Innate Immunity

Immunology/ CC – 13/ Unit - 1

Immunity:

All mechanisms used by the body to protect itself against all things foreign

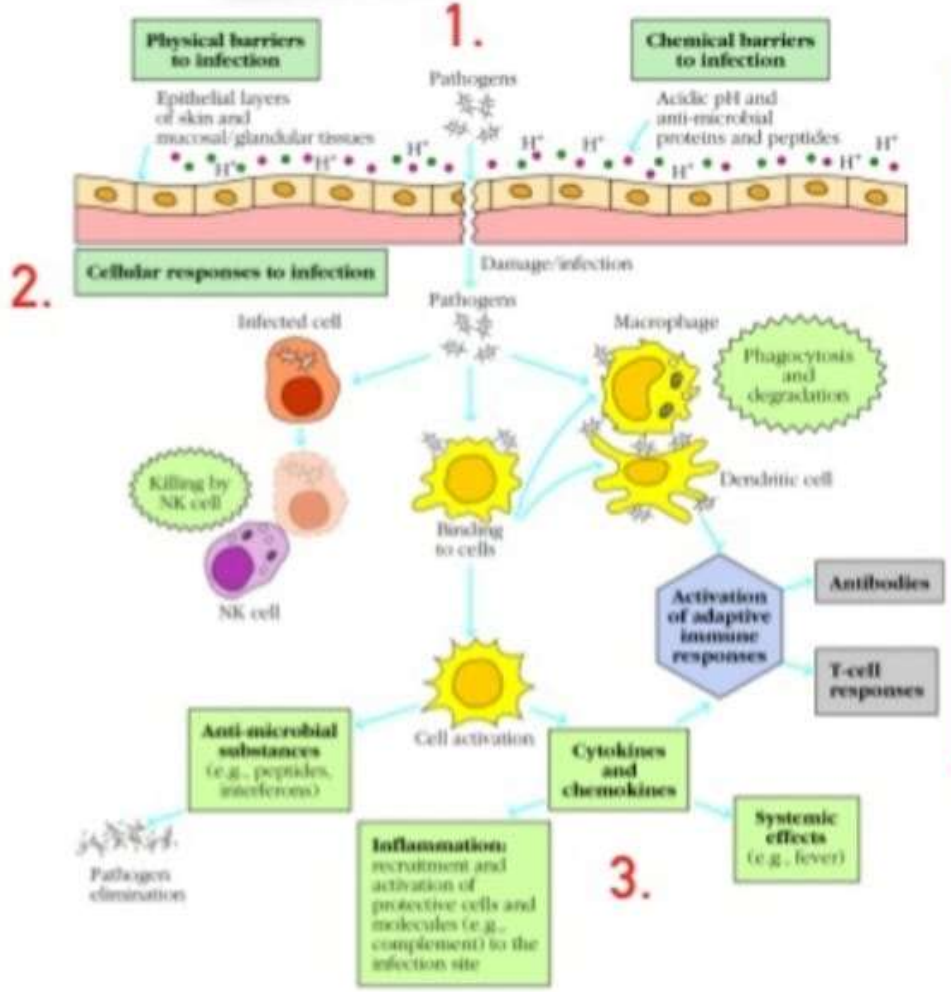
Immunity: innate or acquired

Innate immunity:

- all elements with which we are born,
- non-specific, has no memory,
- does not improve after exposure to antigen
- always present,
- available on short notice to protect;

- **consists of:**
  - **physical barriers:** skin, mucous membranes
  - **cells:** phagocytes and NK cells
  - **proteins:** complement, acute phase proteins and interferons

Component of innate immunity



1. Anatomical barrier
   - Physical barriers
   - Chemical barriers
2. Cell
   - Phagocytic cells
   - Dendritic cell
   - NK cells, ILC
3. Soluble proteins
   - Complement
   - Cytokines, Chemokines
   - Anti-microbial substances

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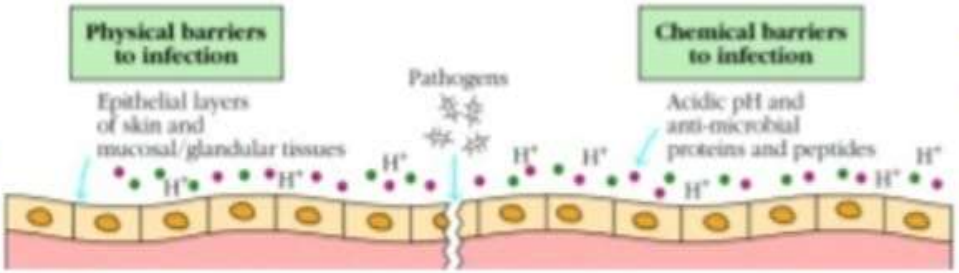
1.) Anatomical barriers

- Skin
- Mucosal & Glandular tissues
- Mechanical :Cilia



- Enzyme
- Antimicrobial peptides (AMPs)
- pH

TABLE 5-2 Some human antimicrobial proteins and peptides at epithelial surfaces

Proteins and peptides*	Location	Antimicrobial activities
Lysozyme	Mucosal/glandular secretions (e.g., tears, saliva, respiratory tract)	Cleaves glycoside bonds of peptidoglycans in cell walls of bacteria, leading to lysis
Lactoferrin	Mucosal/glandular secretions (e.g., milk, intestine mucus, nasal/respiratory and urogenital tracts)	Binds and sequesters iron, limiting growth of bacteria and fungi; disrupts microbial membranes; limits infectivity of some viruses
Secretory leukocyte protease inhibitor	Skin, mucosal/glandular secretions (e.g., intestines, respiratory, and urogenital tracts, milk)	Blocks epithelial infection by bacteria, fungi, viruses; antimicrobial
S100 proteins, e.g.: - psoriasin - calprotectin	Skin, mucosal/glandular secretions (e.g., tears, saliva/tongue, intestine, nasal/respiratory and urogenital tracts)	 - Disrupts membranes, killing cells - Binds and sequesters divalent cations (e.g., manganese and zinc), limiting growth of bacteria and fungi
Defensins (α and β)	Skin, mucosal epithelia (e.g., mouth, intestine, nasal/respiratory tract, urogenital tract)	Disrupt membranes of bacteria, fungi, protozoan parasites, and viruses; additional toxic effects intracellularly; kill cells and disable viruses
Cathelicidin (LL37)**	Mucosal epithelia (e.g., respiratory tract, urogenital tract)	Disrupts membranes of bacteria; additional toxic effects intracellularly; kills cells
Surfactant proteins SP-A, SP-D	Secretions of respiratory tract, other mucosal epithelia	Block bacterial surface components; promotes phagocytosis

*Examples listed in this table are all produced by cells in the epithelia of mucosal and glandular tissues; examples of prominent epithelial sites are listed. Most proteins and peptides are produced constitutively at these sites, but their production can also be increased by microbial or inflammatory stimuli. Many are also produced constitutively in neutrophils and stored in granules. In addition, synthesis and secretion of many of these molecules may be induced by microbial components during innate immune responses by various myeloid leukocyte populations (monocytes, macrophages, dendritic cells, and mast cells).

**While some mammals have multiple cathelicidins, humans have only one.

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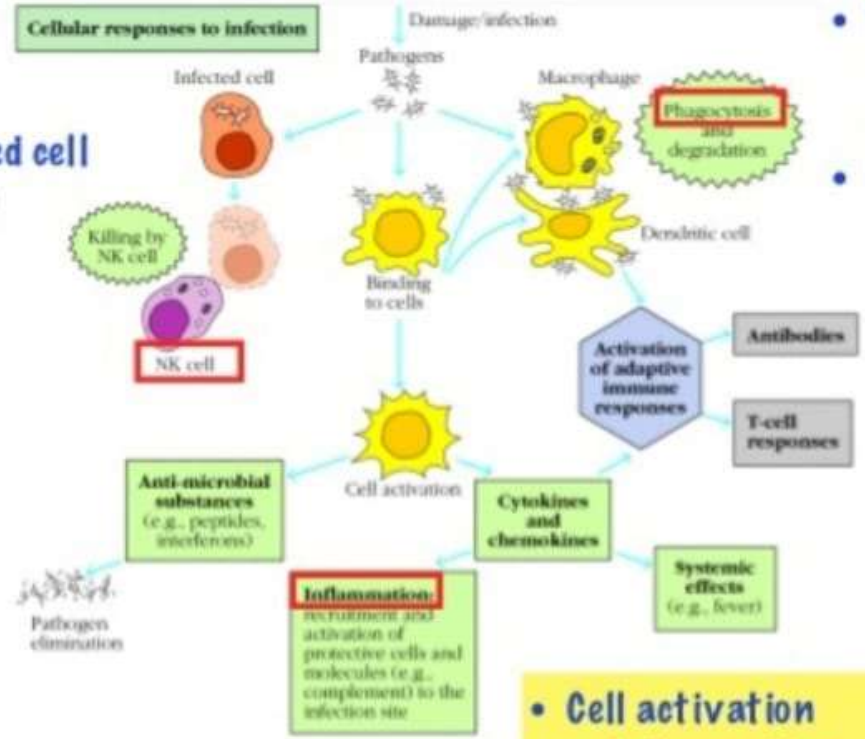
2.) Cellular Response (Recognized pathogen by receptors : PRRs)
3.) Soluble proteins

- NK cell
  - Viral infected cell
  - Malignancy



- Phagocytic cells
  - -Macrophage, Neutrophil
  - " Phagocytosis "
- Dendritic cell
  - >> Activated adaptive immune response

- Cell activation
  - >> Inflammation
  - >> Antiviral defense

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Functions of innate immunity

- Killing invading microbes
- Activating the acquired (adaptive) immune mechanism

INNATE IMMUNITY

- Provides signals to activate and regulate the type of adaptive immune response generated
  - Stimulation of co-stimulatory molecules
    - B7 family (CD80/86, PD-L, ICOSL)
    - TNFR family (OX40L)
  - Induction of a cytokine/chemokine response
    - Cytokines: IL-12, IL-23, IL-4
    - Chemokine's: CXCR1, CXCR2, CCL20
      - a variety and depends on stimulus

The Innate Immune System composed of ?

- includes physical, chemical, and cellular barriers
- **physical** barriers include skin and mucus membranes
- **chemical** barriers include stomach acidity, secreted anti-microbial peptides
- **cellular** barriers include macrophages, neutrophils
- innate immune response activation occurs within minutes of pathogen recognition

Host defense mechanisms

A. Outer barriers

Skin and epithelial linings

Skin: keratin

sweat (NaCl), sebum (unsat. fatty acids)

dead skin cells are shed

Mucous membranes: mucus and ciliated epithelium

stomach – acid (pH 2-3)

mucus - prevent attachment & entry

M cells - **endocytose pathogens**, aids presentation to B and T lymphocytes

Tears & saliva - flushing; lysozyme

Saliva - aggregation of bacteria

Urinary tract - urinary flow

- Small intestine - pancreatic enzymes, bile, intestinal enzymes, and secretory IgA
- Peristalsis and loss of columnar epithelial cells help eliminate pathogens (shedding/sloughing off every 2-5 days)

- **Normal indigenous microbiota may be involved in the following ways:**
  - **Bacteriocin production** (colicin by E. coli in large intestine)
  - **Competition** for space and nutrients
  - **Prevention of pathogen attachment**

HOW INNATE IMMUNITY PROTECTS

- 1. Provides a barrier to prevent the spread of infection
  - Mechanical (tight junctions, movement)
  - Chemical (fatty acids, enzymes, pH, antimicrobial peptides)
  - Microbiological (normal flora)

  - Mucosal surfaces
    - Nasopharyngeal, Oral, Respiratory, Intestinal tract

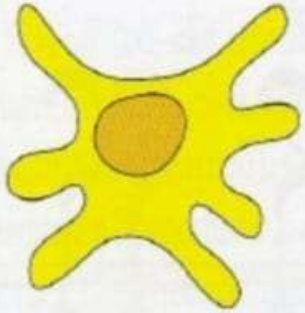
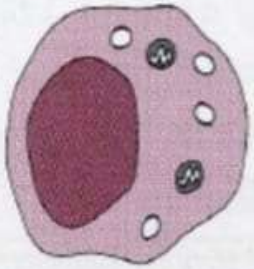
    Urogenital tract

  - Skin (epithelial cells)
    - Wounds, burns, insect bites

INNATE IMMUNITY

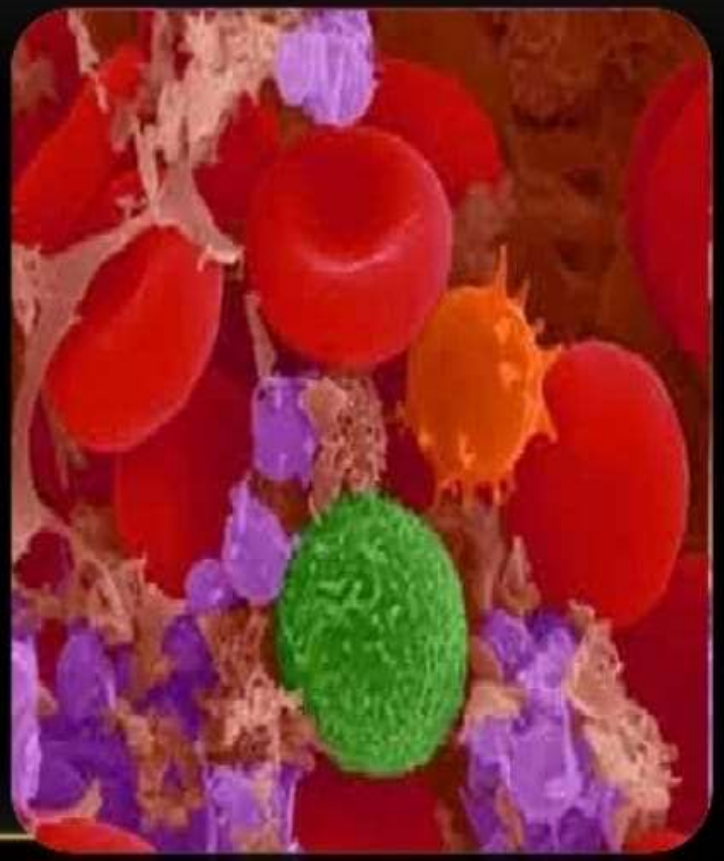
- 3. Initiates an inflammatory response
  - Reaction to injury or infection
    - Trauma to tissues or cells
    - Presence of foreign matter (self vs. non-self)
    - Infectious agents (viruses, bacteria, fungi)
  - Delivers effector molecules & immune cells to the site of infection
  - Components
    - Leukocytes & secreted factors
    - Blood vessels
    - Plasma proteins

Leukocyte Players of Innate Immune Responses

Cell type	Neutrophils	Macrophages	Dendritic cells	Natural killer cells
				
Function	Phagocytosis Reactive oxygen and nitrogen species Antimicrobial peptides	Phagocytosis Inflammatory mediators Antigen presentation Reactive oxygen and nitrogen species Cytokines Complement proteins	Antigen presentation Costimulatory signals Reactive oxygen species Interferon Cytokines	Lysis of viral-infected cells Interferon Macrophage activation

CELLS OF INNATE IMMUNITY

- Neutrophils
- Eosinophil's
- Basophils/Mast Cells
- Monocytes
- Macrophages
- Natural Killer Cells
- Platelets

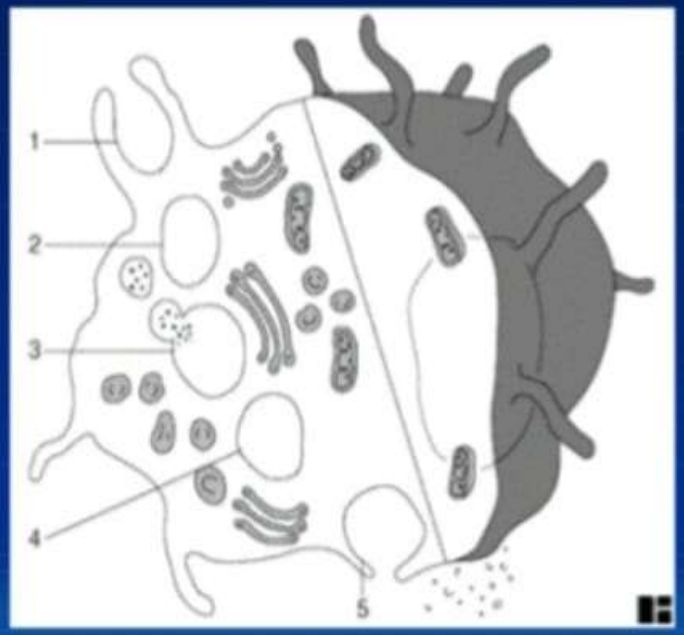


Phagocytosis

- Professional phagocytic cells
  - Macrophages and Neutrophils
- These cells have phagocytic receptors
  - External receptors: FcR, CR3, Mannose receptor
  - Internal receptors: TLRs
- Oxygen consumption increases
- Increased generation of superoxide (O_2-)
- Increased release of H_2O_2
- Increased HMP activity
- Lysosomal rupture and release of hydrolytic enzymes

B. Phagocytosis

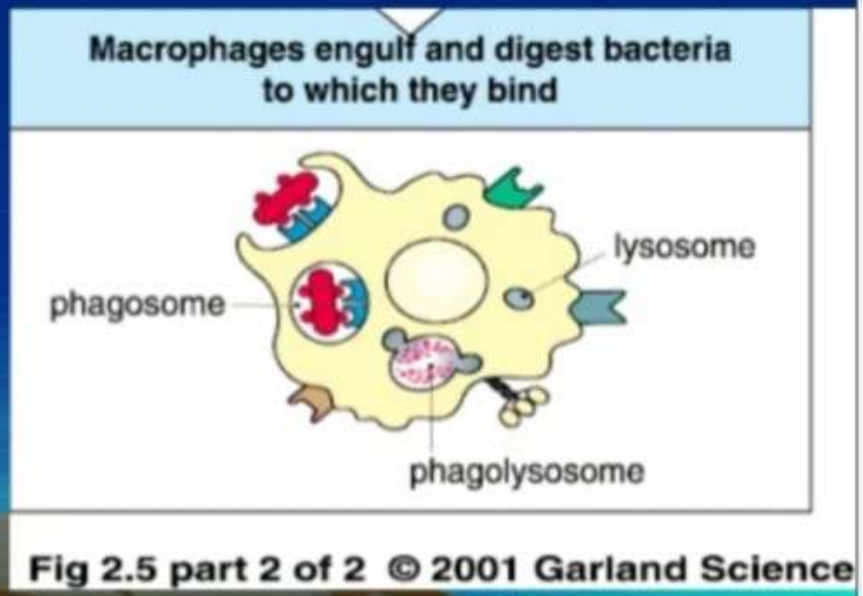
cells in blood & lymph
active without exposure
enhanced by immune system



1. Bacterium binds to 'arm'
2. Bacterium engulfed into membrane vesicle; phagosome
3. Vesicle fuses with lysosome
4. Digestive enzymes destroy bacterial cell; peroxide & superoxide also formed
5. Wastes emptied out of cell

Phagocytosis (MQ & PMN)

- Active process initiated by binding to pathogen
- Pathogen is surrounded and then internalized

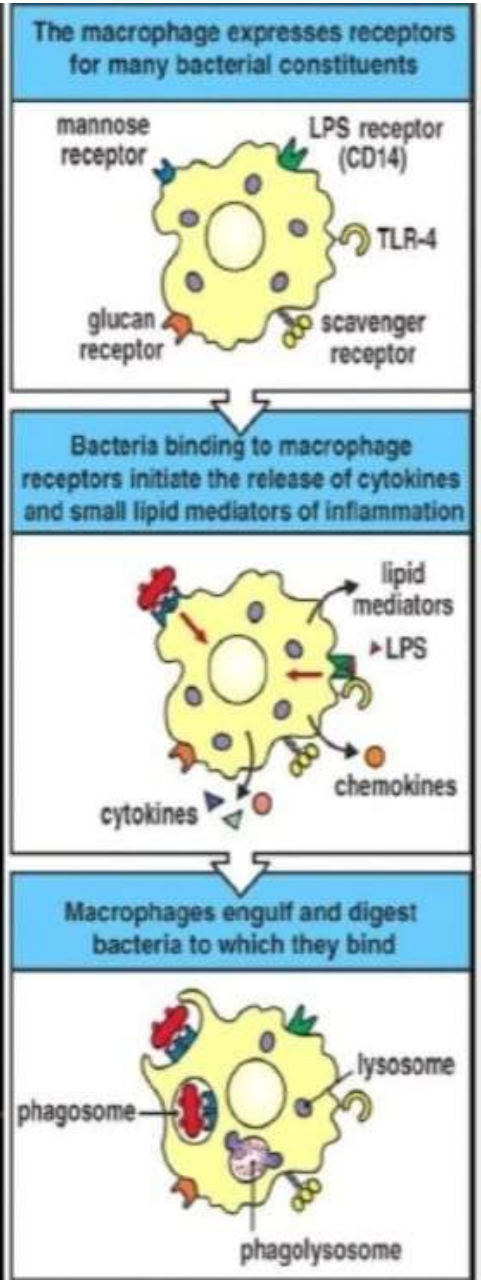


Macrophage Microbial Killing

Once the PRRs are activated by the PAMPs, phagocytosis is initiated

Phagocytosis is active process:

- Internalization of pathogen into phagosome
- Acidification of phagosome
- Fusion of phagosome with lysosomes that contain anti-microbial compounds (**phagolysosome**)
- This may be sufficient to kill the pathogen
- If not, reactive oxygen and nitrogen species may need to be generated



Innate Immune Receptors

- Innate immune receptors are not clonally distributed
- Binding of receptors results in rapid response
- Innate immune receptors mediate three functions:
  - phagocytic receptors to stimulate pathogen uptake
  - chemotactic receptors that guide phagocytes to site of infection
  - stimulate production of effector molecules and cytokines that induce innate responses and also influence downstream adaptive immune responses

Pathogen Recognition

- Most microorganisms express repeating patterns of molecular structures termed **Pathogen Associated Molecular Patterns (PAMPs)**

- Innate immune system has evolved mechanisms capable of recognizing these repeating patterns termed **Pattern Recognition Receptors (PRRs)**

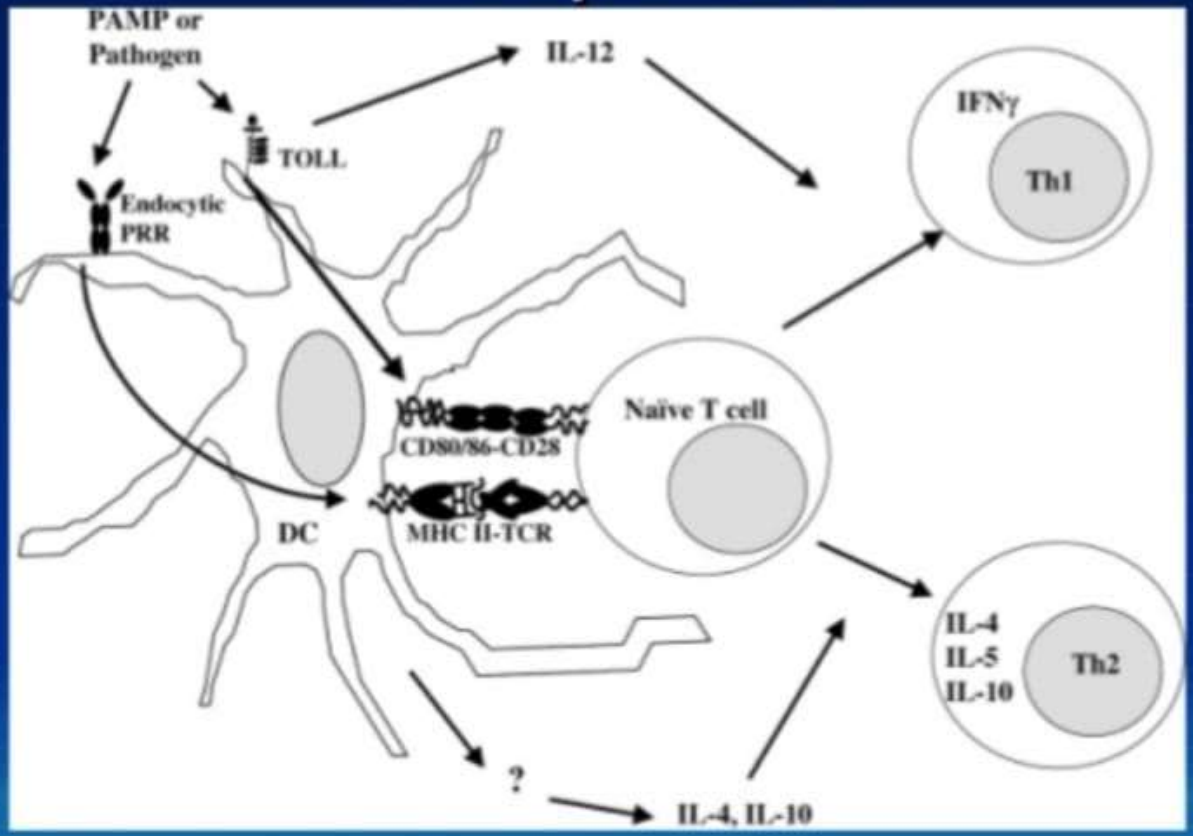
- Examples of Pattern Recognition Receptors:
  - Mannose-Binding Lectin (MBL)
  - Macrophage Mannose Receptor
  - Scavenger Receptors
  - Toll-like Receptors (TLRs)
  - Nod-like Receptors (NLRs)
  - RNA helicases (RIG-I, MDA-5)

Cellular response

- Innate immune system recognizes
  - PAMPs (Pathogen-associated molecular pattern)
    : molecular structures of microbial pathogen
    that required for survival
  - DAMPs (Damage-associated molecular pattern)
    : result of cell damage by infections

- Cellular receptors : PRRs (Pattern recognition receptors)

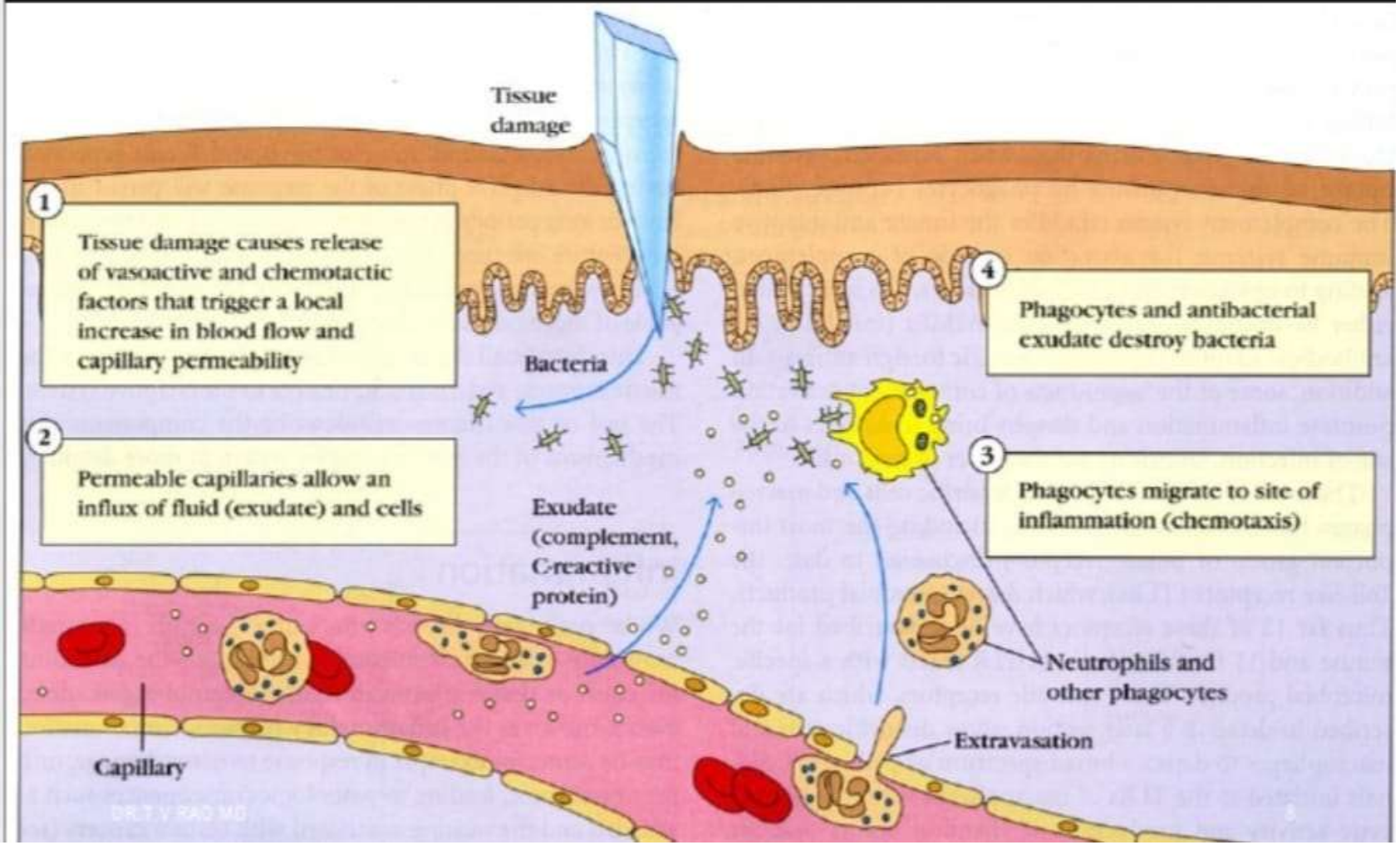
Regulation of Adaptive Response



Veterinary Immunology & Immunopathology 91: 1, 2003

- Inflammation
  - Response to tissue injury through the release of chemical signals (inflammatory mediators – vasoactive and chemotactic factors)
    - Histamine
    - Serotonin
    - Bradykinin
    - Prostaglandins
  - Vasodilation, increased capillary permeability, influx of phagocytic cells

What happens when the physical and chemical barriers are breached?



Inflammatory Response

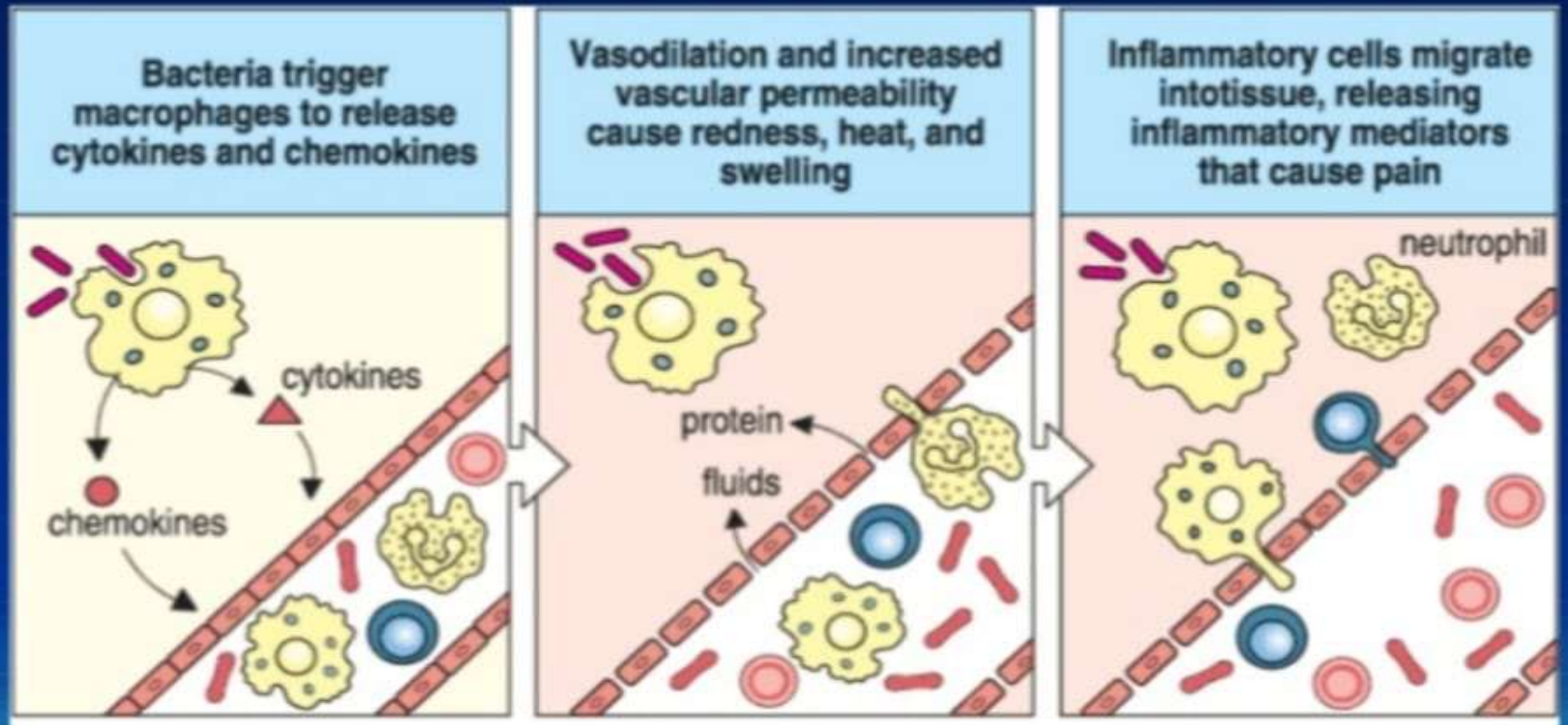


Fig 1.12 © 2001 Garland Science

Clinical symptoms of inflammation: pain, redness, heat, swelling

1. Increased vascular diameter, increased blood flow (heat, redness)
2. Activation of vascular endothelium to express adhesion molecules, increases leukocyte binding
3. PMNs are first cell type recruited to site, followed later by monocytes
4. Increased vascular permeability results in local swelling and pain

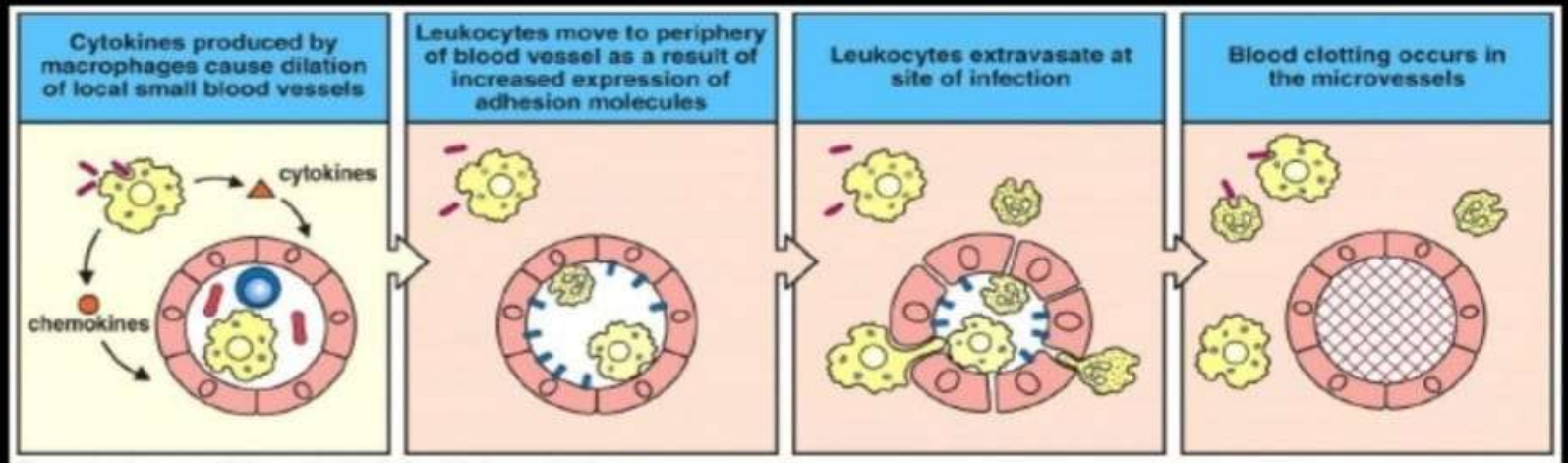
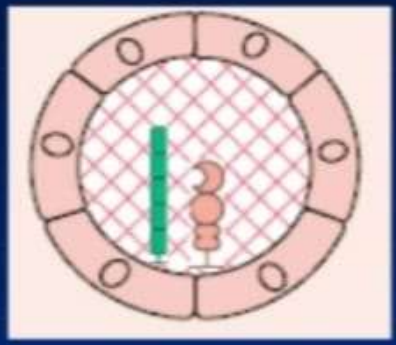


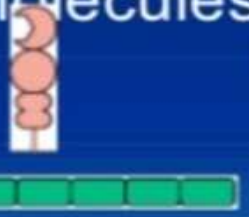
Figure 2-8 Immunobiology, 6/e. (© Garland Science 2005)

Microvascular coagulation helps prevent pathogen spread into bloodstream (physical barrier)

Activation of Vascular Endothelium



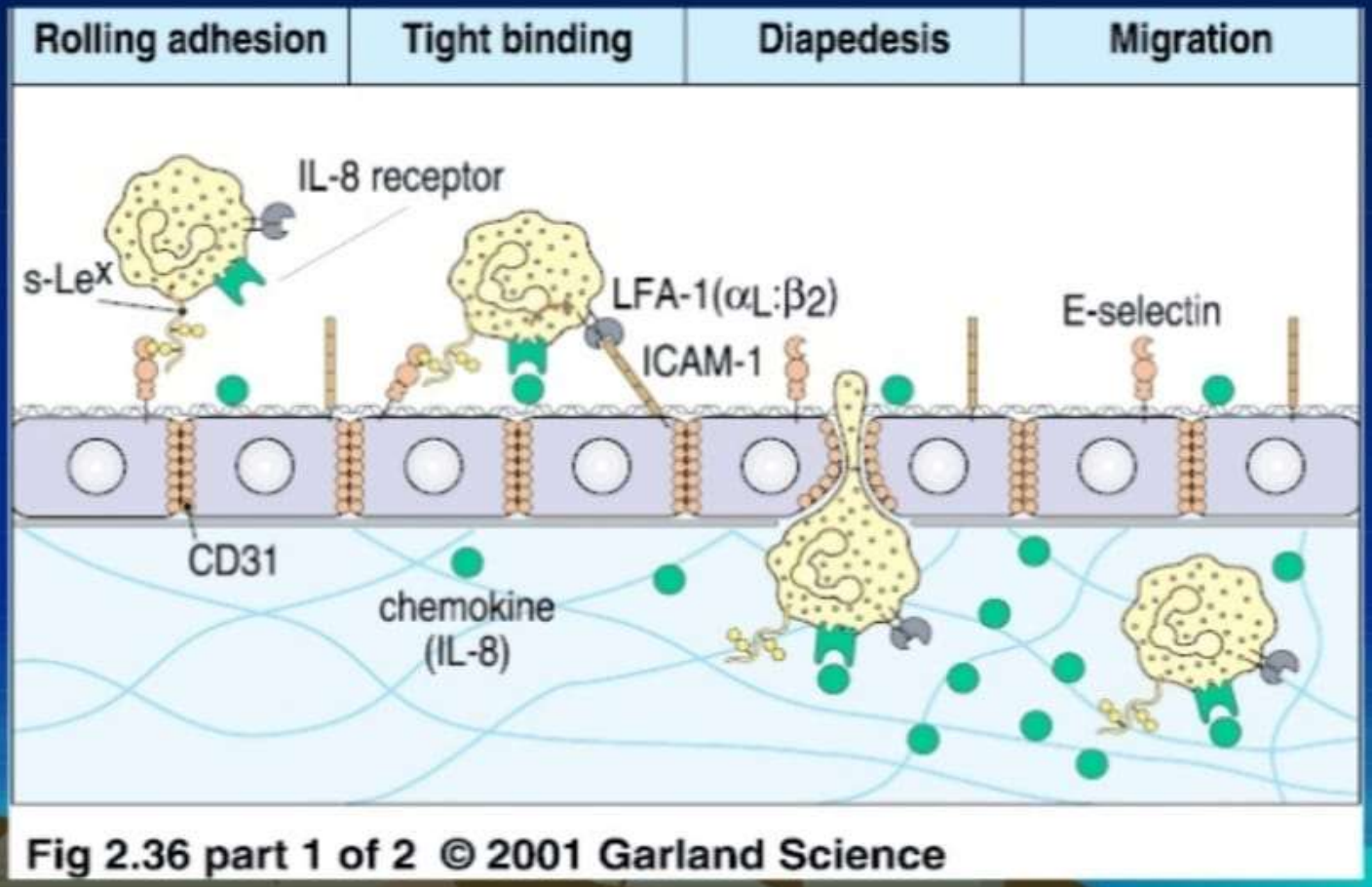
- Endothelium:
  - Endothelial cells that line blood vessels
  - TNFα & IL-1 induces the expression of adhesion molecules on endothelium:
  - P-selectin
  - E-selectin
  - ICAM-1
  - Initiates Leukocyte Extravagation



Immediately released

Synthesized in 2 hours

Leukocyte Adhesion



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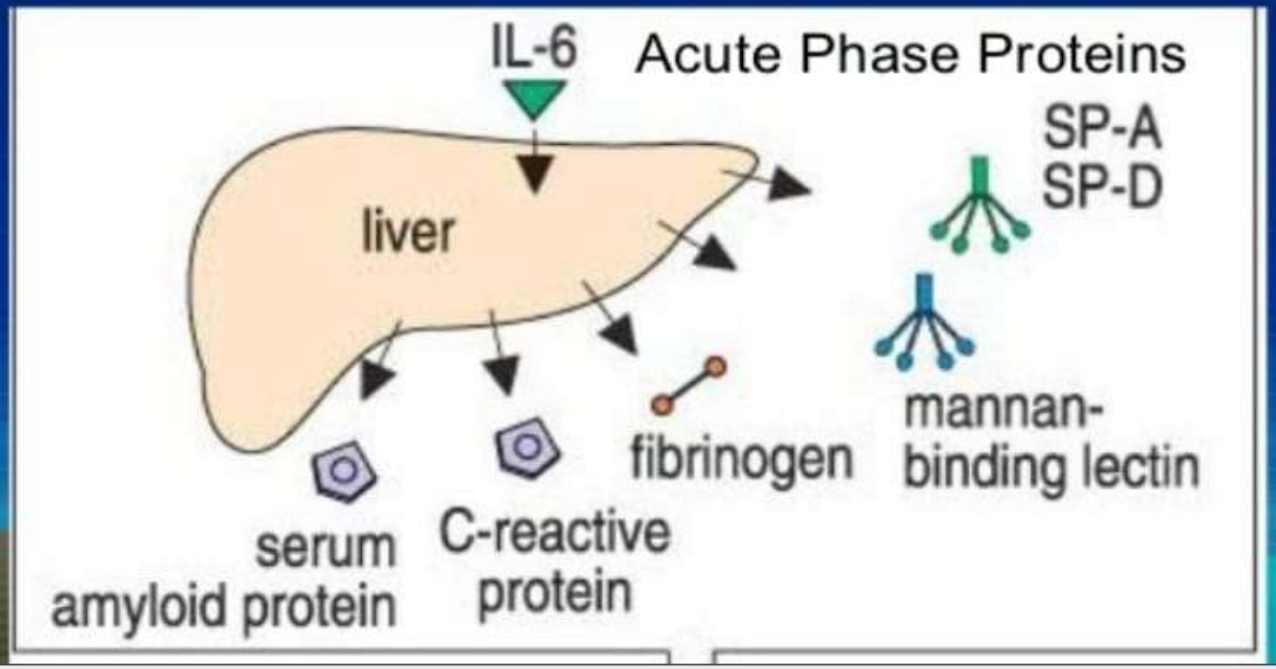
Acute-phase reactants

- During an acute infection, qualitative and quantitative changes in the host's blood occur
- Bacteria induce macrophages to make interleukin 6 (IL-6)
  - The hepatocytes in the liver respond to IL-6 and produce acute phase, bacterial-specific proteins

- Influences inflammatory & tissue repair processes
- Recognizes some foreign pathogens
- Activates complement system
- Bonds to phagocytic cells
- Induces production of inflammatory cytokines
- Main initiator of blood coagulation
- Net effect may be anti-inflammatory

Secreted Pattern Recognition Molecules

Activation of Complement
Opsonization of microbial cells
Primarily produced by the liver but can be produced by phagocytes

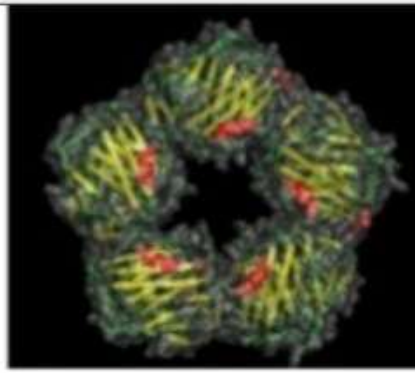


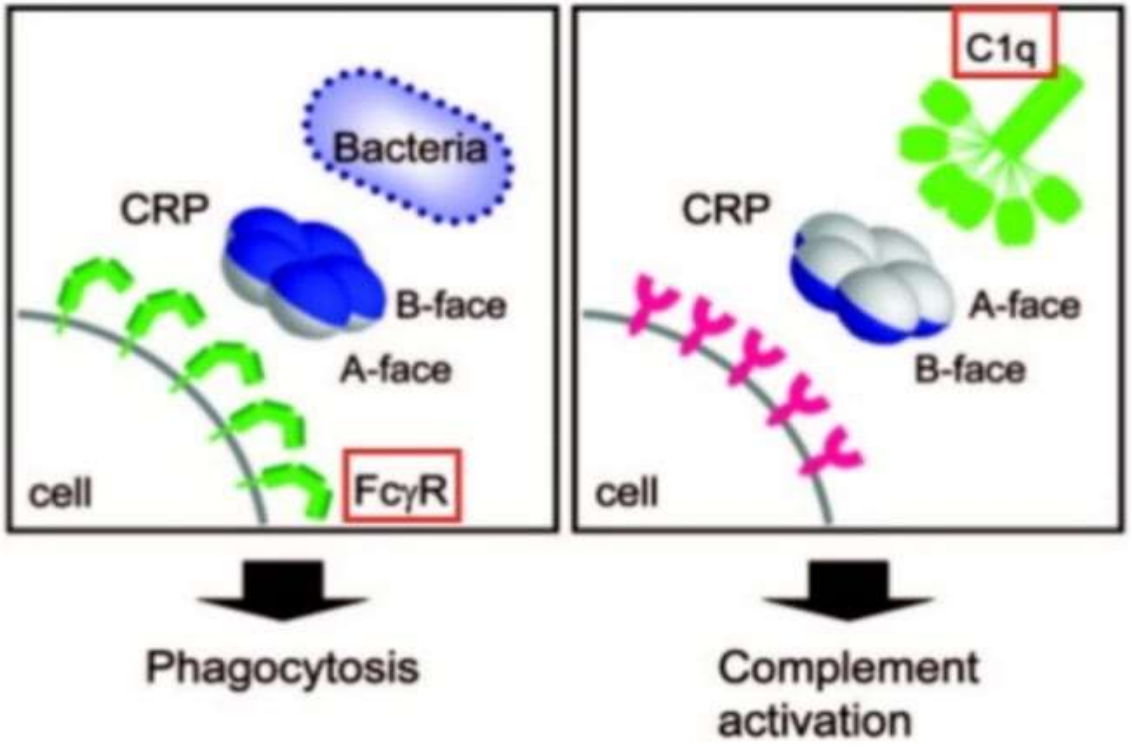
Examples of Acute Phase Reactants

- C-Reactive Protein (CRP) (a pentaxin)
  - Binds phosphorylcholine on bacterial surface
  - Activates complement
    - Induces opsonization
    - Membrane attack complex (MAC) is formed = cell lysis
- Serum amyloid protein (homologus to CRP, another pentaxin)

Pentraxins

C-reactive protein (CRP)



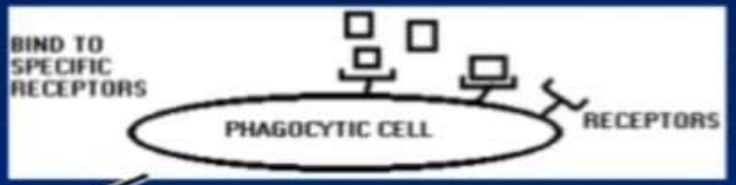


Fujita Y. et al. Clinical Chemistry 57:10, 1398–1405 (2011).

- Mannose binding protein
  - Binds mannose on bacteria
  - Activates complement
    - Induces opsonization
    - Membrane attack complex (MAC) is formed
- Iron redistribution – Release of lactoferrin by neutrophils
  - Sequestered by host = hypoferremia
  - Uptake of iron by liver

DURING SOME INFECTIONS

CERTAIN COMPONENTS OF INVADING MICROBES



PHAGOCYTIC CELL

INTERLEUKIN - 1 PRODUCE

WHICH

ACTS AS CHEMICAL MESSENGER WHICH TELLS HYPOTHALAMUS THAT INFECTION IS OCCURRING

BODY TEMPERATURE RAISED

- Fever
  - Thermal set point altered in hypothalamus
  - Induced by pyrogens
    - Exogenous pyrogens
      - Endotoxins of Gram negative bacteria
      - Staphylococcal enterotoxin
      - Group A streptococcal erythrogenic toxin
  - Endogenous pyrogens
      - IL-1 (made by macrophages)
      - TNF-alpha
      - IL-6

Result of fever

- **Stimulates leukocytes** into action
- Enhances **bacterial growth inhibition** by decreasing availability of iron
- Enhances **Ab production and T cell proliferation**
- Host cells protected from the effects of TNF-alpha

INTERFERON

- Defense against viral infections
- Cytokine produced & released by host cells invaded by virus
- Prevents virus from infecting healthy cell
- Stimulates uninfected cells to produce antiviral proteins
- INF-α & INF-β are antiinflammatory
- INF-γ is proinflammatory and enhances cell-mediated immunity

Effects of interferons:

- Activation of endoribonuclease and protein kinase
  - Destruction of viral mRNA
  - Inhibition of protein synthesis (EF-2 phosphorylation)
- Upregulation of MHC class I
- Enhancement of T_{cyt} activity
- Activation of Natural Killer (NK) cells

- Tumor necrosis factors (a and b)

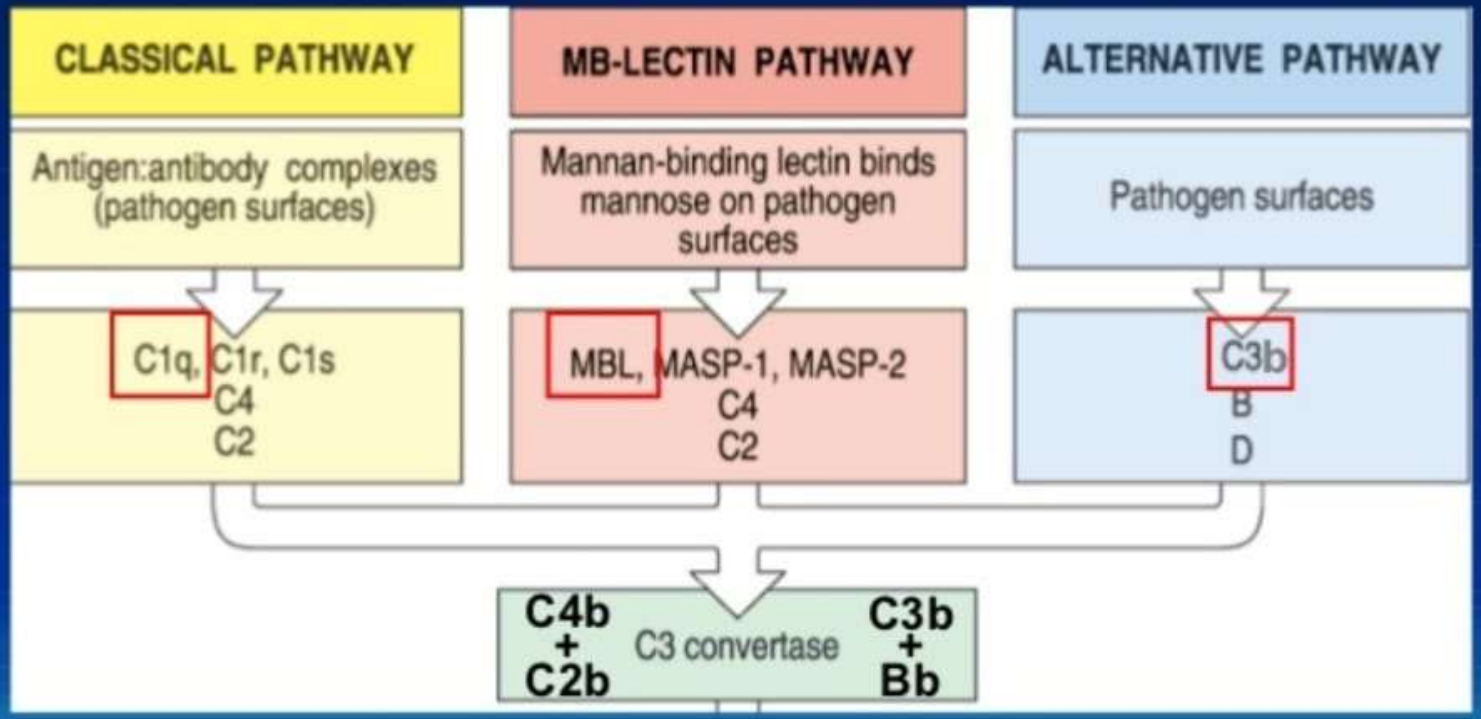
- TNF alpha is released from monocytes or macrophages, natural killer cells or various lymphocytes mediate
  - the inflammatory response,
  - enhance phagocytosis

- TNF beta is cytotoxic for tumor cells

Alternative pathway of complement activation

- Does not require antibodies
- Immediate
- Activates the terminal complement components which destroy bacteria by creating holes (pores) in the bacterial membrane - MAC

Activation of C' System - cont.



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