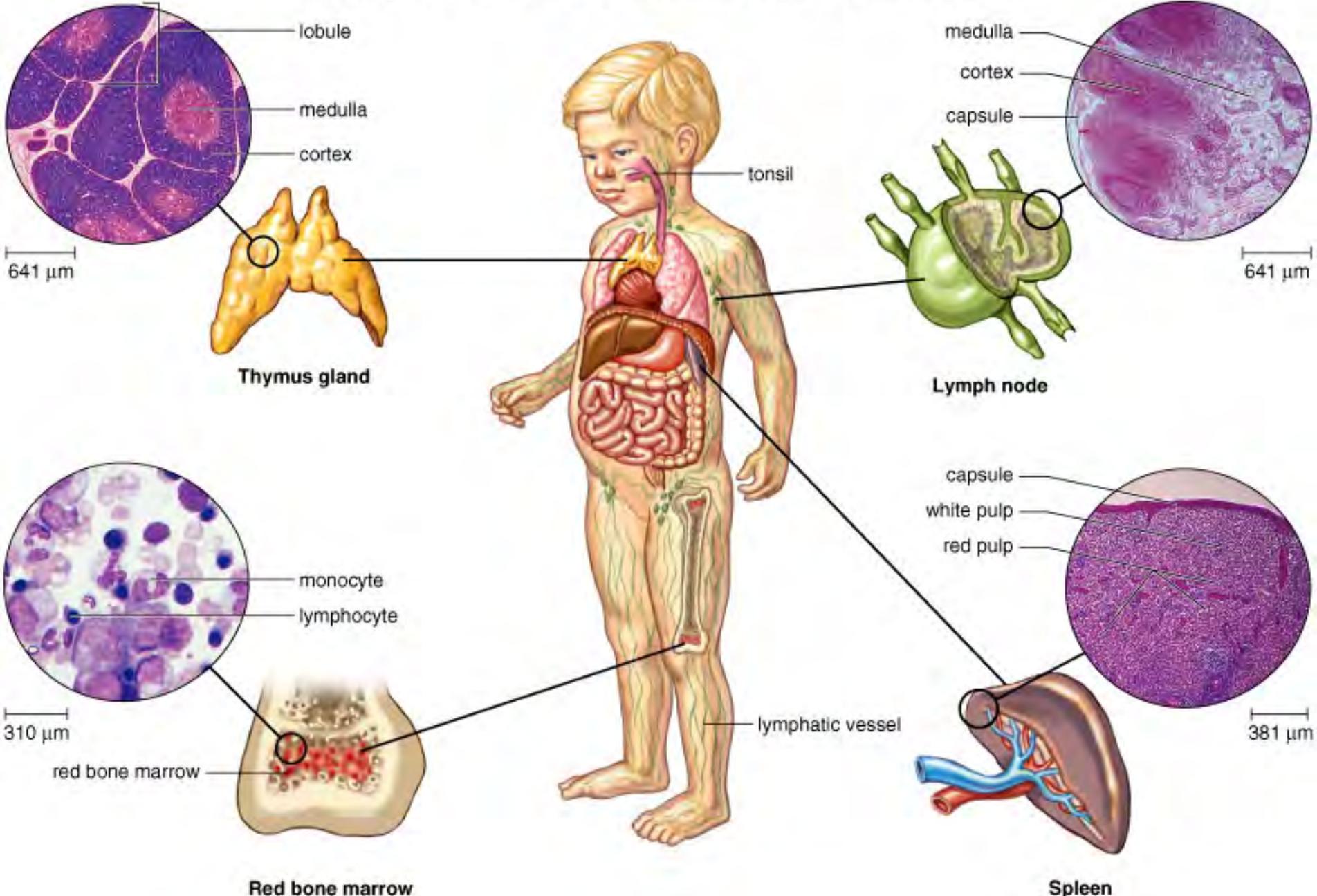
Component	Functions
FIRST LINE OF DEFENSE: SKIN AND MUCOUS MEMBRANES	
Physical Factors	
Epidermis of skin	Forms a physical barrier to the entrance of microbes.
Mucous membranes	Inhibit the entrance of many microbes, but not as effective as intact skin.
Mucus	Traps microbes in respiratory and gastrointestinal tracts.
Lacrimal apparatus	Tears dilute and wash away irritating substances and microbes.
Saliva	Washes microbes from surfaces of teeth and mucous membranes of mouth.
Hairs	Filter out microbes and dust in nose.
Cilia	Together with mucus, trap and remove microbes and dust from upper respiratory tract.
Epiglottis	Prevents microbes from entering lower respiratory tract.
Urine	Washes microbes from urethra.
Vaginal secretions	Move microbes out of female reproductive tract.
Defecation and vomiting	Expel microbes from body.

Roles of the Normal Microbiota

The “normal microbiota” are the microorganisms that live on the body surfaces of a healthy individual and inhibit the growth of pathogens in the following ways:

- **acidifying body surfaces**
 - e.g., in the female reproductive tract, inhibits yeast inf.
- **the production of bacteriocins and other toxins**
 - i.e., toxins that are specific for other microorganisms
 - e.g., in the large intestine (*E. coli*)
- **out-competing pathogens for nutrients**
 - on the skin and basically all mucous membranes

Organs of the Immune System



The Lymphoid Organs

Bone Marrow

- **blood cell formation**
 - “where all blood cells (red & white) are born”

Thymus

- **where T cells are “educated”**
 - **weeds out T cells that would react to “self” molecules**

Spleen

- **immune response to pathogens, foreign material in blood**

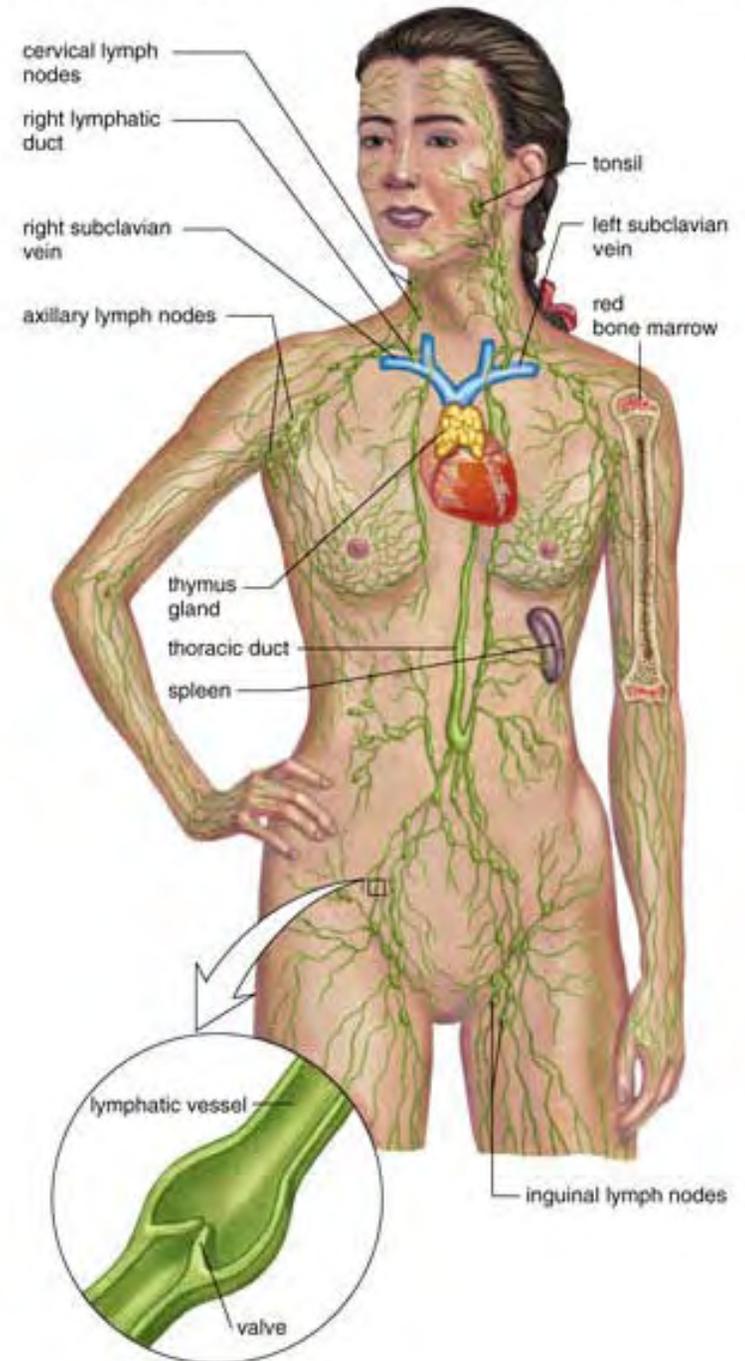
...the Lymphatic System

Lymph Nodes

- immune response to pathogens, foreign material in lymph

Lymph (& Blood)

- fluids through which immune cells patrol the body



Cells of the Immune System...

These include all of the white blood cells (aka leukocytes), some of which appear “granular” ...

TABLE 16.1 Formed Elements in Blood (continued)

Granulocytes

Type of Cell

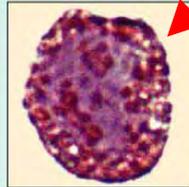
Leukocytes (White Blood Cells)

A. Granulocytes (stained)

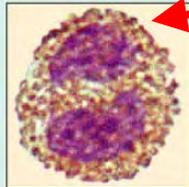
1. Neutrophils (PMNs)
(60–70% of leukocytes)



2. Basophils (0.5–1%)



3. Eosinophils (2–4%)



4. Dendritic cells



Neutrophils

- phagocytes w/strangely shaped nuclei, poorly stained granular vesicles

Basophils

- release histamine, other mediators of inflammation, vesicles bind basic dyes

Eosinophils

- phagocytic, attack parasites w/toxic proteins, vesicle bind acidic eosin dye

Dendritic Cells

- phagocytes with very important roles in initiating adaptive immune response

...more Cells of the Immune System

...& others which have an “agranular” appearance

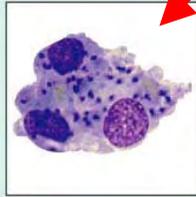
TABLE 16.1 Formed Elements in Blood (continued)

Agranulocytes

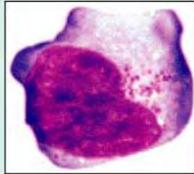
Type of Cell

Numbers per
Microliter (μL) of
Cubic mm (mm^3)

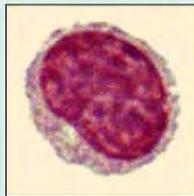
B. Agranulocytes (stained)
1. Monocytes (3–8%)



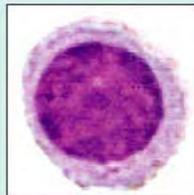
2. Lymphocytes (20–25%)
• Natural killer (NK) cells



• T cells



• B cells



*Discussed in Chapter 17.

Monocytes/Macrophages

- monocytes become actively phagocytic macrophages when stimulated via infection, injury

Natural Killer (NK) cells

- recognize and destroy cells with features of tumor cells, cells with intracellular pathogens

T & B cells

- have central roles in adaptive immunity (covered in ch. 17)

2. Inflammation & Phagocytosis

What is Inflammation?

Inflammation is a localized response initiated by damaged or infected tissues to aid tissue repair and the elimination of pathogens.

The basic stages of inflammation are as follows:

Vasodilation & increased capillary permeability

- increases blood flow to area, blood fluid in tissue**

Migration of phagocytes, phagocytosis

- phagocytes exit the blood, enter affected tissue via chemotaxis & consume pathogens**

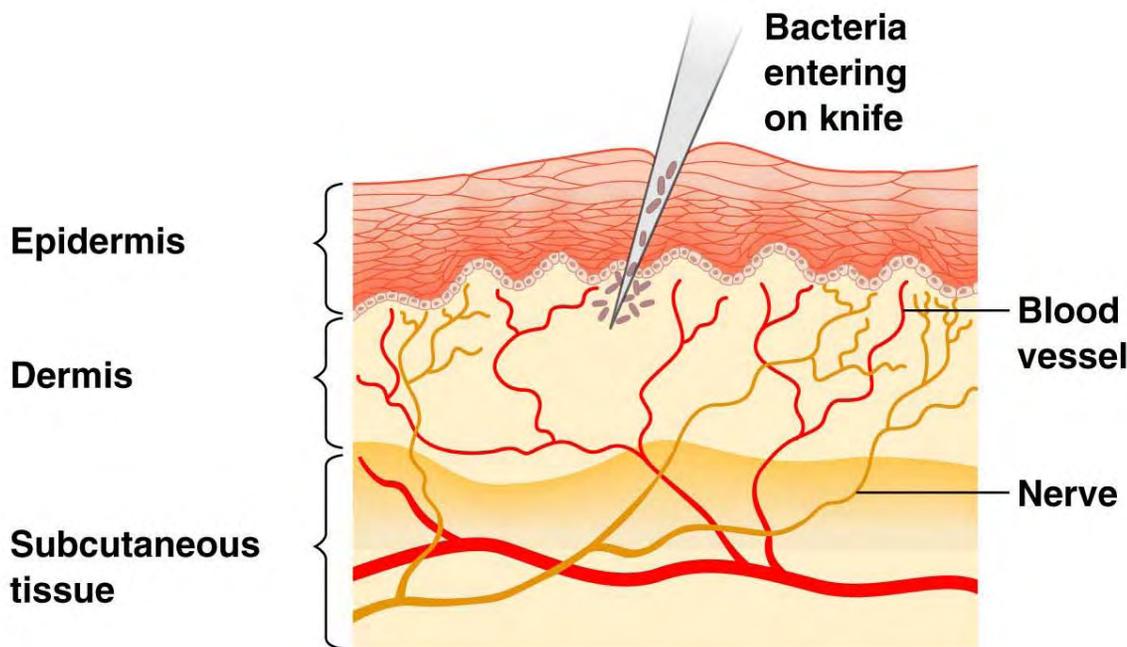
Tissue repair

- removal of dead cells, regeneration of the tissue**

Inflammation Triggers

Any type of physical damage to and/or microbial penetration of a tissue will trigger a local inflammatory response:

- can be short-lived (acute) or extended (chronic)



- initiated by the release of inflammatory mediators from cells in the tissue that is damaged

e.g.

histamine
prostaglandins
leukotrienes

(a) Tissue damage

Vasodilation & Increased Permeability

Increased blood flow due to vasodilation and the increased permeability of capillaries results in fluid from blood seeping into affected tissue:

- causes swelling of the region (edema)

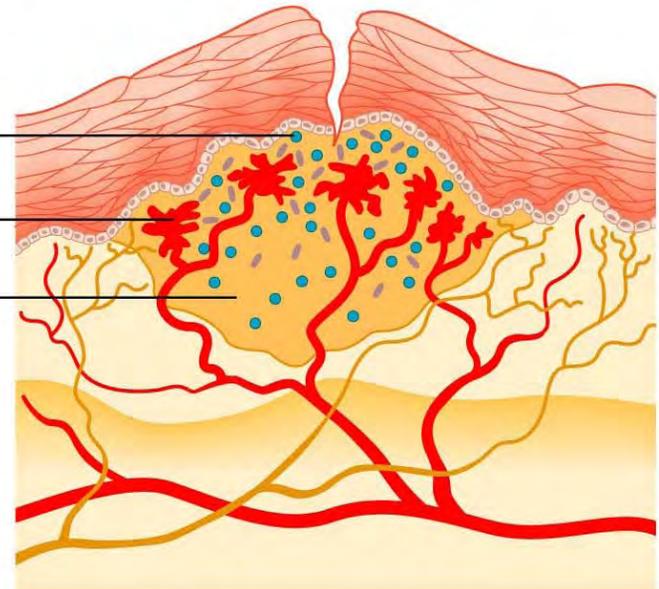
- facilitates clotting
- facilitates entry of antimicrobial proteins, leukocytes

1 Chemicals such as histamine, kinins, prostaglandins, and leukotrienes (represented as blue dots) are released by damaged cells.

2 Blood clot forms.

3 Abscess starts to form (dark yellow area).

(b) Vasodilation and increased permeability of blood vessels



Phagocyte Migration (Chemotaxis)

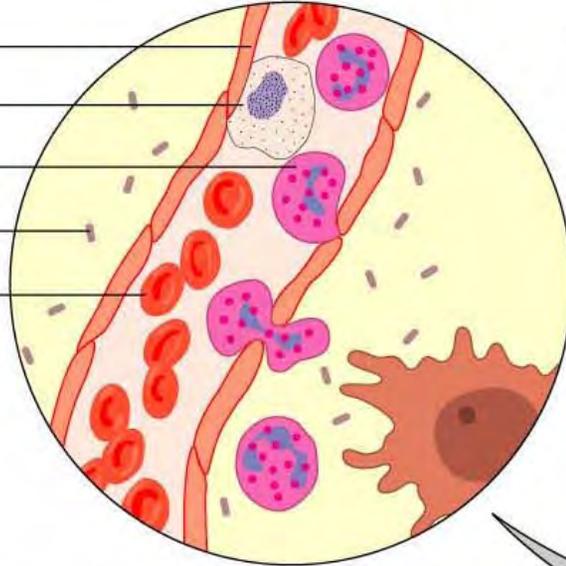
Blood vessel
endothelium

Monocyte

Neutrophil

Bacterium

Erythrocyte

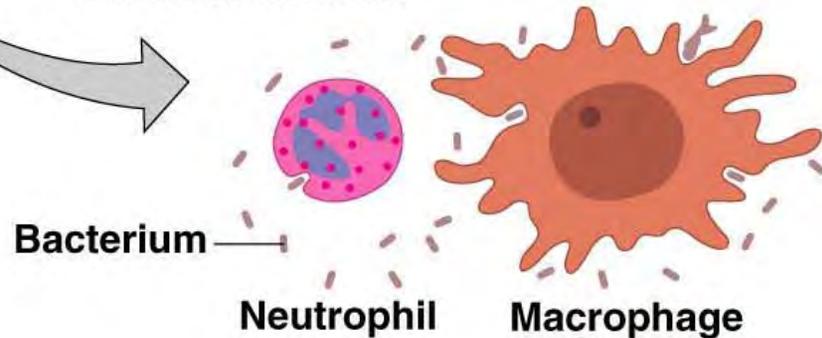


4 Margination—
phagocytes
stick to
endothelium.

5 Emigration—
phagocytes
squeeze between
endothelial cells.

6 Phagocytosis
of invading
bacteria.

(c) Phagocyte migration and phagocytosis

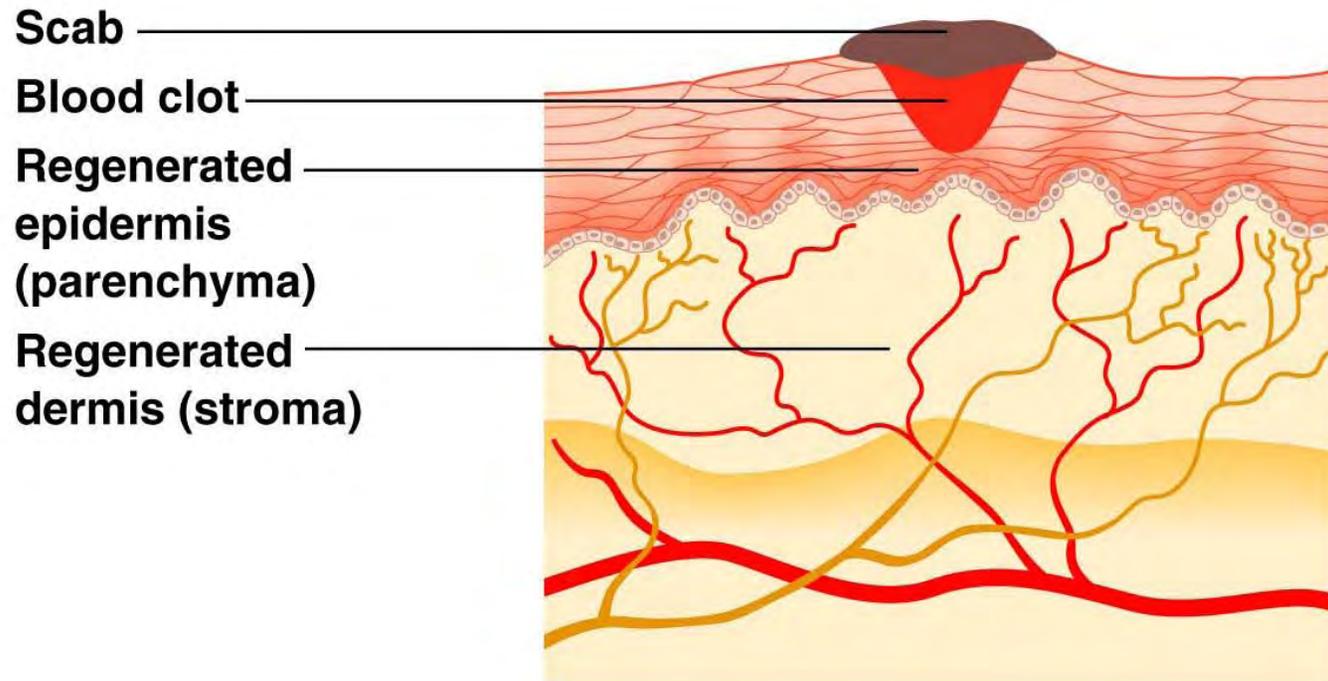


- endothelium of capillaries in the area expresses proteins that “stick to” phagocytes

- phagocytes then “squeeze” their way out into the tissue and follow a “trail” of chemical signals toward the source (chemotaxis) and gobble up microbes

Tissue Repair

Once the area has been secured (all pathogens are destroyed, all breaches are sealed), dead & damaged cells can be broken down and the tissue can regenerate.

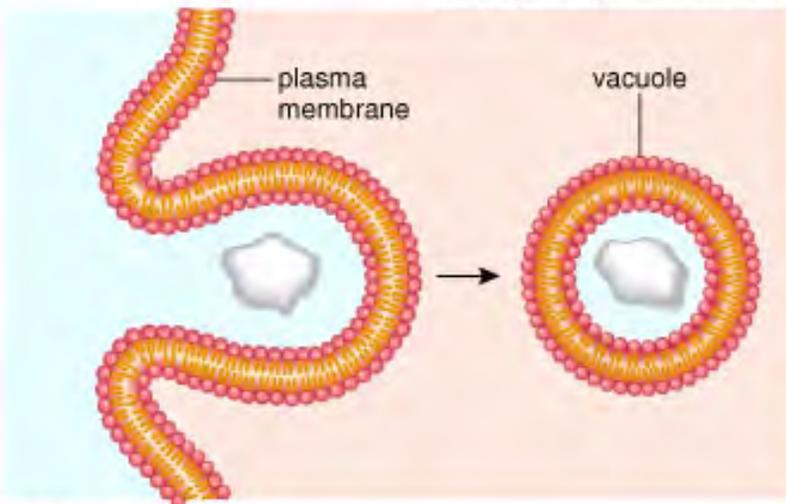


(d) Tissue repair

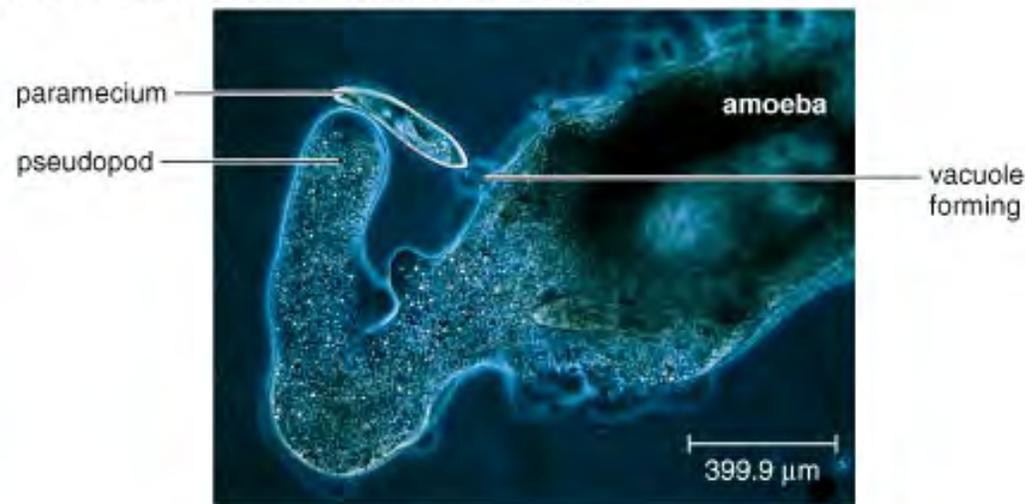
What is Phagocytosis?

It's the process by which a cell ingests a solid extracellular particle (such as a bacterium) by engulfing it within a membrane enclosed vesicle (sometimes called a vacuole).

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a. Phagocytosis



- cells that normally carry out this function are referred to as *phagocytic*, or simply as phagocytes

Types of Phagocytes

All of the phagocytes in the human body are types of white blood cells (leukocytes):

Neutrophils

- highly phagocytic cells that rapidly exit the blood into damaged or infected tissue, “gobble up” bacteria, etc...

Macrophages

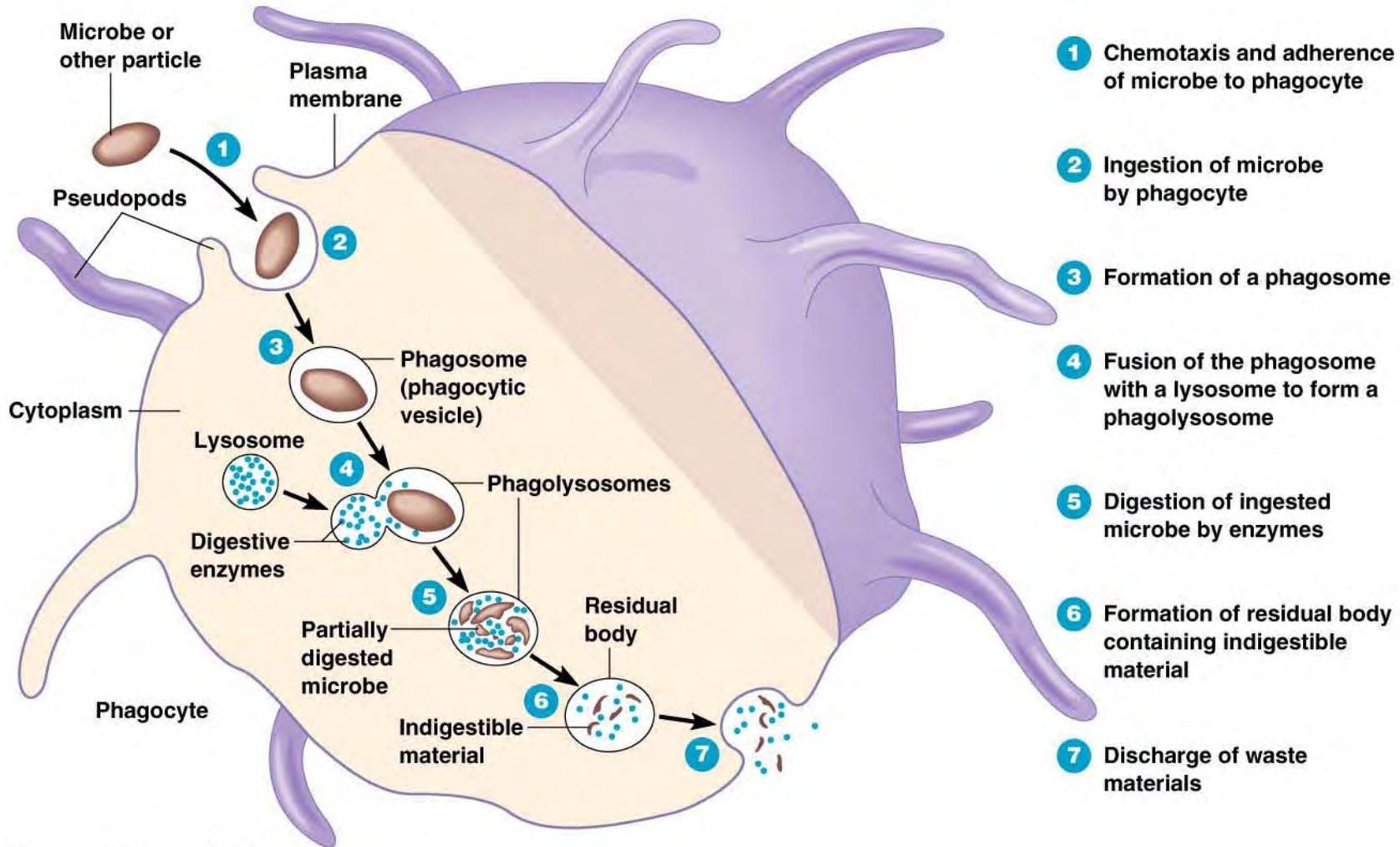
- monocytes migrate to damaged, infected tissue from blood & differentiate into highly phagocytic macrophages
- some are fixed (non-mobile) in various tissues & organs

Dendritic Cells

- found in skin, mucous membranes, thymus, lymph nodes

Eosinophils (occasionally)

The Phagocytic Process



Phases of phagocytosis

- all phagocytic white blood cells ingest & destroy pathogens & other debris by this basic process

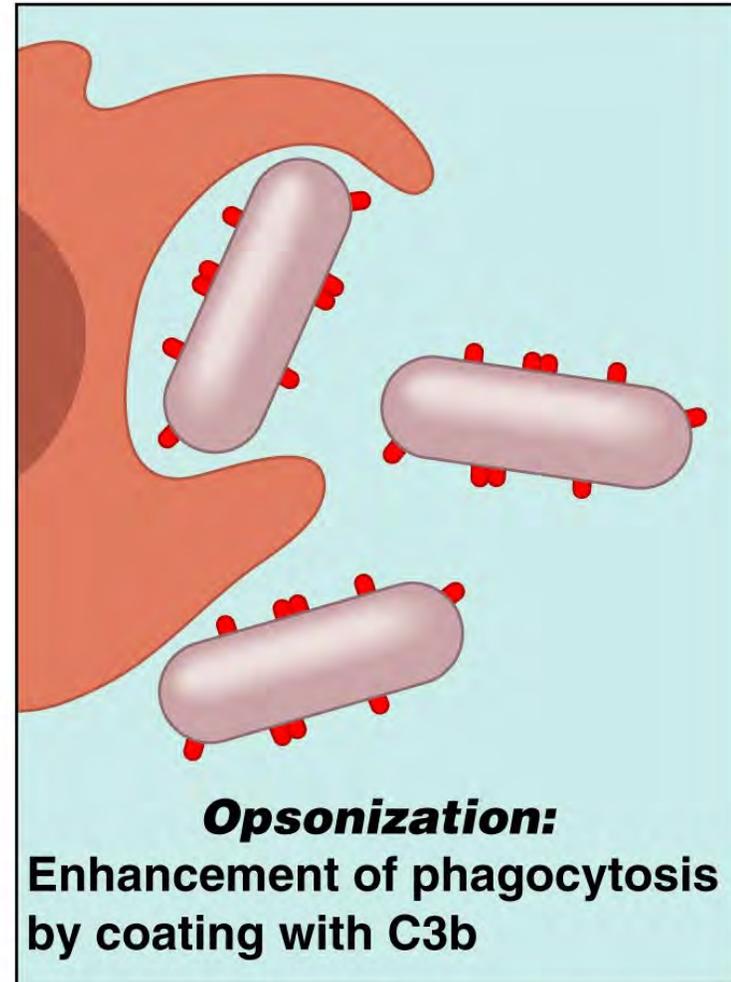
Opsonization

As we learned in the previous chapter, bacteria have a variety of ways to resist phagocytosis.

2 kinds of molecules involved in the immune response bind to pathogens and greatly enhance phagocytosis:

- antibodies
- complement protein C3b

This process is called opsonization and such proteins are called opsonins.



3. Antimicrobial Substances

Some Antimicrobial Substances

There are many different kinds of antimicrobial substances, however we will focus our attention on 2 of the more interesting ones*:

***Complement system**

- a set of proteins present in the blood important for the destruction of pathogenic cells**

***Interferons**

- a class of cytokines that are especially important in controlling viral infections**

Transferrins (bind & keep iron away from pathogens)

Antimicrobial peptides (cause lysis of microbes)

The Complement System

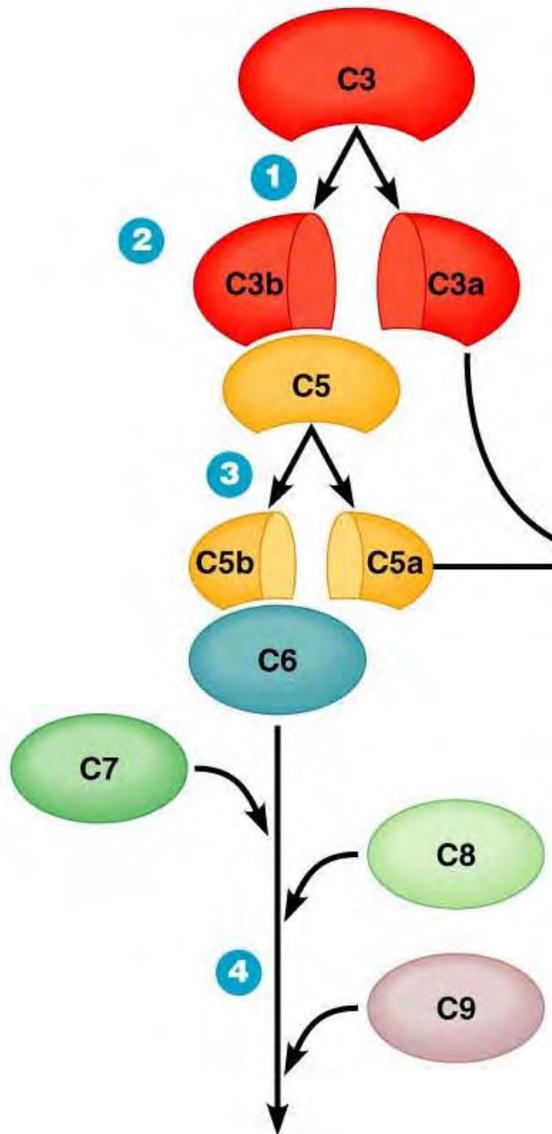
The complement system (aka “complement”) is a set of >30 proteins produced by the liver that circulate in the blood in an inactive state.

The presence of microbial pathogens activates the “complement cascade” in 1 of 3 ways to eliminate the pathogens by:

- cytolysis (cell lysis)
 - eukaryotic pathogens, Gram⁻ bacteria (not Gram⁺)
- triggering inflammation
- enhancing phagocytosis (opsonization)

The Complement Cascade

- the activation of complement proteins C3 & C5-C9 as shown is central to complement carrying out its roles

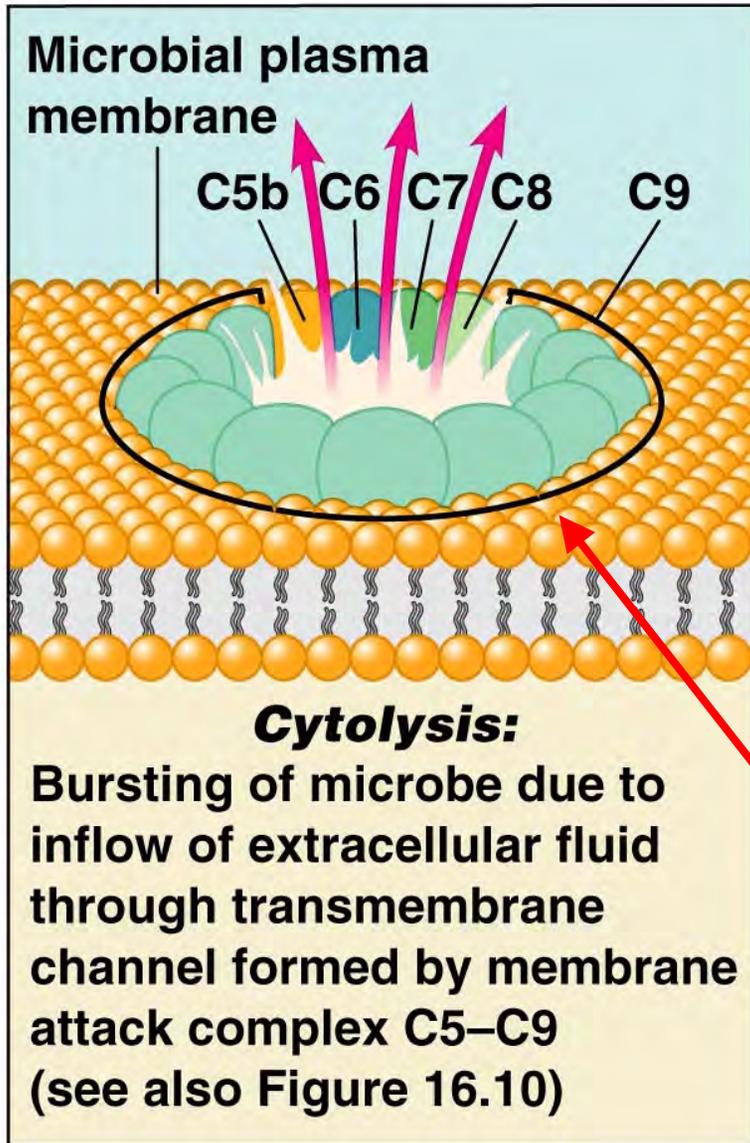


- 1 Activated C3 splits into C3a and C3b.
- 2 C3b binds to microbe, resulting in opsonization.
- 3 C3b splits C5 into C5a and C5b.
- 4 C5b binds to C6 through C9 to form membrane attack complex, forming channels in the invading cell's membrane and resulting in cell cytolysis.
- 5 C3a and C5a cause mast cells to release histamine, resulting in inflammation; C5a attracts phagocytes.

- the key event setting off the process is the splitting of C3 protein into C3a & C3b fragments

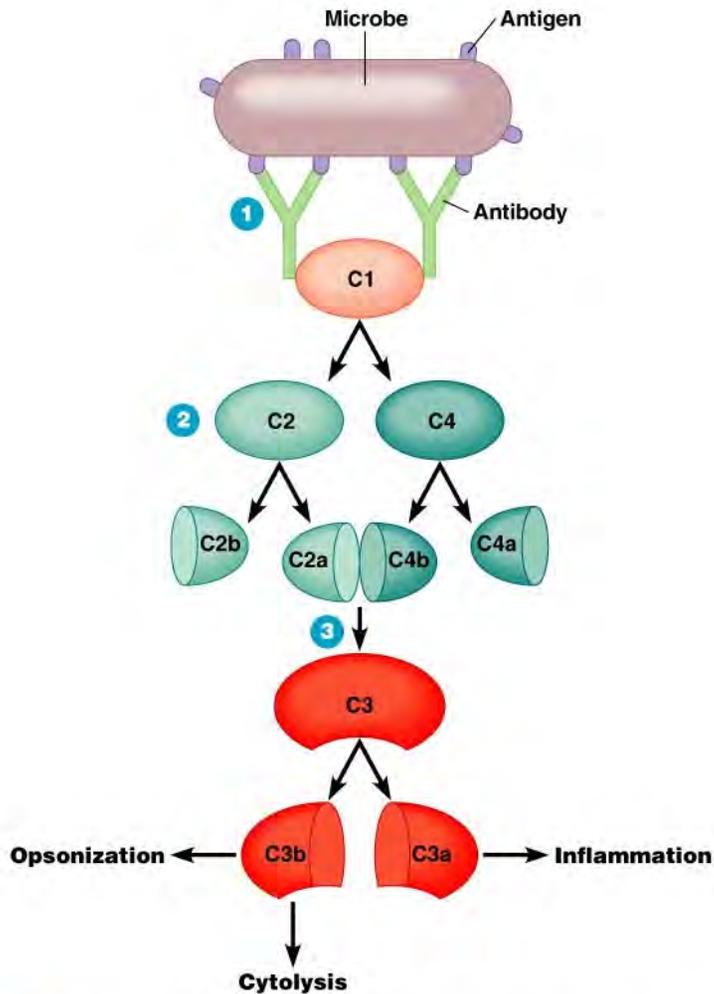
- C3b triggers the cascade resulting in a cytolytic structure...

Cytolysis by Complement



- C3b binds to outer membrane of Gram⁻ bacteria and splits C5 into C5a & C5b
 - C5b on the outer membrane then recruits C6, C7, & C8
 - the C5b-C8 complex triggers multiple C9 proteins to complete the circular membrane attack complex (MAC)
 - MAC formation produces a hole in membrane & cytolysis
- **C3b also functions as an opsonin to aid phagocytosis****

The Classical Complement Pathway



- 1 C1 is activated by binding to antigen–antibody complexes.
- 2 Activated C1 splits C2 into C2a and C2b and C4 into C4a and C4b.
- 3 C2a and C4b combine and activate C3, splitting it into C3a and C3b (see also Figure 16.9).

The “classical” pathway was characterized first and activates C3 as follows:

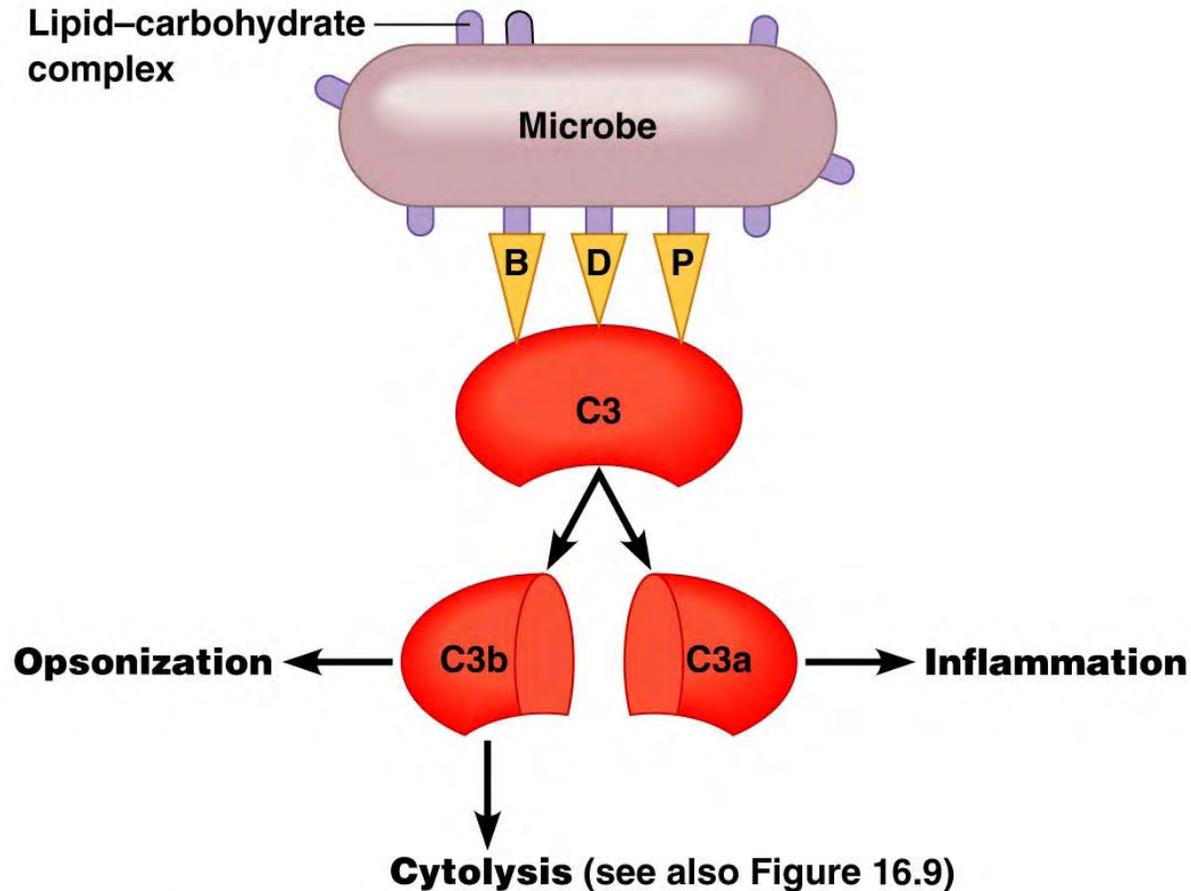
- specific antibody binds to the surface of a target cell
- this activates C1 which then splits C2 into C2a & C2b, and C4 into C4a and C4b
- C2a & C4b form a complex which then cleaves C3 setting off the formation of the MAC

Alternative Complement Pathway

The “alternative” pathway activates C3 in a different way:

- spontaneously formed yet unstable complexes of C3 & Factors B, D & P become stabilized on the surface of a pathogen
- stabilized C3-BDP acts to cleave other C3 molecules and trigger cascade

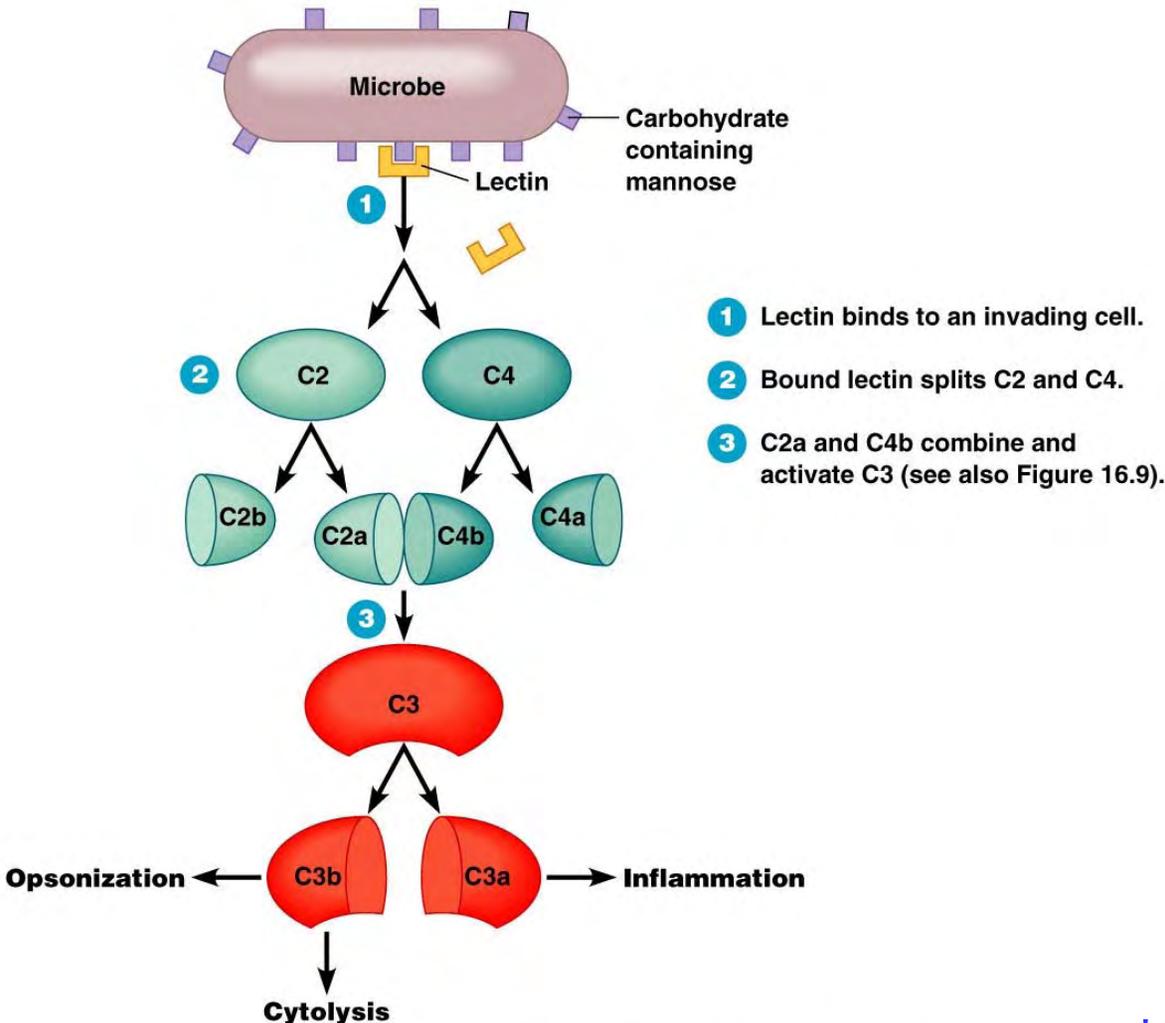
****This is antibody-independent!****



Key:  B factor  D factor  P factor

Lectin Complement Pathway

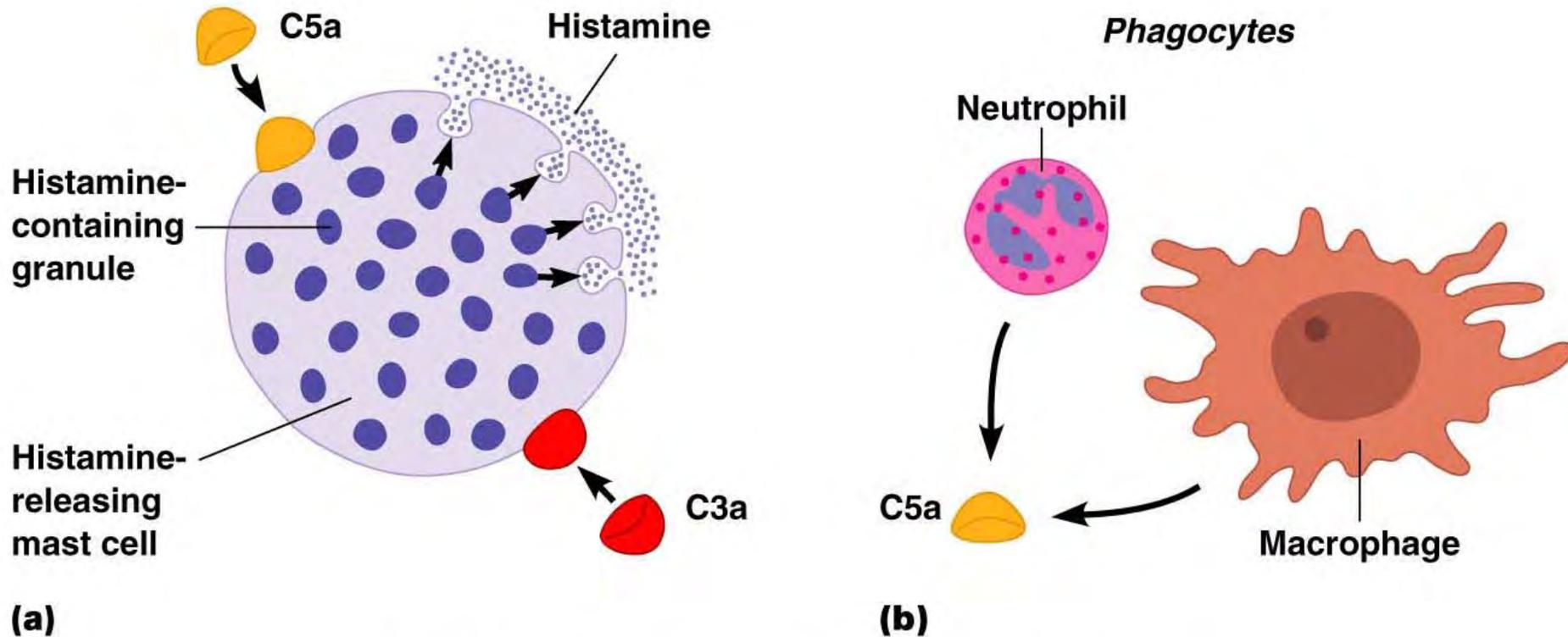
Lectins are protein produced by the liver that bind specific carbohydrate structures



- mannose-binding lectin (MBL) is produced during infections and binds carbohydrates with the sugar mannose on pathogens
- MBL on the cell surface triggers the complement cascade as does C1 in the classical pathway

****Antibody-independent!****

Inflammation via Complement



C3a and C5a are powerful inducers of inflammation

- bind to receptors on mast cells triggering the release of histamine, etc, causing vasodilation, incr. in permeability

C5a is also a powerful chemoattractant for phagocytes

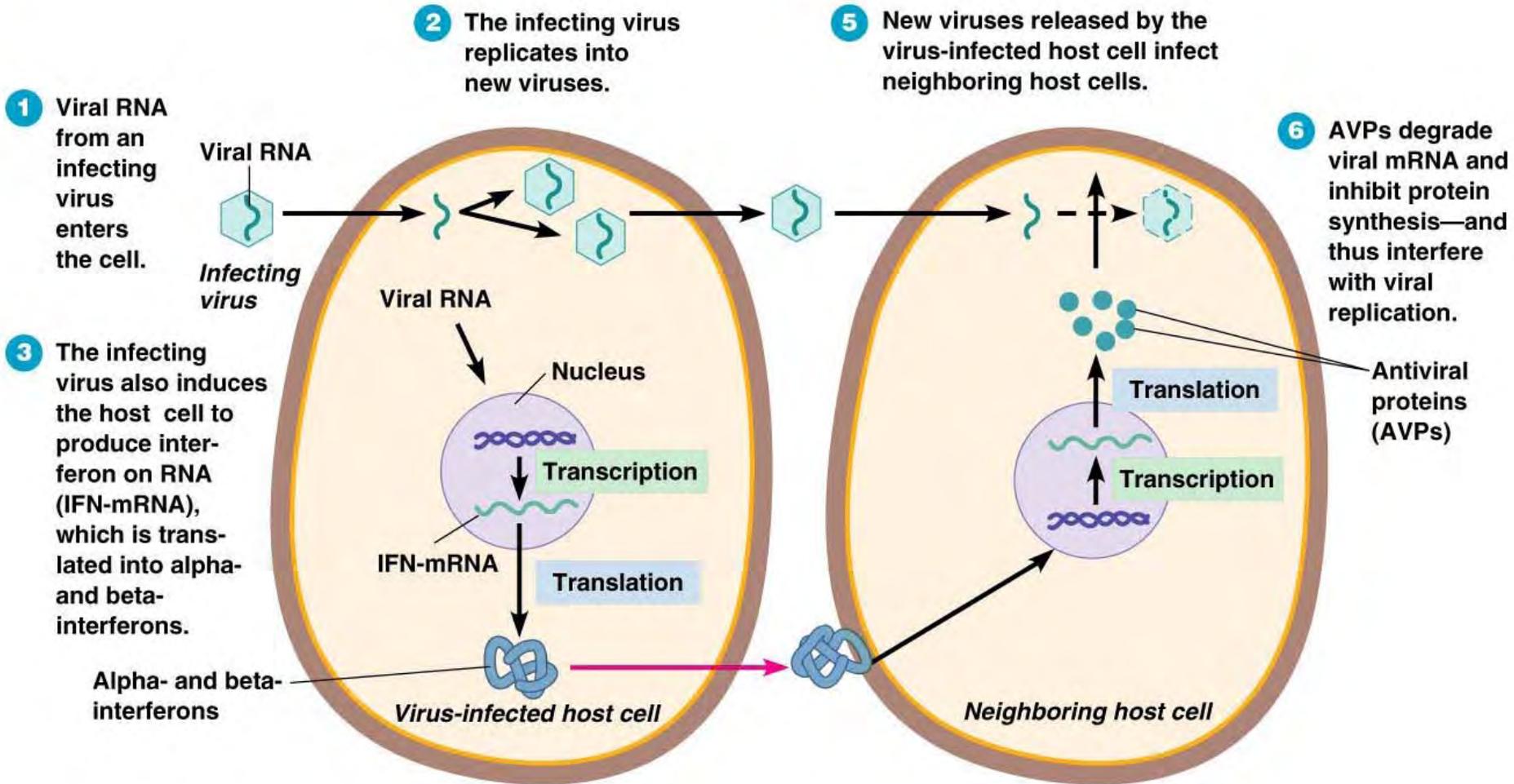
- phagocytes follow gradient of C5a to site of infection

Interferons

The interferons (IFN- α , IFN- β & IFN- γ) are a class of cytokines (soluble protein signals) released by virally infected cells and certain white blood cells to stimulate other cells to protect themselves from viral infection:

- the presence of viral proteins, RNA in a cell triggers IFN production & release**
- neighboring cells bind IFNs via specific receptors**
- this triggers the expression of various anti-viral genes in the cell receiving the IFN signal**
- the resulting anti-viral proteins (AVPs) degrade viral RNA, thus protecting cell from infection**

Effects of Interferons on Cells



Key Terms for Chapter 16

- **innate vs adaptive immunity**
- **granulocytes: neutrophils, basophils, eosinophils dendritic cells**
- **agranulocytes: monocytes, macrophages, NK cells, T & B cells**
- **opsonization, opsonin**
- **complement: classical, alternative, MBL paths**
- **lectins, interferons, cytokines, transferrins**

Relevant Chapter Questions

rvw: 1-5, 7-9, 12, 13, 15, 16 MC: 1-6, 10