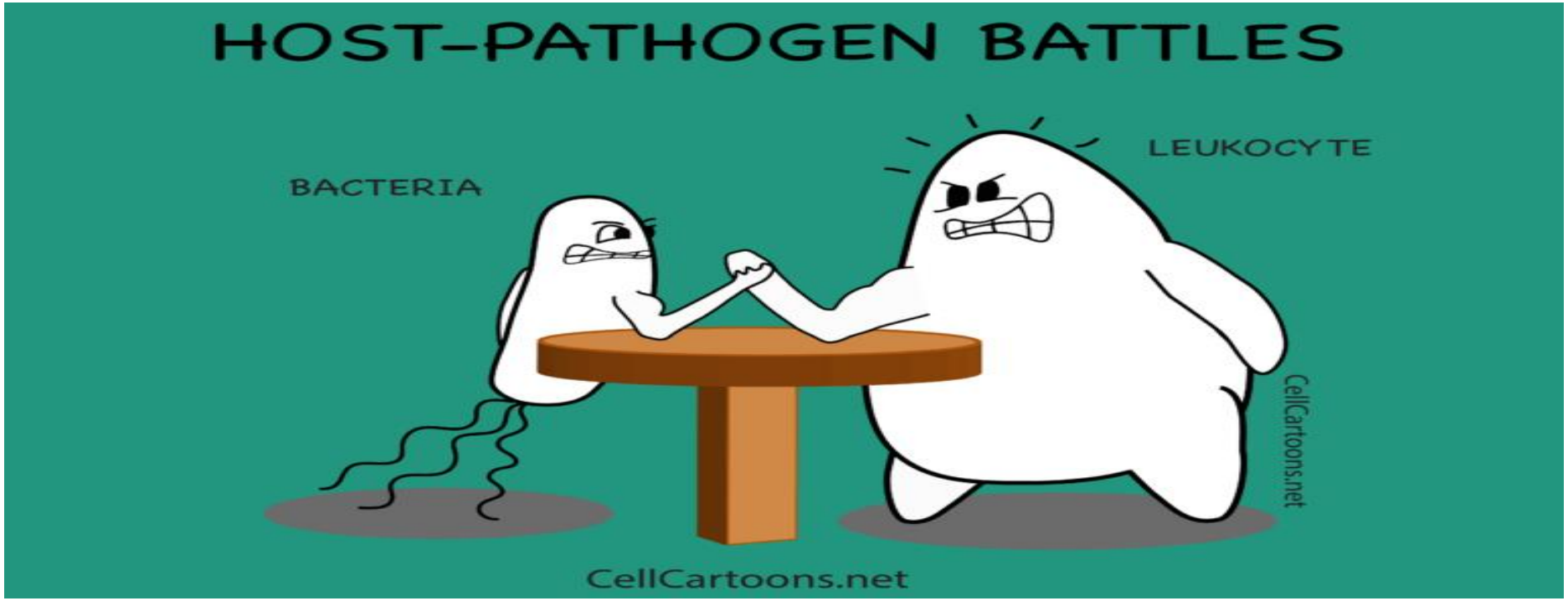


Host Immune Response to Pyogenic Infection

Prof. Dr. Batool Hassan Al-Ghurabi

Immunity to bacteria

The defense mechanisms used depend on:-

Ø Site of infection

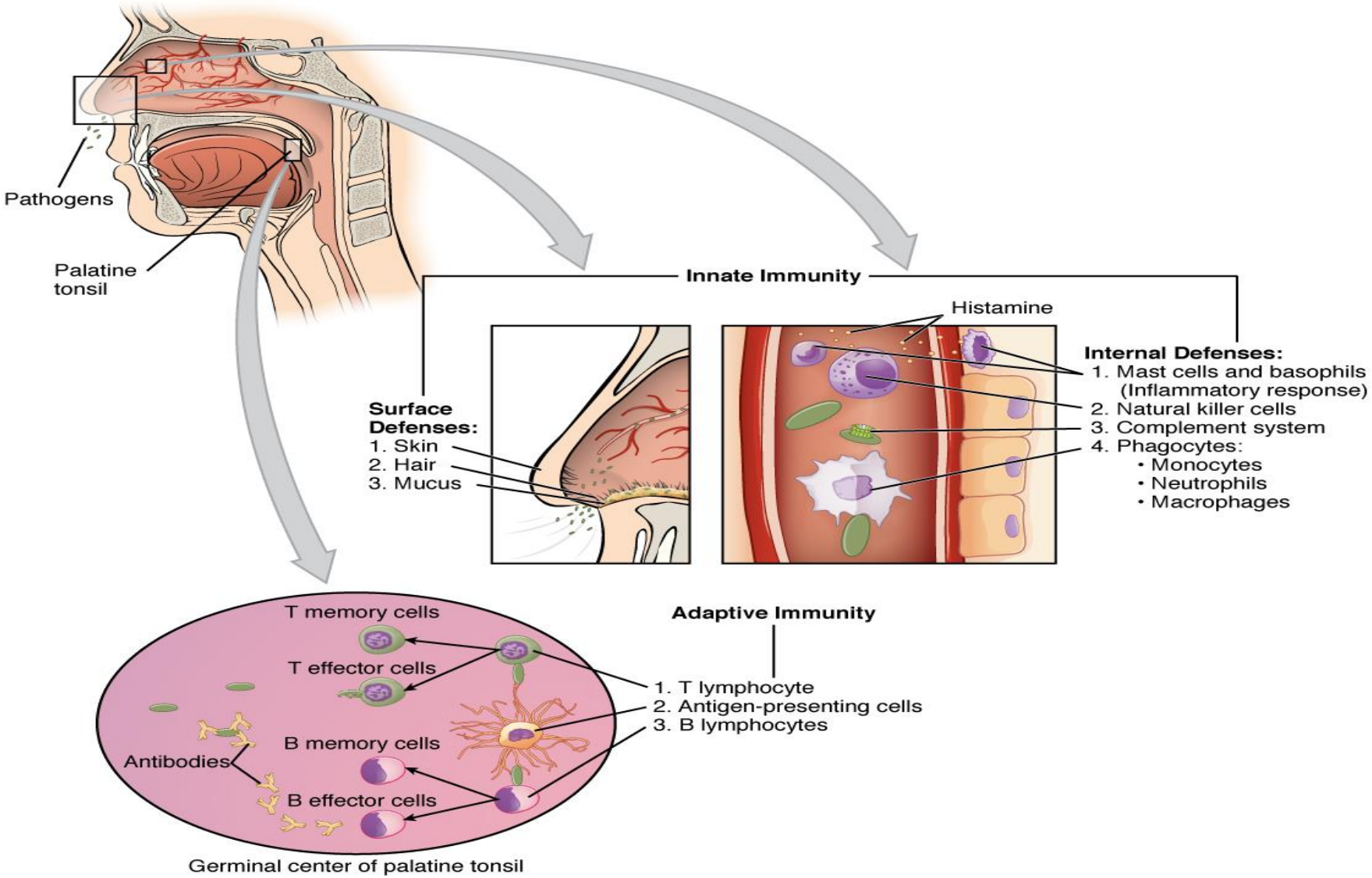
Ø Structure of the invading bacteria

Ø How they cause damage

Ø Intracellular vs. extracellular location

Barrier Defenses and the Innate Immune Response to Pyogenic Infection

- The immune system can be divided into two overlapping mechanisms to destroy pathogens: **the innate immune response**, which is relatively rapid but nonspecific and thus not always effective, **and the adaptive immune response**, which is slower in its development during an initial infection with a pathogen, but is highly specific and effective at attacking a wide variety of pathogens.



Cooperation between Innate and Adaptive Immune Responses. The innate immune system enhances adaptive immune responses so they can be more effective.

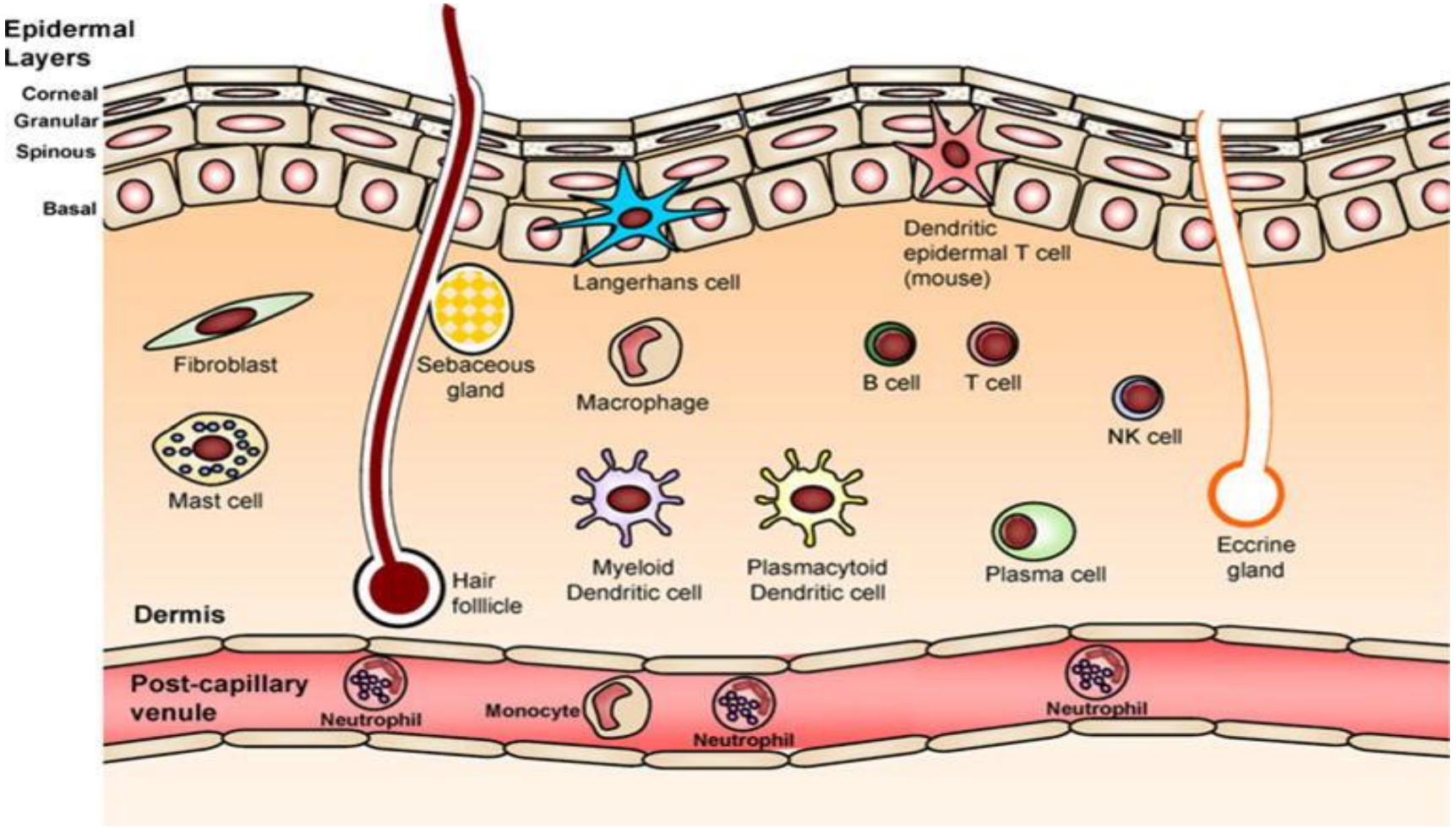
Immunity to bacteria

- In general, the innate response is important in preventing an **infection** becoming established, the adaptive subsequently in combating an established infection.

Barrier Defenses

Site	Specific defense	Protective aspect
Skin	Epidermal surface	Keratinized cells of surface, Langerhans cells
Skin (sweat/secretions)	Sweat glands, sebaceous glands	Low pH, washing action
Oral cavity	Salivary glands	Lysozyme
Stomach	Gastrointestinal tract	Low pH
Mucosal surfaces	Mucosal epithelium	Non-keratinized epithelial cells
Normal flora (nonpathogenic bacteria)	Mucosal tissues	Prevent pathogens from growing on mucosal surfaces

The immune barrier of the skin



Keratinocytes have multiple mechanisms to promote early innate immune responses against pyogenic bacteria.

First, it produce antimicrobial peptides that have direct bacteriostatic or bactericidal activity against pyogenic bacteria, including β-defensin and cathelicidin.

Second, keratinocytes express PRRs such as Toll-like receptors which recognize pyogenic bacterial, lipoteichoic acid, and peptidoglycan, LPS.

Antimicrobial peptides

- Antimicrobial peptides are a group of polypeptides that are possess antimicrobial activity at physiologic conditions.

- Most antimicrobial peptides are cationic peptides that interact with the anionic membrane surfaces of bacteria leading to lysis.

Antimicrobial peptides

	Cellular source in the skin	Mechanism of *S. aureus* evasion
α-Defensins	Neutrophils	Staphylokinase, MprF, *dlt*ABCD operon
hBD2	Keratinocytes, macrophages, and dendritic cells	IsdA
hBD3	Keratinocytes	
hBD4	Keratinocytes	
LL-37	Keratinocytes, macrophages, and neutrophils	IsdA, Aureolysin, MprF, *dlt*ABCD operon
Dermcidin	Sweat glands	Extracellular proteases
RNase 7	Keratinocytes	

Phagocyte

The phagocyte takes the organism inside itself as a phagosome, which subsequently fuses with a lysosome and its digestive enzymes, effectively killing many pathogens.

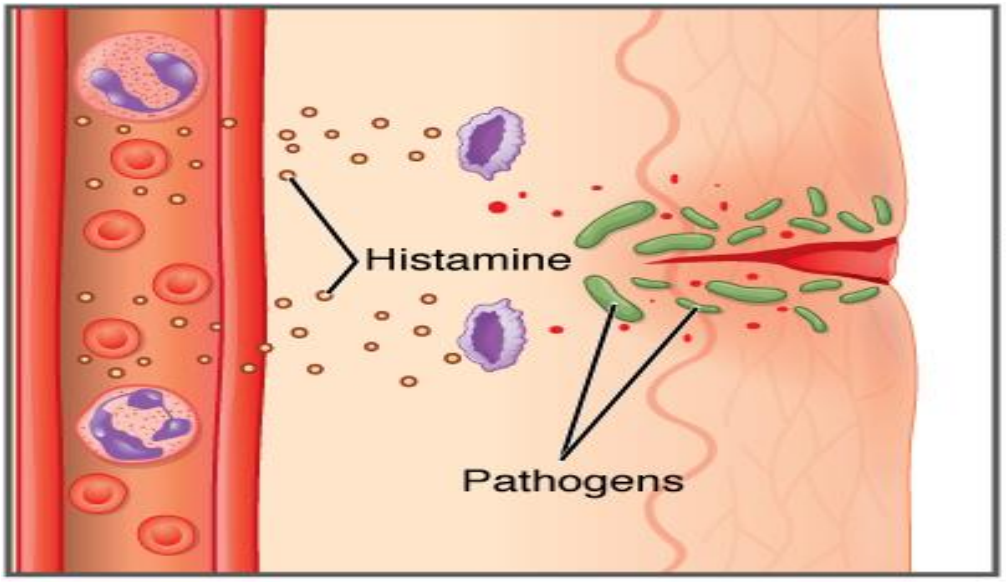
the macrophages, neutrophils, and dendritic cells are major phagocytes of the immune system.

Macrophage

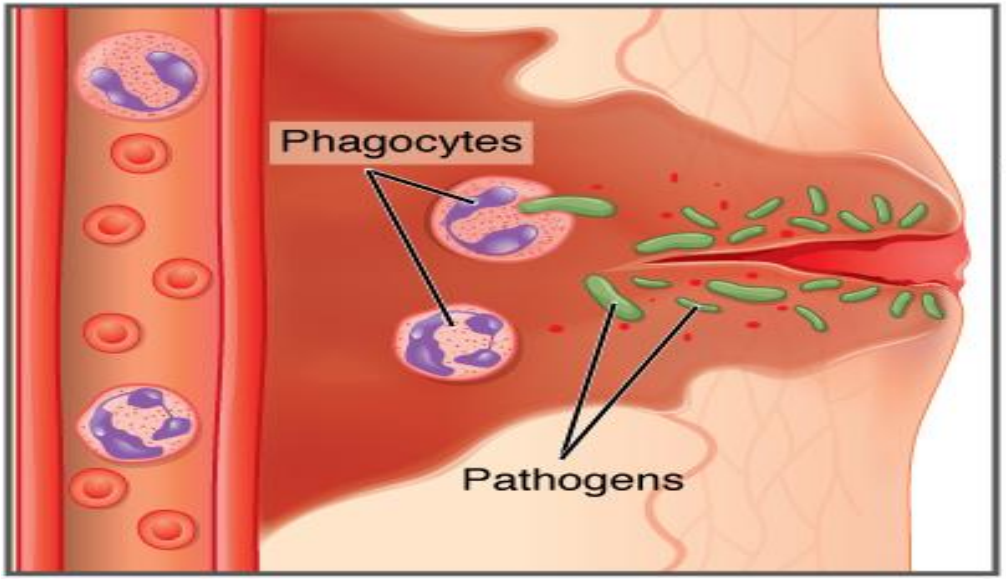
Macrophages are the first line of defense. They are called different names, depending on the tissue: Kupffer cells in the liver, histiocytes in connective tissue, and alveolar macrophages in the lungs.

Neutrophil

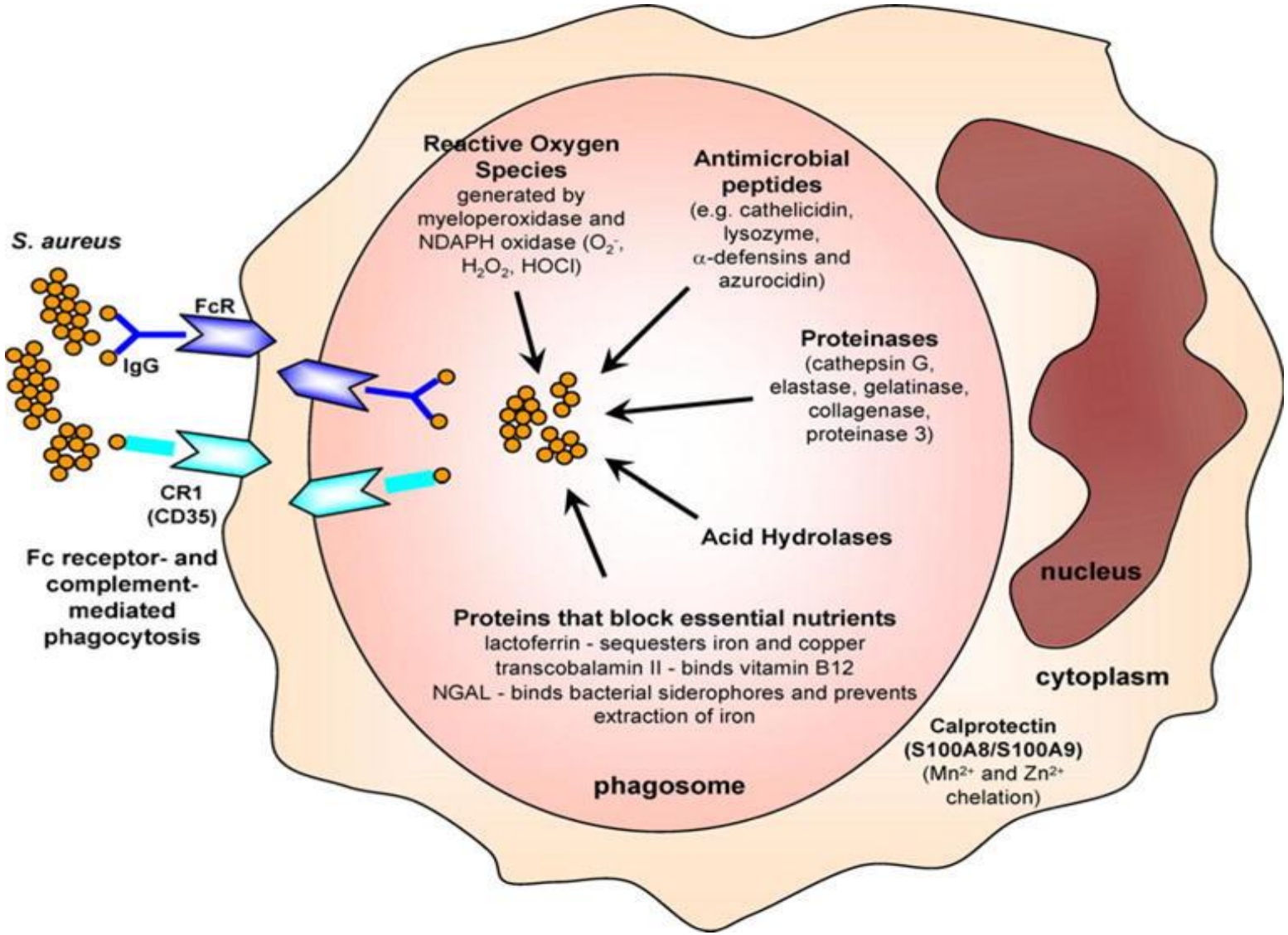
A **neutrophil** is a phagocytic cell that is attracted via chemotaxis from the bloodstream to infected tissues. A granulocyte contains cytoplasmic granules, which in turn contain a variety of vasoactive mediators such as histamine.



(1) Mast cells detect injury to nearby cells and release histamine, initiating inflammatory response.



(2) Histamine increases blood flow to the wound sites, bringing in phagocytes and other immune cells that neutralize pathogens. The blood influx causes the wound to swell, redden, and become warm and painful.


S. aureus
FcR
IgG
CR1
(CD35)
Fc receptor- and
complement-
mediated
phagocytosis
Reactive Oxygen
Species
generated by
myeloperoxidase and
NDAPH oxidase (O_2^-,
H_2O_2, HOCl)
Antimicrobial
peptides
(e.g. cathelicidin,
lysozyme,
α-defensins and
azurocidin)
Proteinases
(cathepsin G,
elastase, gelatinase,
collagenase,
proteinase 3)
Acid Hydrolases
Proteins that block essential nutrients
lactoferrin - sequesters iron and copper
transcobalamin II - binds vitamin B12
NGAL - binds bacterial siderophores and prevents
extraction of iron
phagosome
nucleus
cytoplasm
Calprotectin
(S100A8/S100A9)
(Mn^{2+} and Zn^{2+}
chelation)

Natural Killer Cells

- **NK** cells are a type of lymphocyte that have the ability to induce apoptosis, that is, programmed cell death, in cells infected with intracellular pathogens.

- The granules of the NK cells release perforins and granzymes. A **perforin** is a protein that forms pores in the membranes of infected cells. A **granzyme** is a protein-digesting enzyme that enters the cell via the perforin pores and triggers apoptosis intracellularly.

Recognition of Pathogens

Cells of the innate immune response recognize patterns of pathogen-specific molecules (PAMP), such as bacterial cell wall components or bacterial flagellar proteins, using pattern recognition receptors. A **pattern recognition receptor (PRR)** is a membrane-bound receptor that recognizes characteristic features of a pathogen and molecules released by stressed or damaged cells.

Soluble Mediators of the Innate Immune Response

These soluble factors are secreted during innate or early induced responses, and later during adaptive immune responses.

A cytokines is signaling molecule that allows cells to communicate with each other over short distances. Cytokines are secreted into the intercellular space, and the action of the cytokine induces the receiving cell to change its physiology.

A chemokine is a soluble chemical mediator similar to cytokines except that its function is to attract cells (chemotaxis) from longer distances.

Complement System

The **complement** system is a series of proteins constitutively found in the blood plasma. As such, these proteins are not considered part of the **early induced immune response**, even though they share features with some of the antibacterial proteins of this class.

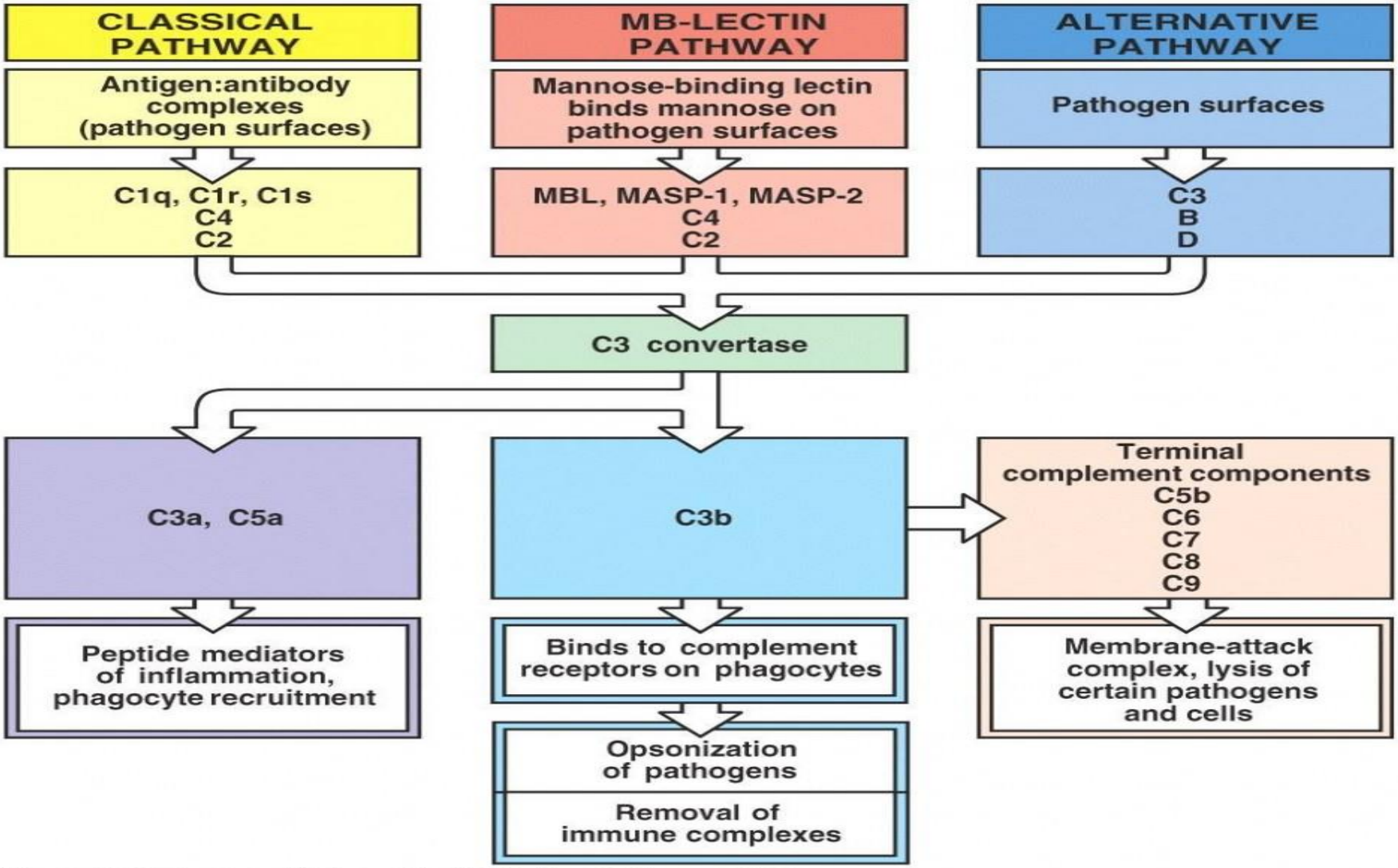


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

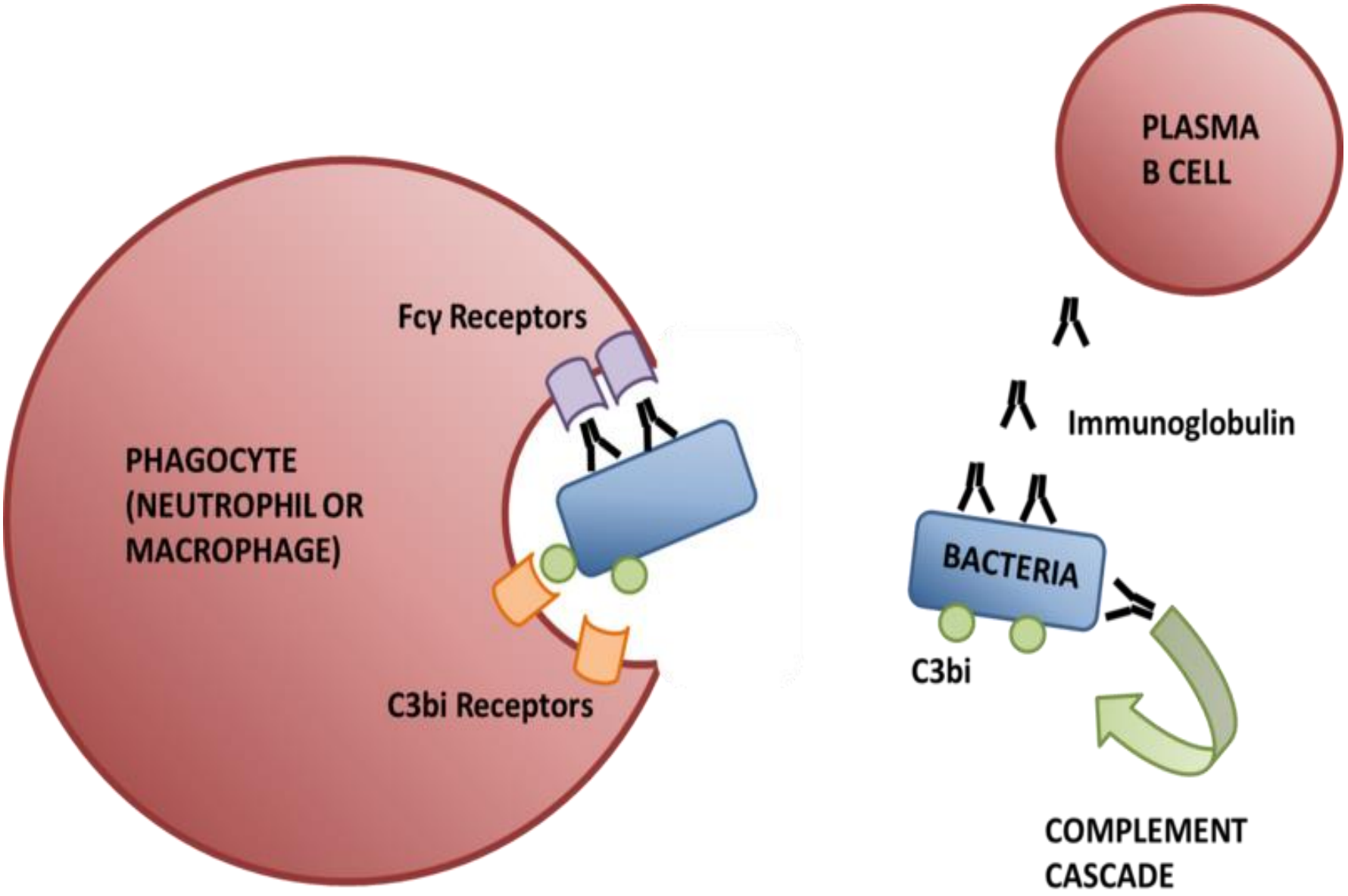
The Adaptive Response

The adaptive response ensures the innate response is carried out efficiently.

There are two major branches of the adaptive immune response, humoral immunity and cell-mediated immunity.

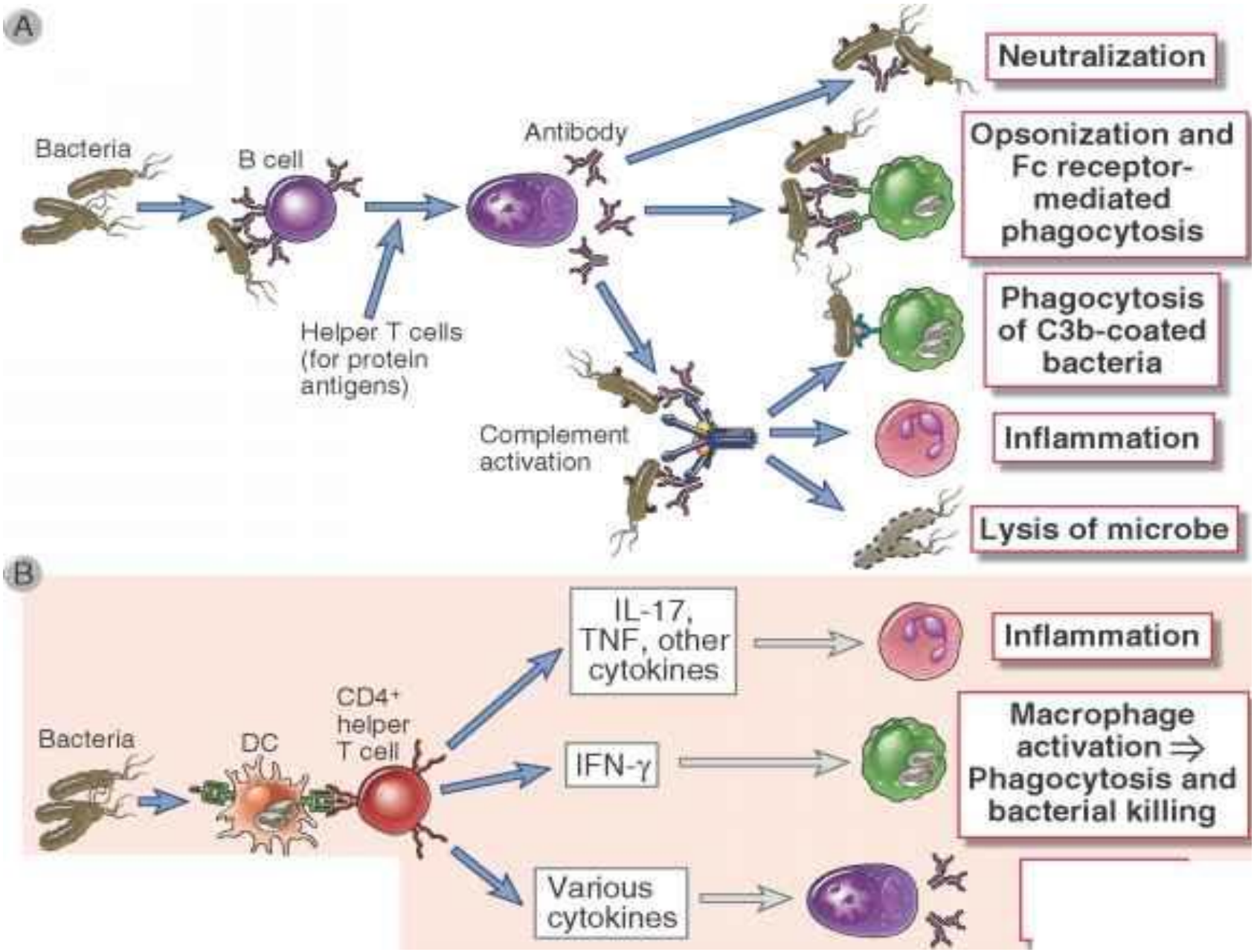
Humoral

Humoral immunity includes **complement activation** of the classical pathway. It results in the production of **IgM** and **IgG** and makes the complement system more efficient.


PLASMA
B CELL
Immunoglobulin
BACTERIA
C3bi
COMPLEMENT
CASCADE
Fcγ Receptors
PHAGOCYTE
(NEUTROPHIL OR
MACROPHAGE)
C3bi Receptors

Cell-Mediated

Cell-mediated immunity provides help for macrophages. *It includes **IgG** production (through T-helper type II (**T_H2**) cell interaction with **B cells**), *which improves phagocytosis by **opsonisation**. Infected macrophages are rescued by T-helper type I (**T_H1**) cells when phagocytosis and digestion mechanisms fail to eliminate the pathogen.


A
Bacteria
B cell
Antibody
Helper T cells
(for protein
antigens)
Complement
activation
Neutralization
Opsonization and
Fc receptor-
mediated
phagocytosis
Phagocytosis
of C3b-coated
bacteria
Inflammation
Lysis of microbe
B
Bacteria
DC
CD4+
helper
T cell
IL-17,
TNF, other
cytokines
IFN-γ
Various
cytokines
Inflammation
Macrophage
activation ⇒
Phagocytosis and
bacterial killing

Extracellular Infection

The response to extracellular infection involves:

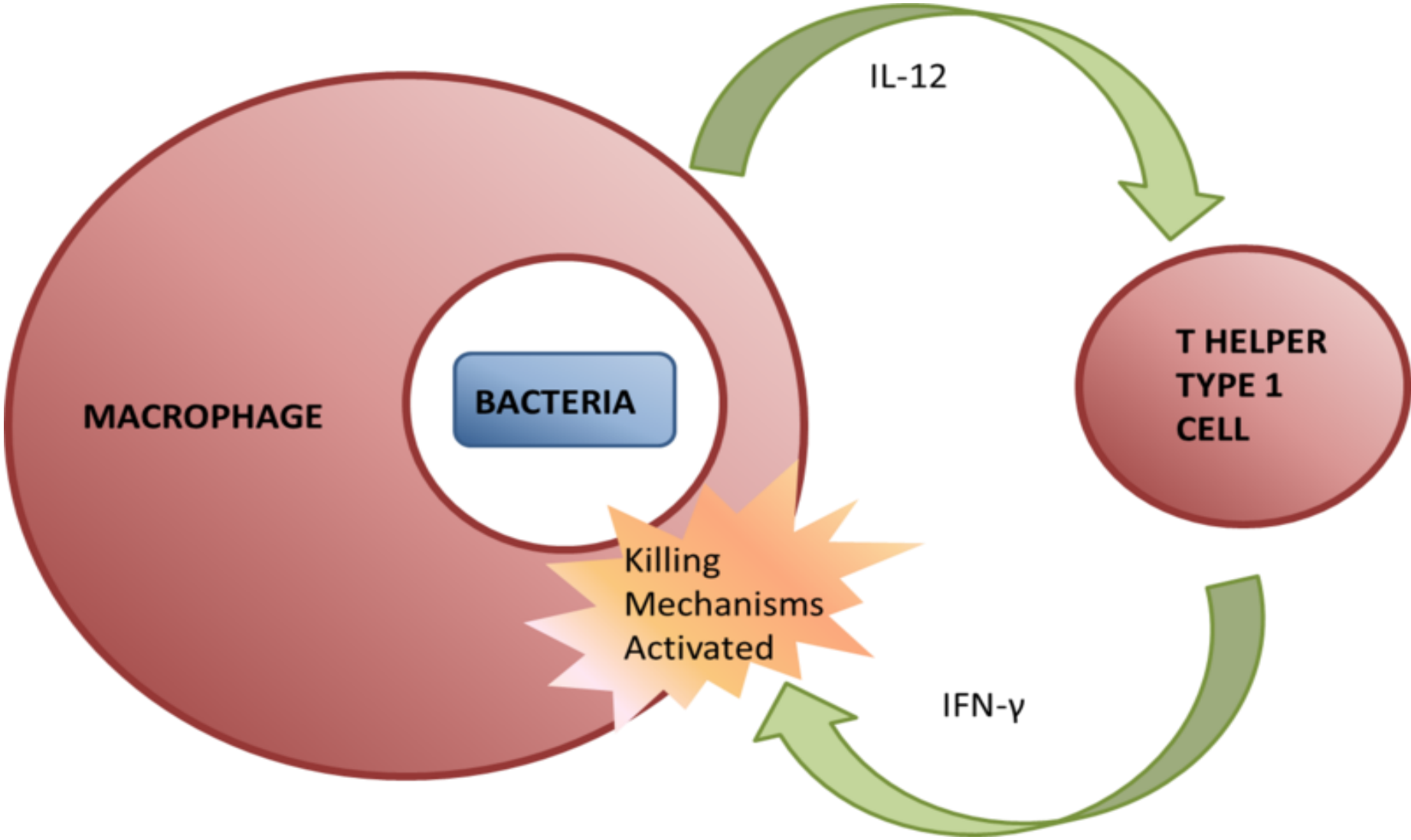
- Complement and phagocytosis.
- B cell and **T_H2** cell stimulation and the production of **IgM**, which activates the classical cascade.
- T_H17 stimulation also enhances extravasation of **neutrophils**.
- There is also class switching of IgM to IgG, which is a good opsonin and targets bacterial receptor.

Intracellular Infection

During a intracellular infection, the infected **macrophage** secretes **IL-12**.

IL-12 stimulates T-helper type I cells which release **IFN-γ**.

IFN-γ then triggers the **macrophages** to kill the pathogens inside.


IL-12
MACROPHAGE
BACTERIA
T HELPER
TYPE 1
CELL
Killing
Mechanisms
Activated
IFN-γ

Strategies of Pyogenic Bacteria to Evade the Immune System

- Production of toxins that inhibit the phagocytosis
- They are preventing killing by encapsulation
- The release of catalase inactivates hydrogen peroxide
- They infect cells and then cause impaired antigenic presentation
- The organism may kill the phagocyte by apoptosis or necrosis