Innate Immune Response

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Innate immune response:

natural immune response:

No-specific immune response:

--Any inborn resistance mechanisms to an invaded pathogen

--present from birth

--operate against almost any substance that threatens the body.

--consist of many factors that are relatively nonspecific

Three Characteristics of innate immune response:

--No antigen-specific:

Most of pathogens can be recognized and destroyed by innate immune defenses mechanisms(barriers, cells and molecules) without antigen-specific fashion.

--No induction period:

Innate immune defenses do not require a prolonged period of induction by antigen or pathogens. Several mins to 72h.

--No immune reminding:

It does not require prior exposure and is not modified significantly by repeated exposures to the pathogen over the life of an individual.

Chapter 1 Components involved in innate immune response

The skin and mucosal membranes:

skin

respiratory tract

digestive tract

urogenital tract

Immune cells:

Phagocytes

NK

NKT

B1 cell

γδ T cell

Humoral proteins:

complements

antimicrobial enzymes and binding proteins

peptide antibiotics

acute-phase response

the skin and the mucosal membranes:

--Mechanical barriers: physical barriers

the first line of defense, such as the intact skin and intact mucosal surface, which cover body surfaces and respiratory, digestive, urogenital tracts, prevent microorganisms and other potentially injurious agents from entering the tissues beneath. This is structurally impervious barriers.

--Chemical barriers:

The skin and mucosal cells can secret many chemical agents to cytolyses or inhibit the invaded pathogens.

Such as lactic acid and other substances in sweat maintain the surface of the epidermis at an acidic pH, which help prevent colonization by bacteria and other organisms.

Various fatty acids, hydrolytic enzymes(e.g., lysozymes)

Interferons, Complement system

--Biological barriers:

Normal flora present in the surface of skin and mucosal membranes have anti-microbial effects.

Immune cells involved in innate immune response:

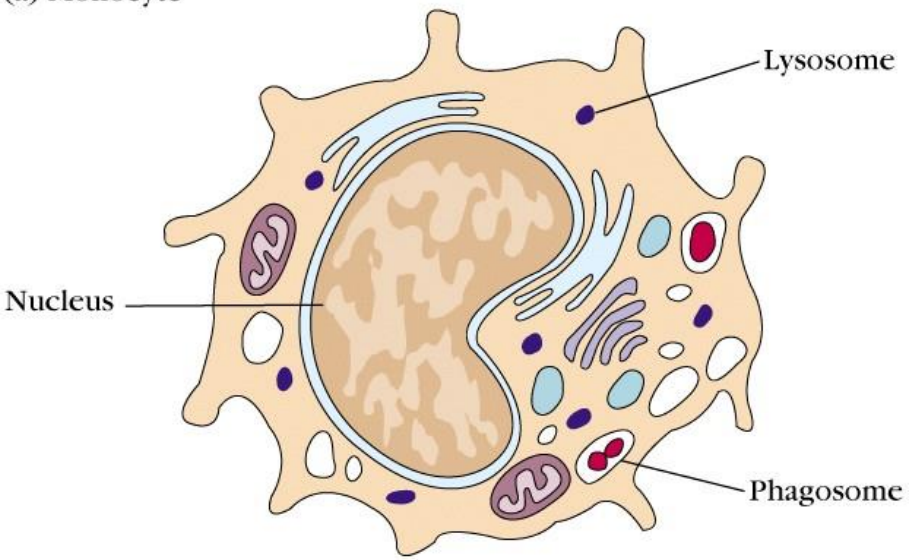
Phagocytes:

Neutrophils, monocytes and macrophage

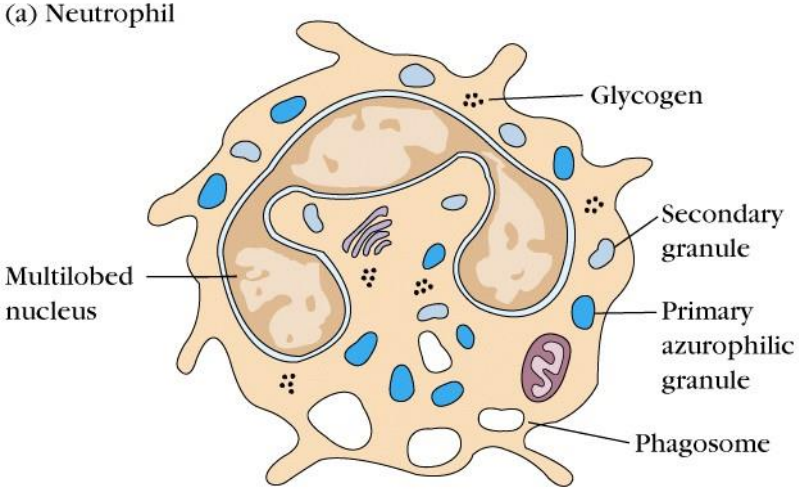
Act primarily by engulfing and digesting bacteria, cellular debris and other particulate matter.

Phagocytes can kill many pathogens directly and so be the most important cellular effectors of the innate immune system.

(a) Monocyte

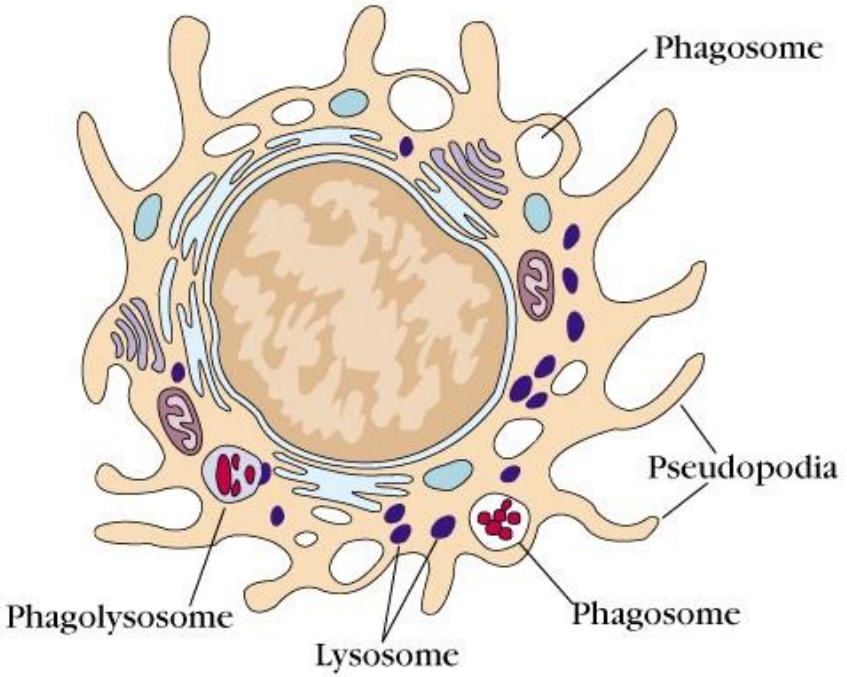


(a) Neutrophil



granymes

(b) Macrophage



1. Phagocytosis function:

First, migrate towards the site of infection by a process of chemical attraction: LPS, C3a, C5a, proinflammatory cytokines;

anaphylatoxin ⟶ chemokine ⟶ chemotaxis

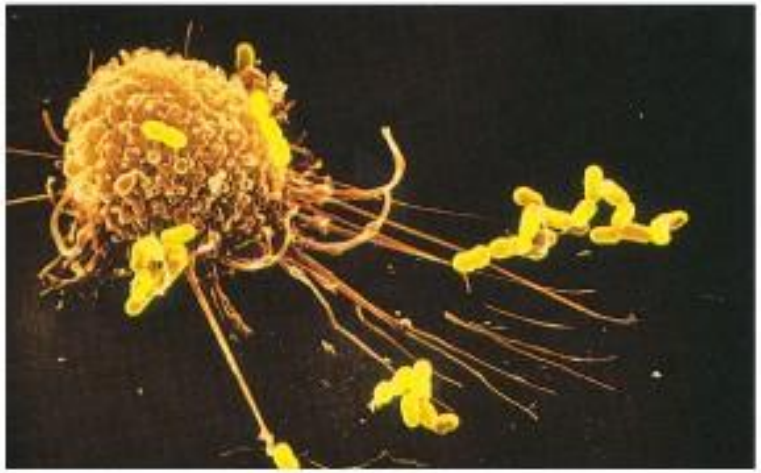
Then, engulfing immediately any bacteria, cellular debris, or foreign particulate matter in the area on arrival at an injured site;

Finally, kill or degrade the bacteria or dissolve other phagocytized materials by these agents:

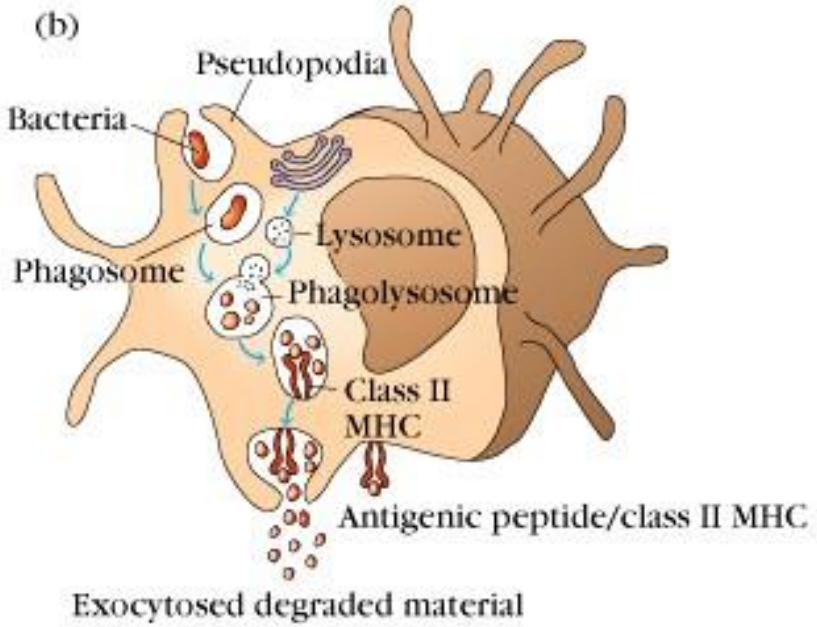
phagocytes contain extensive array of enzymes and other substances;

phagocytes acidifies the phagosome by actively pumping hydrogen ions into its interior; this not only promotes hydrolysis of the target directly, but also enhances the activities of many granular enzymes.

(a)



(b)



2. Secreting function:

Phagocytes can specifically secrete an enormous variety of biologically active substances into the surrounding tissues.

have anti-microbial activity: lysozyme,complements, hydrogen peroxide

liquefy and remodel the extracellular matrix: elatases, collagenases

3.Antigen presenting:

Natural killer cells (NK):

Function:

1. Kill target cells directly, such as tumor cells ,virally infected cells, without prior immunization.

--Killing target cells using cytoplasmic granules containing perforins and granymes

--ADCC: the CD16 Fc receptor on NK cells permits them to bind and lyse cells that are coated with IgG antibody specific for antigen present on the surface of target cells.

The antibody dependent cell-mediated cytotoxicity provides a bridge between the innate and acquired immune systems.

2. Regulate the immune response:

Activated NK cells produce cytokines such as IFN-γ, TNF-α.

IFN-γ can serve to bias a T_H0 cells toward T_H1 differentiation.

Marker:

CD16 and CD56 are marker molecules specific for NK. CD16 present on the surface of macrophage, granulocytes and NK cells, but CD56 only find on the NK cells.

NKT cells:

Co-express CD3 and NK1.1 molecules

1. NKT do not response to peptide antigens complexed with classical MHC molecules, but response to glycolipid antigens bound to a noclassical class I protein called CD1d.
2. NKT is like NK cells to demonstrate spontaneous cytotoxicity. And produce cytokines such as IFN-γ , IL-4.

B1 cells:

Marker molecule is CD5

1. B1 cells responds mainly to carbohydrate antigens of TI-2 type.
2. Produce IgM antibodies which are rather of low affinity than that produced by B2 cells.

   since B1 cells do not undergo somatic hypermutation and class switching.

Humoral proteins of innate immunity:

The body's innate resistance to many pathogens is provided by enzymes and other proteins in the blood and tissue fluids.

First, these proteins are continually expressed throughout life, regardless of whether or not their protective effects are needed at a given moment.

Second, these proteins never change their intrinsic properties, although many of these proteins can be produced in higher quantities in times of need.

Third, they generally recognize targets or substrates that are found on a wide range of different microorganisms but that are not normally present in the human body.

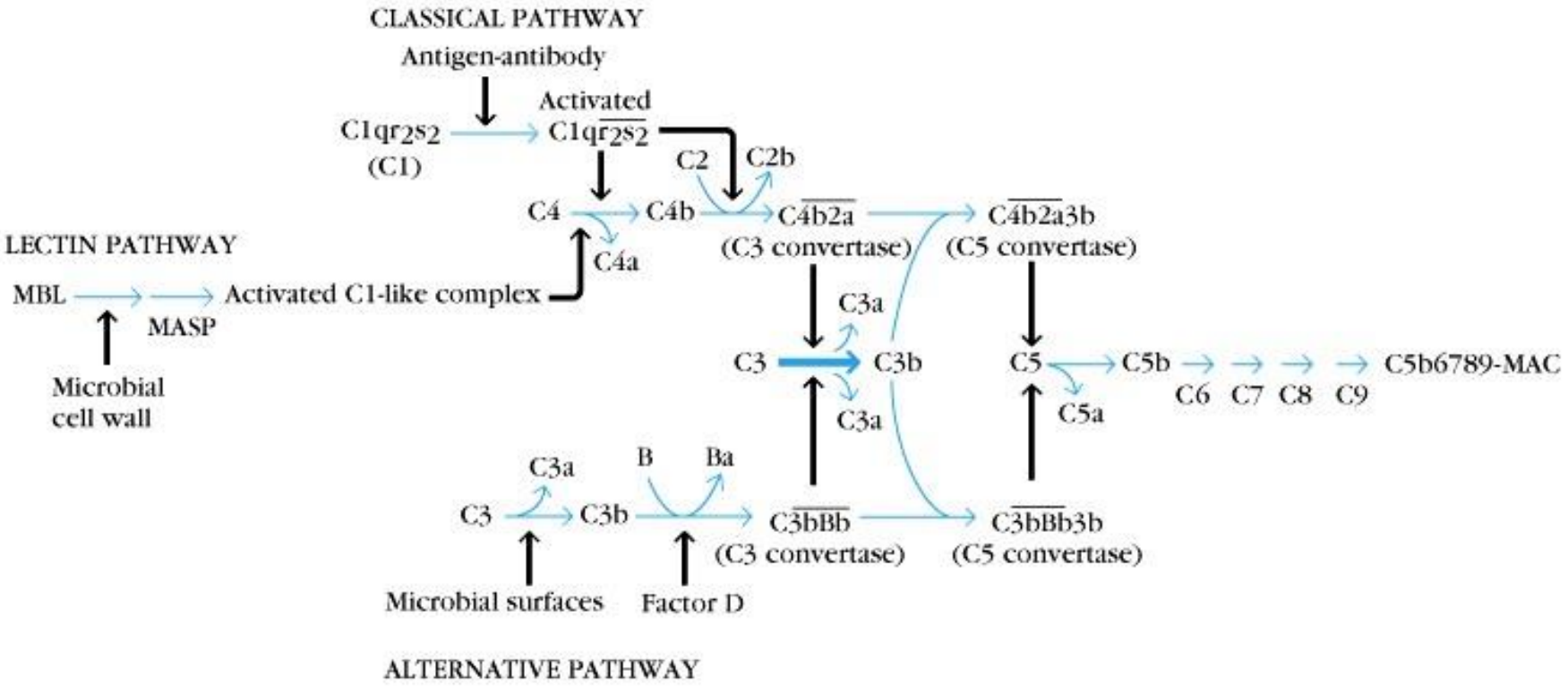
1. The complement system:

Three pathways of the complement activation:

classical pathway;

alternative pathway;

lectin pathway


CLASSICAL PATHWAY
Antigen-antibody
Activated
C1qr2s2
(C1)
C1qr2s2
C2
C2b
C4
C4b
C4b2a
(C3 convertase)
C4b2a3b
(C5 convertase)
LECTIN PATHWAY
C4a
MBL
Activated C1-like complex
MASP
Microbial
cell wall
C3a
C3
C3b
C5
C5b
C6
C7
C8
C9
C5b6789-MAC
C5a
C3a
B
Ba
C3
C3b
C3bBb
(C3 convertase)
C3bBb3b
(C5 convertase)
Microbial surfaces
Factor D
ALTERNATIVE PATHWAY

After invasion of pathogen, the complement system will be immediately activated by alternative pathway and lectin pathway:

--MAC will result in membrane perforation
--enhancing the killing function of host defensive cells, such as neutriphil, monocytes, macrophage
--facilitate the inflammation by:
the anaphylatoxin:
chemotaxis:

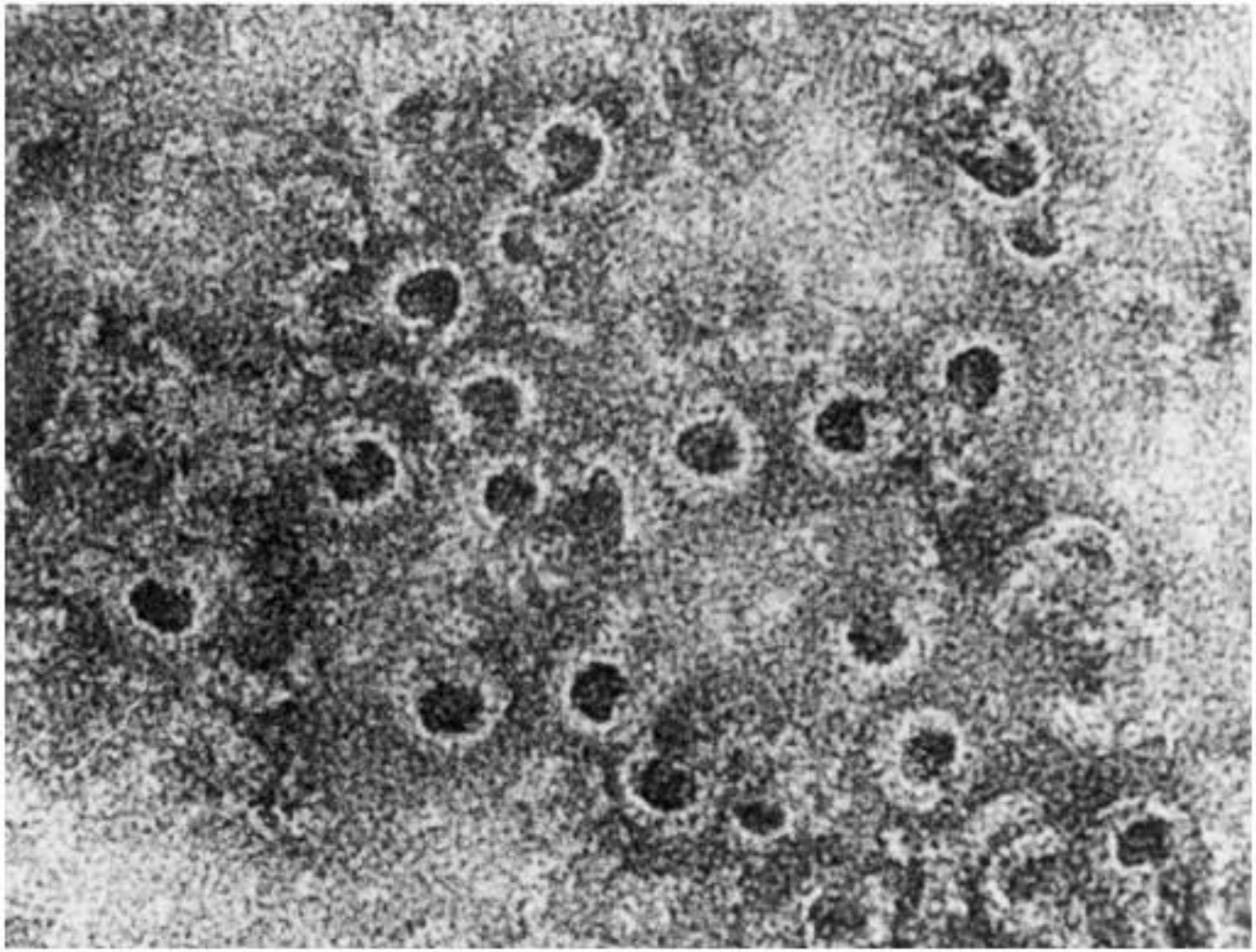
TABLE 13-7 SUMMARY OF BIOLOGICAL EFFECTS MEDIATED BY COMPLEMENT PRODUCTS

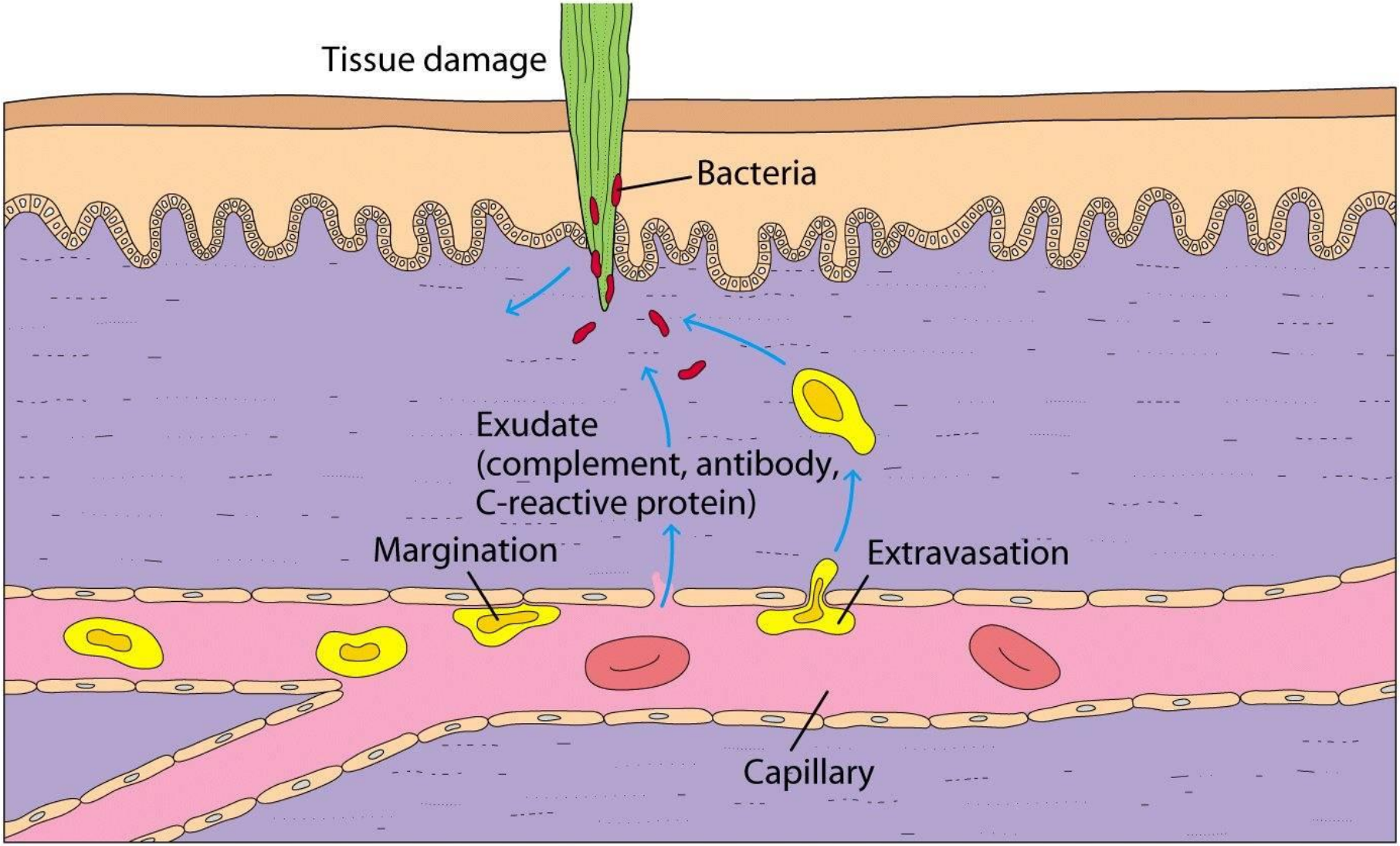
Effect	Complement product mediating*
Cell lysis	C5b–9, the membrane-attack complex (MAC)
Inflammatory response	
Degranulation of mast cells and basophils†	C3a, C4a, and C5a (anaphylatoxins)
Degranulation of eosinophils	C3a, C5a
Extravasation and chemotaxis of leukocytes at inflammatory site	C3a, **C5a,** C5b67
Aggregation of platelets	C3a, C5a
Inhibition of monocyte/macrophage migration and induction of their spreading	Bb
Release of neutrophils from bone marrow	C3c
Release of hydrolytic enzymes from neutrophils	C5a
Increased expression of complement receptors type 1 and 3 (CR1 and CR3) on neutrophils	C5a
Opsonization of particulate antigens, increasing their phagocytosis	**C3b,** C4b, iC3b
Viral neutralization	C3b, C5b–9 (MAC)
Solubilization and clearance of immune complexes	C3b

*Boldfaced component is most important in mediating indicated effect.

†Degranulation leads to release of histamine and other mediators that induce contraction of smooth muscle and increased permeability of vessels.

(b)




Tissue damage
Bacteria
Exudate
(complement, antibody,
C-reactive protein)
Margination
Extravasation
Capillary

2. Anti-microbial enzymes and binding proteins:

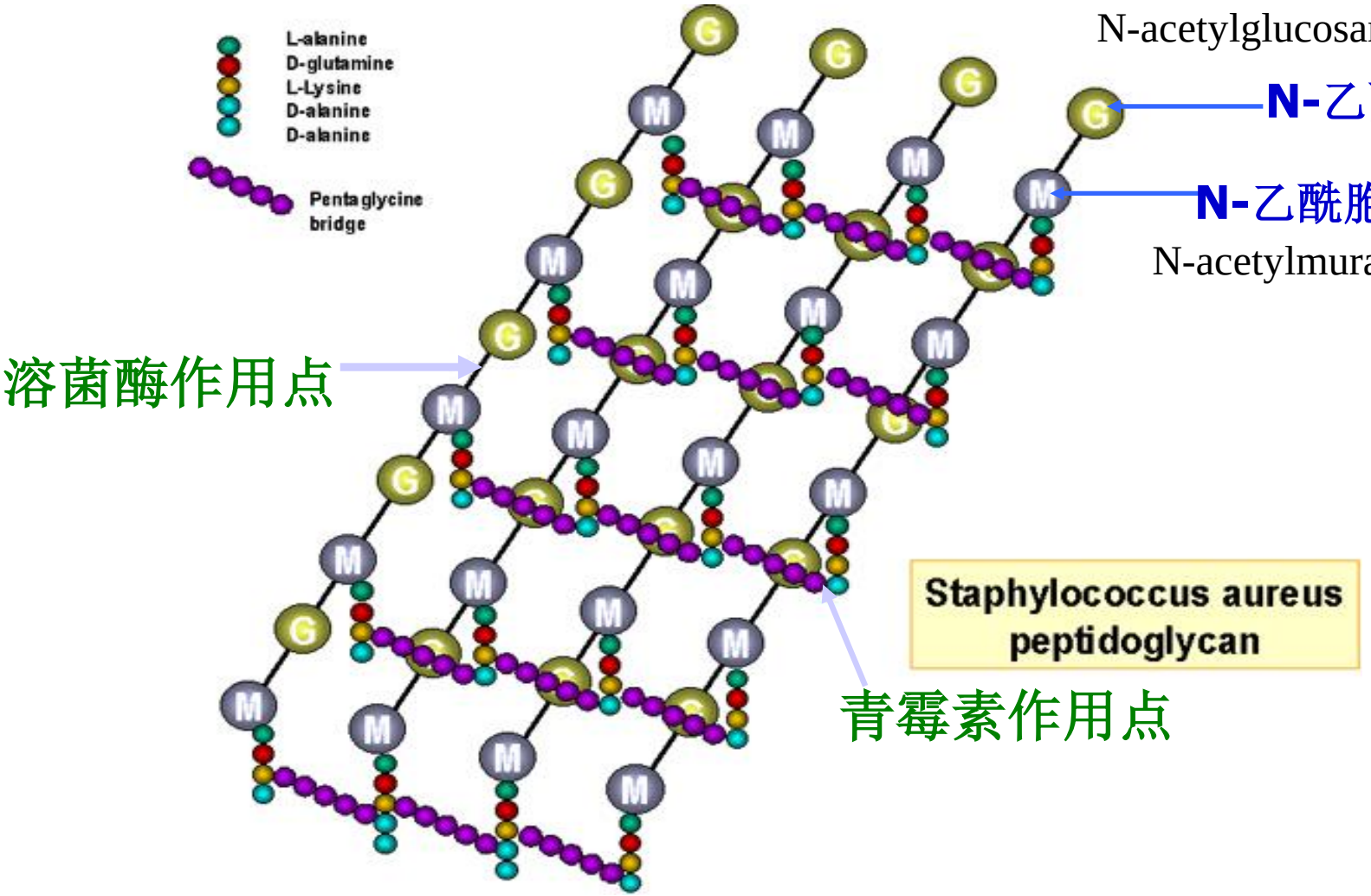
Enzymes: can directly injure or kill microbial pathogens.

Lysozyme, an endoglycosidase found in huaman saliva, mucus, tears, and other secrections, can attacks the cell wall encasing every bacterial cell by cleaving the linkages between carbohydrate residues in the peptideoglycan which is the major constituent of all bacterial cell walls.

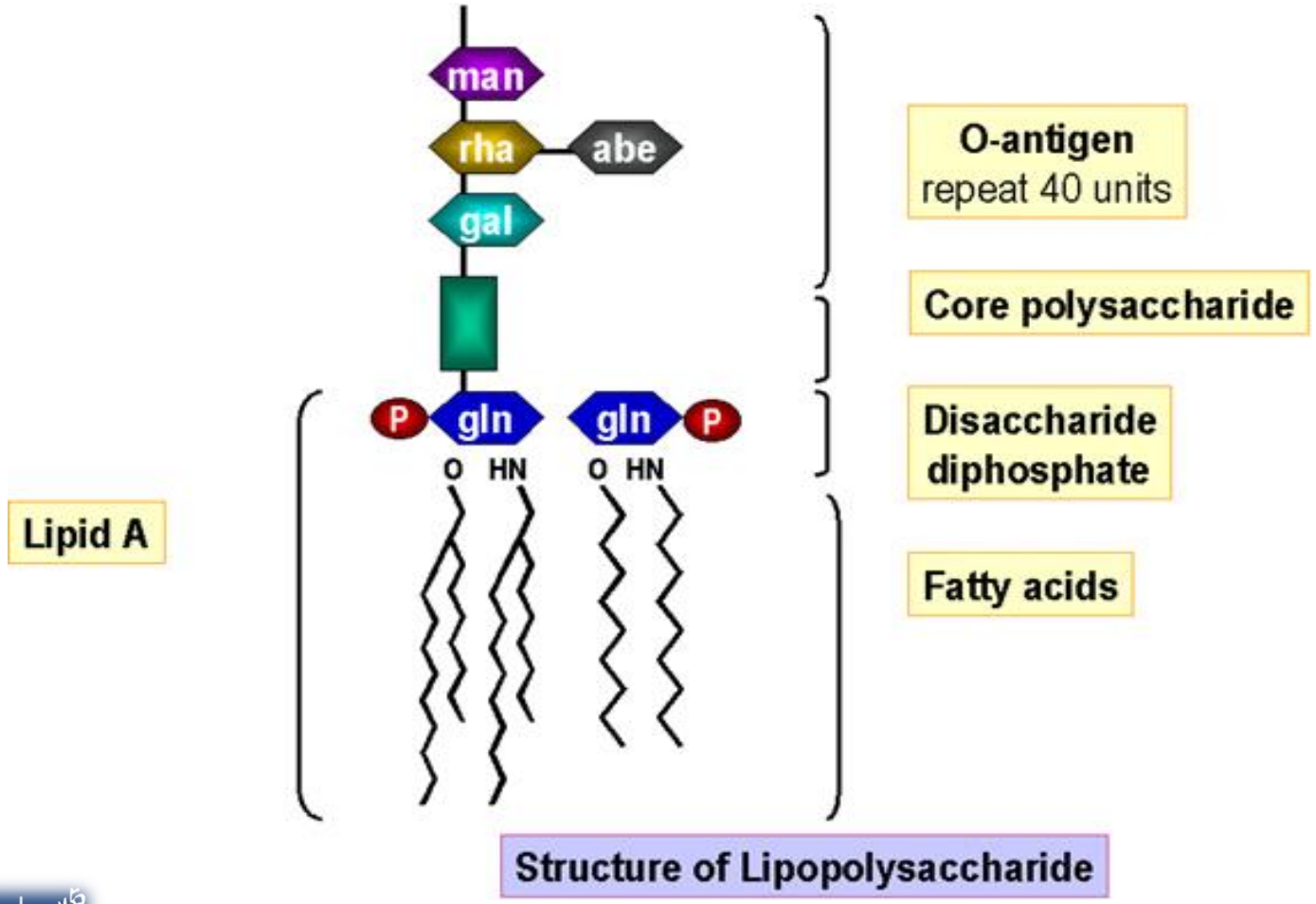
Other humoral factors bind to pathogens:

They produce little or no effect on their own, but they mark the pathogen for destruction by other humoral or cell-mediated processes.

MBL, Serum amyloid protein P, C-reactive protein in blood, each of which binds a subset of carbohydrate or lipid determinants found on many different types of bacteria.


L-alanine
D-glutamine
L-Lysine
D-alanine
D-alanine
Pentaglycine bridge
N-acetylglucosamine residues
N-乙酰葡糖胺
N-乙酰胞壁酸
N-acetylmuramic acid
溶菌酶作用点
Staphylococcus aureus peptidoglycan
青霉素作用点

脂多糖(lipopolysaccharid,LPS)



Structure of Lipopolysaccharide

3. Peptide antibiotics:

A class of small peptide antibiotics known as defensin, which in their active forms are all roughly 30 amino acids long (3-5KD).

Defensin are active against a broad spectrum of bacteria, fungi, and enveloped viruses, but not against mammalian cells.

4. The acute-phase response:

Under normal condition , Most of soluble mediators of innate immunity are in small amounts in the serum,

During infections or other crises, the concentrations of some of them can increase as much as 1000-fold, as part of a coordinated protective reaction called the acute-phase response.

The liver acute-phase response:

Liver can increase its synthesis of more than 30 different proteins, often calls acute-phase proteins:

C3, B, MBL, LBP, C-reactive protein---participate in antimicrobioal defense;

Coagulation factors: fibrinogen, granulocyte colony-stimulating factor,

serum metal-binding proteins

The acute-phase response can be viewed as a primitive, nonspecific defense reaction, mediated by liver, that intensifies some aspects of innate immunity and other protective functions in times of distress.

Chapter 2

The recognition mechanism of innate immnue response

Adaptive immunity have high specificity:

TCR/BCR --- antigen determinant

Innate immunity recognizes a group of pathogens:

PRR -- PAMP

PAMPS: pathogen associated molecular patterns:

--Bacterial DNA which contain high content of cytosine-phosphate-guanosine (CpG) dinucleotides that lack the cytosine methylation found in vertebrate DNA;

--Proteins that are found only in pathogen, such as N-formylmethionine;

--Substrates that are synthesized by pathogens but not by mammalian cells, such as LPS (lipopolysaccharides) in gram-negative bacteria, teichoic acids in gram-positive bacteria.

These molecuels are called pathogen associated molecules patterns. Since these PAMPs belong to pathogens only, the innate immune system can distinguish self (mammalian) from non-self (pathogen).

PRR: Pattern recognition receptor

Most immune cells express these pattern recognition receptors which bind with the PAMP of pathogens

Membrane receptor:

- Mannose receptors
- Scavenger receptors
- Toll-like receptors

Secretary receptors:

- MBL, C-reactive proteins, LBP

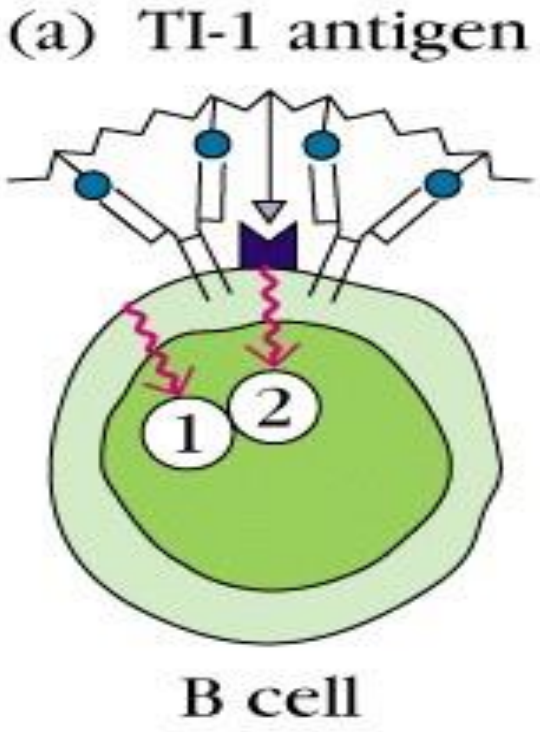
The biological significance of innate immune response

Innate immune system is critical for human health, not only in its own right but also in activating and regulating acquired immunity:

--A critical part of immune response

--Activating adaptive immune response

--Regulating adaptive immune response



The prototypic TI-1 antigen is **lipopolysaccharide (LPS),** a major component of the cell walls of gram-negative bacteria.

At low concentrations, LPS stimulates the production of antibodies specific for LPS.

At high concentrations, it is a polyclonal B-cell activator.

TI-2 antigens :

activate B cells by extensively crosslinking the mIg receptor. However, TI-2 antigens differ from TI-1antigens in three important respects:

--First, they are not B-cell mitogens and so do not act as polyclonal activators.

--Second, TI-1 antigens will activate both mature and immature B cells, but TI-2 antigens activate mature B cells and inactivate immature B cells.

--Third, although the B-cell response to TI-2 antigens does not require direct involvement of T cells, cytokines derived from T cells are required for efficient B-cell proliferation and for class switching to isotypes other than IgM.