IMMUNOLOGY

IMMUNOLOGY

PERIPHERY : INNATE IMMUNE RESPONSE

PERIPHERY-INNATE IMMUNE RESPONSE

Learning Objective

- Describe the structure and function of secondary lymphoid organs
- Describe the structure of lymph nodes
- Answer questions about chemokines and adhesion molecules

PERIPHERY: INNATE IMMUNE RESPONSE

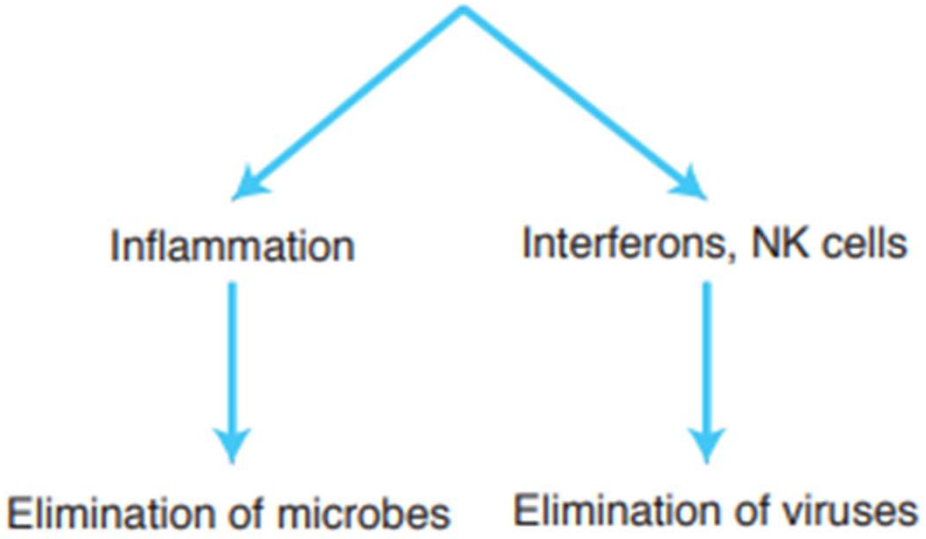
INNATE IMMUNITY

The innate immune system is an important part of any immune response. It is responsible for reacting quickly to invading microbes and for keeping the host alive while the adaptive immune system is developing a very specific response. The innate immune defenses are all present at birth; they have a very limited diversity for antigen, and they attack the microbes with the same basic vigor no matter how many times they have seen the same pathogen.

PERIPHERY: INNATE IMMUNE RESPONSE

INNATE IMMUNITY

The innate immune system handles pathogens in 2 general ways:

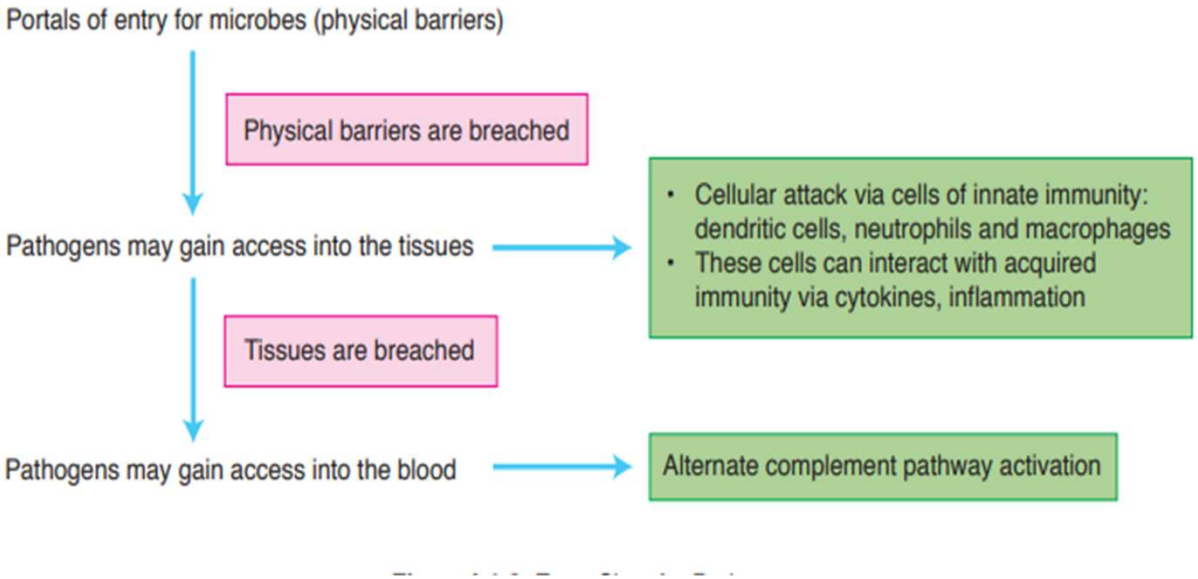


PERIPHERY: INNATE IMMUNE RESPONSE

Microbes may gain access to the tissues if the physical barriers are breached. In the tissues, they come in contact with Phagocytic cells such as neutrophils, macrophages and dendritic cells, which will produce chemical messengers called cytokines that can initiate an inflammatory response. Many times the innate immune components are enough to eliminate the pathogen, but not always. The pathogens may gain access to the blood, in which the alternate pathway for complement activation may provide some additional help. But this is where the adaptive immune system may have to take over to resolve the infection and eliminate the pathogen.

PERIPHERY: INNATE IMMUNE RESPONSE

Entry Site for Pathogen



PERIPHERY: INNATE IMMUNE RESPONSE

INNATE IMMUNE COMPONENTS/BARRIERS

Physical (anatomic) barriers,

Physiologic barriers,

Innate cellular response,

Inflammation.

PERIPHERY: INNATE IMMUNE RESPONSE

Anatomic Barriers

Portals of entry

Skin,

Respiratory tract,

GI tract.

PERIPHERY: INNATE IMMUNE RESPONSE

All of these surfaces are lined with epithelial cells that can produce a few antimicrobial products such as defensins and interferons.

They may also contain a number of specialized intra-epithelial lymphocytes (IEL) called γδ T cells. These specialized T cells are considered part of innate immunity as they can only recognize shared microbial structures.

The skin is a great physical barrier as most pathogens can't invade intact skin.

The pH of the skin is also slightly acidic and can retard the growth of pathogenic organisms.

The respiratory tract is lined with cilia that physically attempt to remove microbes as they enter.

Saliva and mucous are also difficult environments for microbes to live in, as there are many antimicrobial enzymes and chemicals within those entities.

The GI tract is also a mucous membrane with similar properties to the respiratory tract; however, pathogens that enter here must first survive a trip through the stomach with a highly acidic pH that kills many microorganisms.

PERIPHERY: INNATE IMMUNE RESPONSE

Physiologic Barriers

Temperature –

Many microbial pathogens can't survive much past human body temperature. When the inflammatory response is initiated in the local tissues, cytokines may act systemically to alter the temperature set point in the hypothalamus resulting in fever.

pH –

The acidic pH of the stomach impedes the growth and transmission to the gut of many pathogens. – The skin is also acidic and retards the growth of many microorganisms.

PERIPHERY: INNATE IMMUNE RESPONSE

pH

The acidic pH of the stomach impedes the growth and transmission to the gut of many pathogens.

The skin is also acidic and retards the growth of many microorganisms.

PERIPHERY: INNATE IMMUNE RESPONSE

Chemical

Lysozyme present in secretions such as tears, saliva, breast milk and mucous can break down the cell wall peptidoglycan of bacteria. Defensins found within phagocytes can form pores in bacteria and fungi.

PERIPHERY: INNATE IMMUNE RESPONSE

Interferons

IFN-α and IFN-β are anti-viral interferons. They have a direct antiviral effect by transiently inhibiting nascent protein synthesis in cells.

PERIPHERY: INNATE IMMUNE RESPONSE

Innate Cellular Response

Phagocytic cells (monocytes/macrophages, neutrophils and dendritic cells) are part of the first line of defence against invading pathogens. They recognize pathogens via shared molecules that are not expressed on host cells. They are responsible for controlling the infections and sometimes are even capable of eradicating them.

PERIPHERY: INNATE IMMUNE RESPONSE

Receptors of the innate immune system are referred to as

Pattern recognition receptors (PRRs).

PRRs recognize **pathogen-associated molecular patterns (PAMPs),** molecules that are shared by pathogens of the same type (bacterial LPS, n-formyl peptides etc.) or

Damage-associated molecular patterns

DAMPs released from dying or damaged cells. These receptors are present intrinsically, encoded in the germline genes, and are not generated through somatic recombination as the lymphocyte receptors are generated.

PERIPHERY: INNATE IMMUNE RESPONSE

The innate immune system can recognize <1,000 patterns on various pathogens, compared to the adaptive immune system (B and T cells) which can recognize over 1 billion specific sequences on pathogens.

PERIPHERY: INNATE IMMUNE RESPONSE

Inflamasome

The inflammasome is an important part of the innate immune system. It is expressed in Myeloid cells as a signalling system for detection of pathogens and stressors. Activation of the inflammasome results in the production of

- IL-1b
- IL-18

which are potent inflammatory cytokines.

PERIPHERY: INNATE IMMUNE RESPONSE

Inflammasome

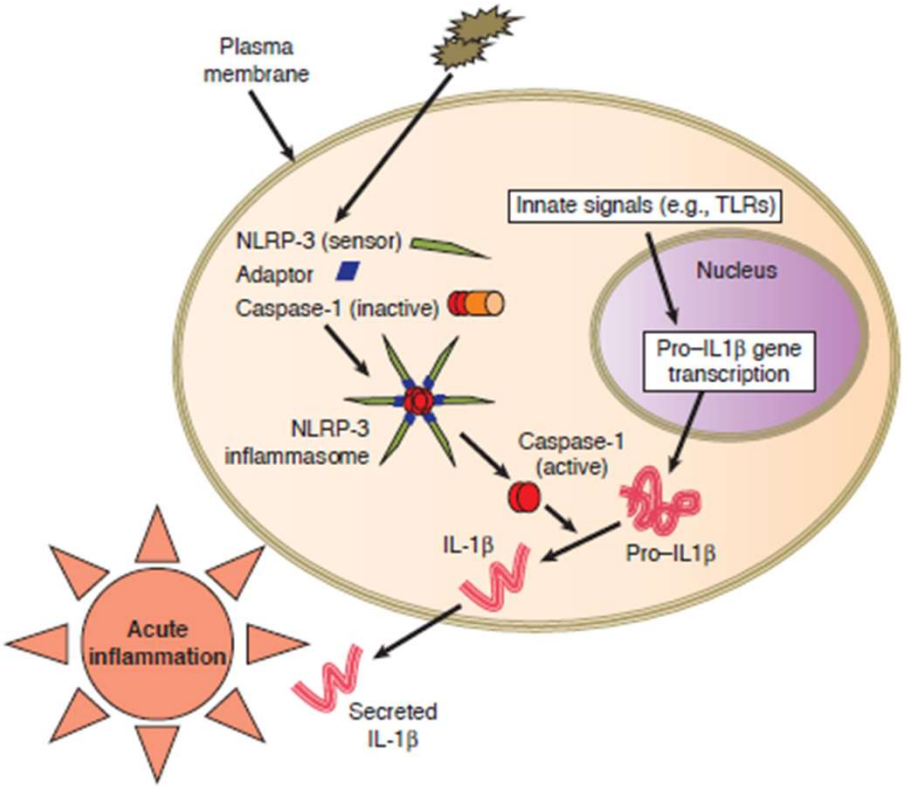


Figure I-4-3. Inflammasome

PERIPHERY: INNATE IMMUNE RESPONSE

Receptor of Innate response

TOLL like receptors

NOD like receptor

RIG like receptors

PERIPHERY: INNATE IMMUNE RESPONSE

Toll-like receptors (TLR)

- Extracellular TLR-1, 2, 6 Bacterial lipopeptides Activation of transcription factors (including NF-κB) which results in the transcription of cytokines, adhesion molecules, and enzymes that are antimicrobial
- TLR-2 Bacterial peptidoglycan
- TLR-4 Lipopolysaccharide(LPS)
- TLR-5 Flagellin Intracellular (endosomal)
- TLR-3 DS RNA
- TLR-7,8 SS RNA
- TLR-9 Unmethylated CpG oligonucleotides

PERIPHERY: INNATE IMMUNE RESPONSE

Innate Receptors

Clinical Correlate

Clinical Correlate

Mutations in Innate Immune Receptors and Correlation with Disease

Mutation	Effect
Mutation in signaling molecules effecting TLRs	Recurrent, severe bacterial infections (pneumonia)
Gain of function mutations in inflam asome	• Gout • Atherosclerosis • Type II diabetes
NOD-2 mutations	IBD
• IL-12 receptor defi iency • IFN-γ receptor defi iency	Recurrent infections with intracellular bacteria (*Mycobacterium*)

PERIPHERY: INNATE IMMUNE RESPONSE

Cells of Innate Immunity

Neutrophils

Monocytes/Macrophages

Dendritic Cell

Mast Cell

Natural Killer Cell

PERIPHERY: INNATE IMMUNE RESPONSE

Neutrophils

- Circulating phagocytes
- Short lived
- Rapid response, not prolonged defence

PERIPHERY: INNATE IMMUNE RESPONSE

Monocytes/Macrophages

- Monocytes circulate in the blood, become macrophages in the tissues
- Provide a prolonged defense
- Produce cytokines that initiate and regulate inflammation
- Phagocytose pathogens
- Clear dead tissue and initiate tissue repair
- Macophages will develop along one of 2 different pathways

PERIPHERY: INNATE IMMUNE RESPONSE

Classical M1	Alternative M2
Induced by innate immunity (TLRs, IFN-γ)	Induced by IL-4, IL-13
Phagocytosis, initiate inflam atory response	Tissue repair and control of inflam ation

Pathways for Macrophages Activation

PERIPHERY: INNATE IMMUNE RESPONSE

Dendritic cells (DCs)

- Found in all tissues
- Antigen processing and presentation
- Two major functions: initiate inflammatory response and stimulate adaptive immune response

PERIPHERY: INNATE IMMUNE RESPONSE

Mast cells

- Skin, mucosa
- 2 pathways for activation: Innate TLRs and Antibody-dependent (IgE)

PERIPHERY: INNATE IMMUNE RESPONSE

Natural killer cells (NK cells)

- Blood, periphery
- Direct lysis of cells, secretion of IFN-γ

PERIPHERY: INNATE IMMUNE RESPONSE

Activation of Macrophages

PERIPHERY: INNATE IMMUNE RESPONSE

Inflammatory Response

Complement

Acute inflammatory response

- Rolling
- Activation of chemoattracts
- Arrest and Adhesion
- Trans endothelial Migration

Phagocytosis

Opsonization

Intracellular Killing

PERIPHERY: INNATE IMMUNE RESPONSE

Complement

The complement system is a set of interacting proteins released into the blood after production in the liver. The components act together as zymogens, activating one another in cascade fashion after initiation from a variety of stimuli. The pathways of activation occur in the body and culminate similarly in the production of important split products that mediate inflammation, enhance phagocytosis by opsonization, and cause lysis of particles by membrane pore formation.

PERIPHERY: INNATE IMMUNE RESPONSE

Complement

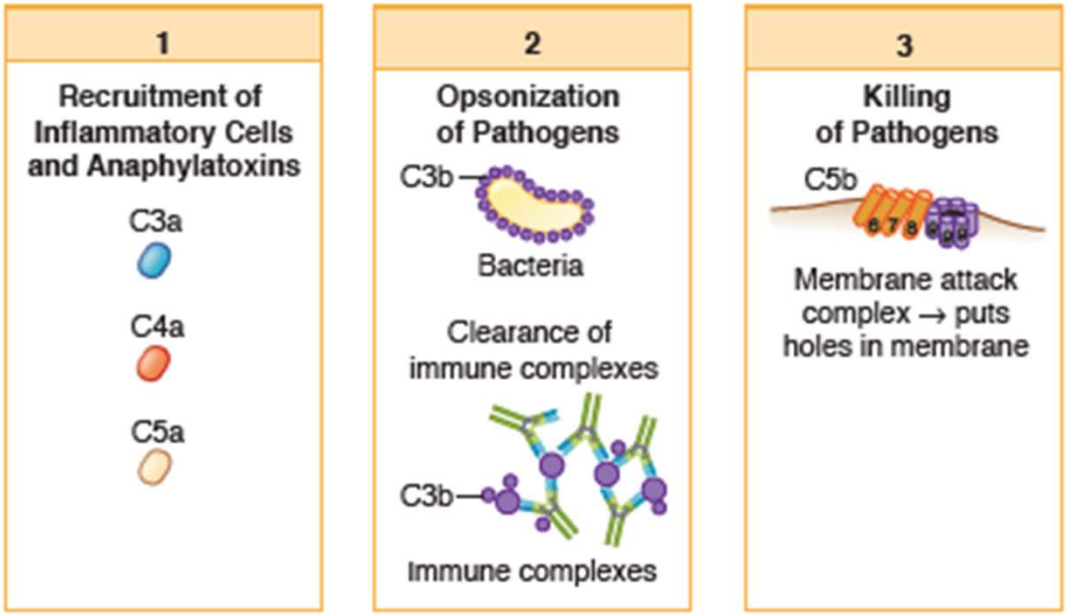


Figure I-4-5. Three Functions of the Complement System

PERIPHERY: INNATE IMMUNE RESPONSE

Two of the pathways are considered part of the innate immune system:

- The alternate pathway
- Lectin-binding or mannose-binding pathway (MBP).

PERIPHERY: INNATE IMMUNE RESPONSE

THE MBP pathway

MBP activates the classical complement pathway but without the use of antibody, and is therefore considered part of innate immunity. The MBP is activated when mannose binding lectin binds to carbohydrates on the pathogen.

PERIPHERY: INNATE IMMUNE RESPONSE

THE ALTERNATE PATHWAY

The alternative pathway of complement activation is probably the more primitive of the pathways because it is initiated by simple attraction of the early factors to the surfaces of microbes. Bacterial polysaccharides and the lipopolysaccharide of the cell envelope of gram-negative bacteria both serve as potent, initiating stimuli.

PERIPHERY: INNATE IMMUNE RESPONSE

Alternative Complement pathway

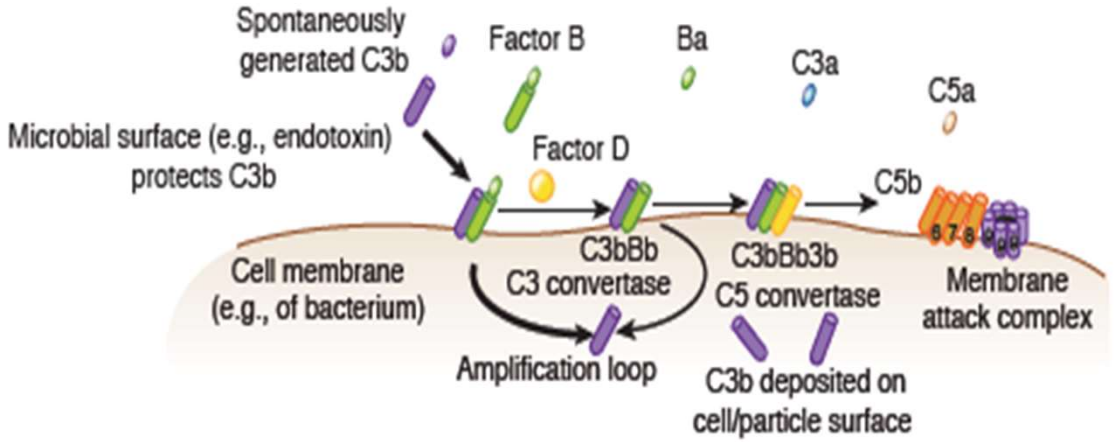


Figure I-4-6. The Alternative Complement Pathway

PERIPHERY: INNATE IMMUNE RESPONSE

Acute Inflammatory Response

- Antigens are normally introduced into the body across the mucosa or the epithelia.
- The **acute inflammatory response** is often the first response to this invasion
- and represents a response of the innate immune system to block the challenge.

PERIPHERY: INNATE IMMUNE RESPONSE

The first step in the acute inflammatory response is activation of the vascular endothelium in the breached epithelial barrier. Cytokines and other inflammatory mediators released in the area as a result of tissue damage induce expression of selectin-type adhesion molecules on the endothelial cells. Neutrophils are the first cells to bind to the inflamed endothelium and extravasate into the tissues, peaking within 6 hours. Monocytes, macrophages, and even eosinophils may arrive 5–6 hours later in response to neutrophil-released mediators.

- **Step 1: Rolling**
- **Step 2: Activation by chemo-attractants**
- **Step 3: Arrest and adhesion**
- **Step 4: Transendothelial migration**

PERIPHERY: INNATE IMMUNE RESPONSE

- **Step 1: Rolling**
- Phagocytes attach loosely to the endothelium by low-affi ty, selectin-carbohydrate
- interactions. E-selectin molecules on the endothelium bind to mucin-like
- adhesion molecules on the phagocyte membrane and bind the cell briefly, but
- the force of blood fl w into the area causes the cell to detach and reattach repeatedly,
- rolling along the endothelial surface until stronger binding forces can
- be elicited.

PERIPHERY: INNATE IMMUNE RESPONSE

Step 2: Activation by chemo-attractants

- Chemokines released in the area during inflammation, such as interleukin 8
- (IL-8), complement split product C5a, and N-formyl peptides produced by
- bacteria bind to receptors on the phagocyte surface and trigger a G-protein–
- mediated activating signal. Th s signal induces a conformational change in integrin
- molecules in the phagocyte membrane that increases their affi ty for
- immunoglobulin-superfamily adhesion molecules on the endothelium.

PERIPHERY: INNATE IMMUNE RESPONSE

Step 3: Arrest and adhesion

- Interaction between integrins and Ig-superfamily cellular adhesion molecules
- (Ig-CAMs) mediates the tight binding of the phagocyte to the endothelial cell.
- These integrin-IgCAM interactions also mediate the tight binding of phagocytes
- and their movement through the extracellular matrix.

PERIPHERY: INNATE IMMUNE RESPONSE

Step 4: Transendothelial migration

- The phagocyte extends pseudopodia through the vessel wall and extravasates
- into the tissues.

PERIPHERY: INNATE IMMUNE RESPONSE

Acute Inflammatory Response

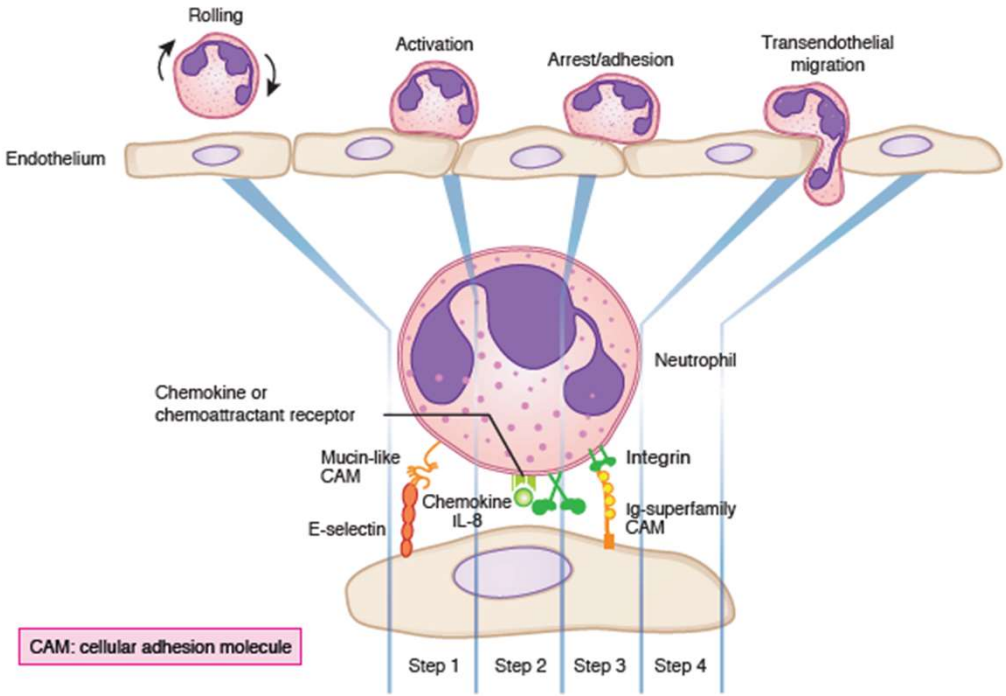


Figure I-4-7. Steps of Phagocyte Extravasation

PERIPHERY: INNATE IMMUNE RESPONSE

Clinical Correlate

Leukocyte adhesion deficiency (LAD)

Rare autosomal recessive disease in which there is an absence of **CD18** (the common β2 chain of a number of integrin molecules). A key element in the migration of leukocytes is integrin-mediated cell adhesion; patients suffer from an inability of their leukocytes to undergo adhesion dependent migration into sites of inflammation. The first indication of this defect is often omphalitis, a swelling and reddening around the stalk of the umbilical cord.

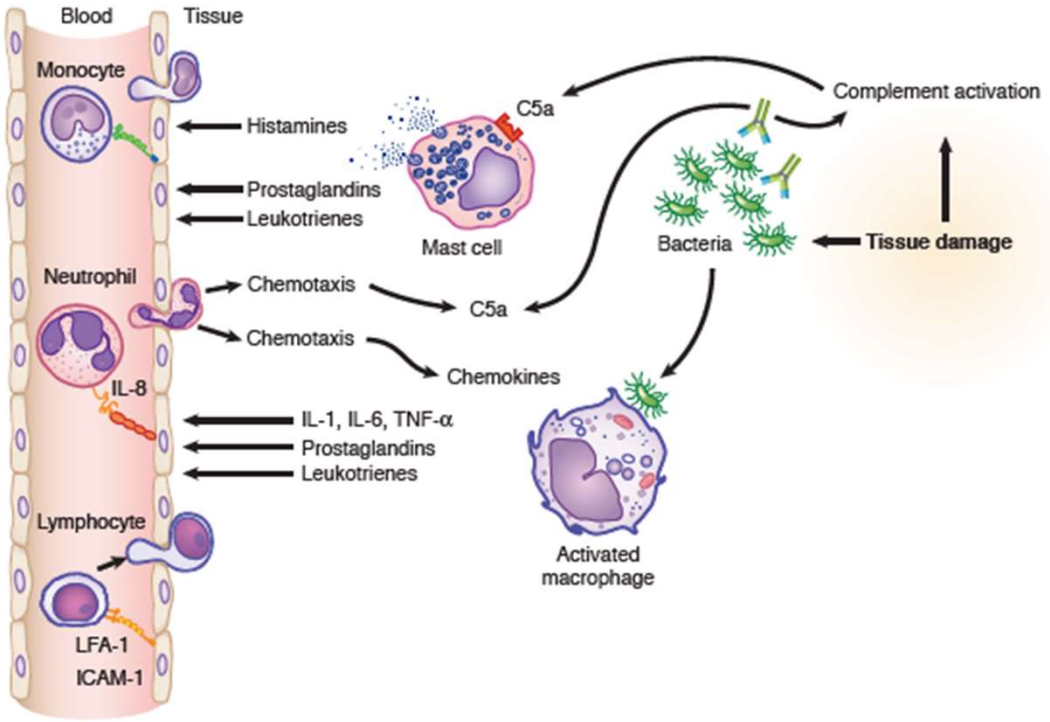
PERIPHERY: INNATE IMMUNE RESPONSE

- Once in the tissues, neutrophils express increased levels of receptors for chemoattractant and exhibit chemotaxis migrating up a concentration gradient toward the attractant. Neutrophils release chemo attractive factors that call in other phagocytes.

Chemoattractive Molecule	Origin
Chemokines (IL-8)	Tissue mast cells, platelets, neutrophils, **monocytes, macrophages,** eosinophils, basophils, lymphocytes
Complement split product C5a	Classical or alternative pathways
Leukotriene B_4	Membrane phospholipids of macrophages, monocytes, neutrophils, mast cells → arachidonic acid cascade → lipoxygenase pathway
Formyl methionyl peptides	Released from microorganisms

PERIPHERY: INNATE IMMUNE RESPONSE

Acute Inflammatory Response



PERIPHERY: INNATE IMMUNE RESPONSE

Phagocytosis

Once chemotaxis of phagocytic cells into the area of antigen entry is accomplished, these cells ingest and digest particulate debris, such as microorganisms, host cellular debris, and activated clotting factors. This process, called phagocytosis, involves the following:

- Extension of pseudopodia to engulf attached material
- Fusion of the pseudopodia to trap the material in a phagosome
- Fusion of the phagosome with a lysosome to create a phagolysosome
- Digestion
- Exocytosis of digested contents

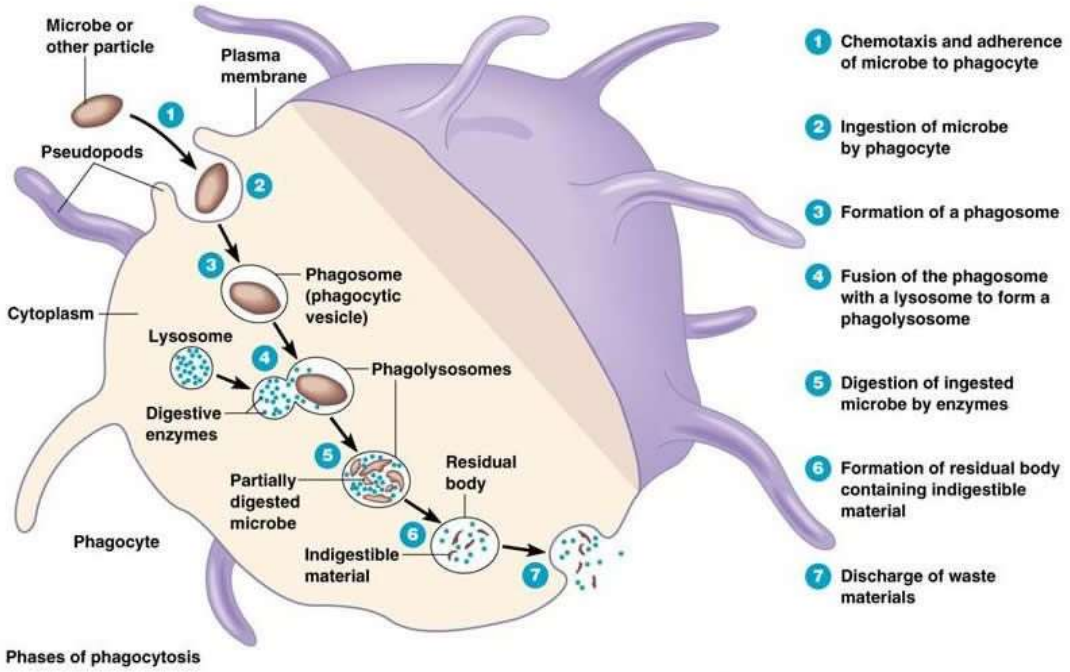
PERIPHERY: INNATE IMMUNE RESPONSE

Neutrophils release granule contents into extracellular milieu during phagocytosis and inflammation in which the neutrophils die, forming what is known as pus. They extrude nuclear contents, histones, neutrophil extracellular traps (NETs) which function to:

- Trap and kill pathogens
- May damage tissues when enzymes, ROS get released into tissues

PERIPHERY: INNATE IMMUNE RESPONSE

Phagocytosis



PERIPHERY: INNATE IMMUNE RESPONSE

Opsonization

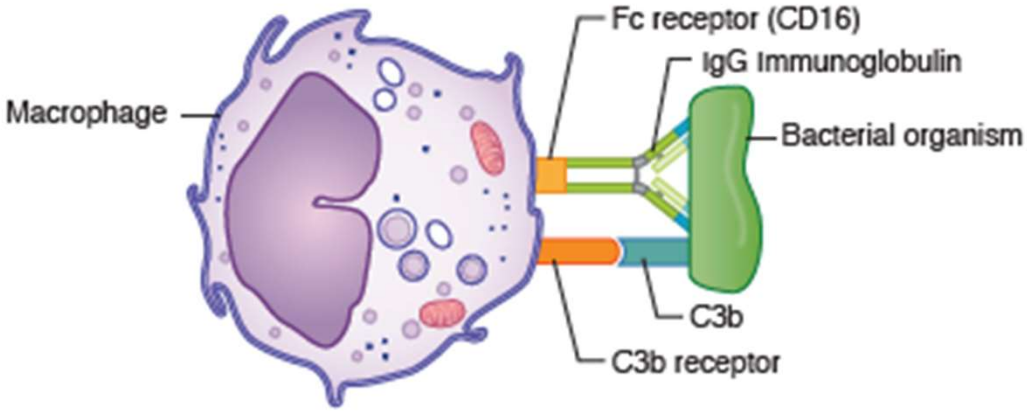
Both macrophages and neutrophils have membrane receptors for certain types of antibody (IgG) and certain complement components (C3b). If an antigen is coated with either of these materials, adherence and phagocytosis may be enhanced by up to 4,000-fold. Thus, antibody and complement are called **Opsonins**, and the means by which they enhance phagocytosis is called opsonization.

IgG

C3b

PERIPHERY: INNATE IMMUNE RESPONSE

Opsonization



PERIPHERY: INNATE IMMUNE RESPONSE

- **Intracellular Killing**

During phagocytosis, a metabolic process known as the respiratory burst activates a membrane-bound oxidase that generates oxygen metabolites, which are toxic to ingested microorganisms. Two oxygen-dependent mechanisms of intracellular digestion are activated as a result of this process.

PERIPHERY: INNATE IMMUNE RESPONSE

Intracellular Killing

- NADPH oxidase reduces oxygen to superoxide anion, which generates hydroxyl radicals and hydrogen peroxide, which are microbicidal.
- Myeloperoxidase in the lysosomes acts on Hydrogen Peroxide and chloride ions to produce hypochlorite (the active ingredient in household bleach), which is microbicidal.

PERIPHERY: INNATE IMMUNE RESPONSE

Additionally, reactive nitrogen intermediates play an important role. Inducible nitric oxide synthase converts arginine to nitric oxide, which has potent antimicrobial properties.

The lysosomal contents of phagocytes contain oxygen-independent degradative materials:

- Lysozyme digests bacterial cell walls by cleaving peptidoglycan
- Defensins form channels in bacterial cell membranes
- Lactoferrin chelates iron
- Hydrolytic enzymes

PERIPHERY: INNATE IMMUNE RESPONSE

Killing with Phagocytes

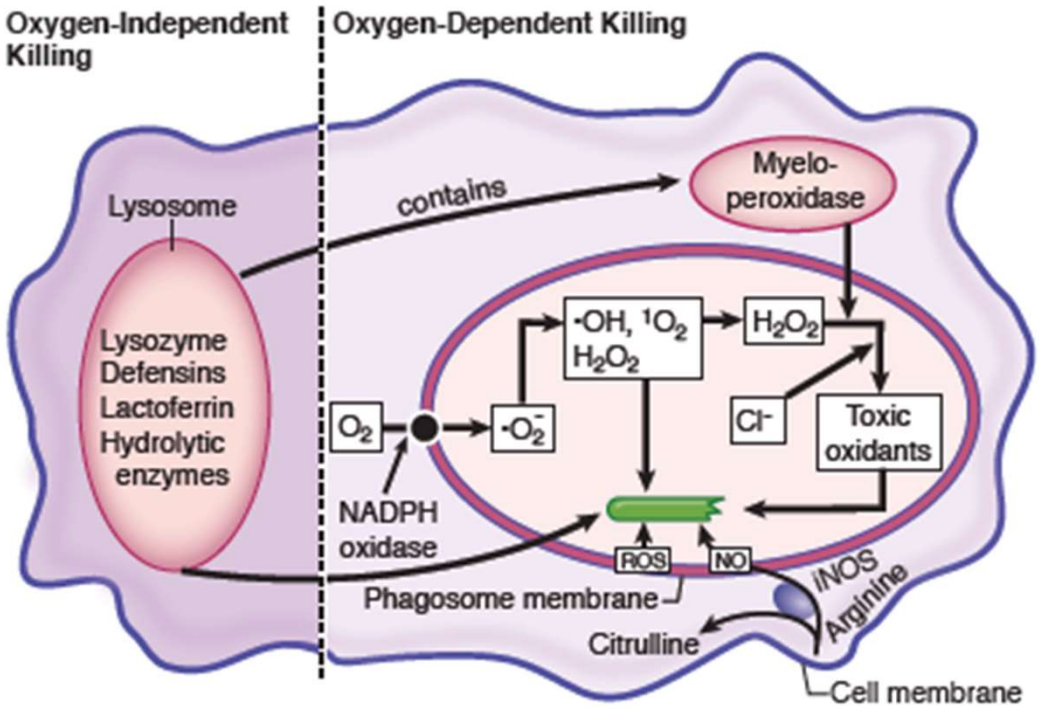


Figure I-4-11. Metabolic Stimulation and Killing Within the Phagocyte

PERIPHERY: INNATE IMMUNE RESPONSE

Systemic Inflammation

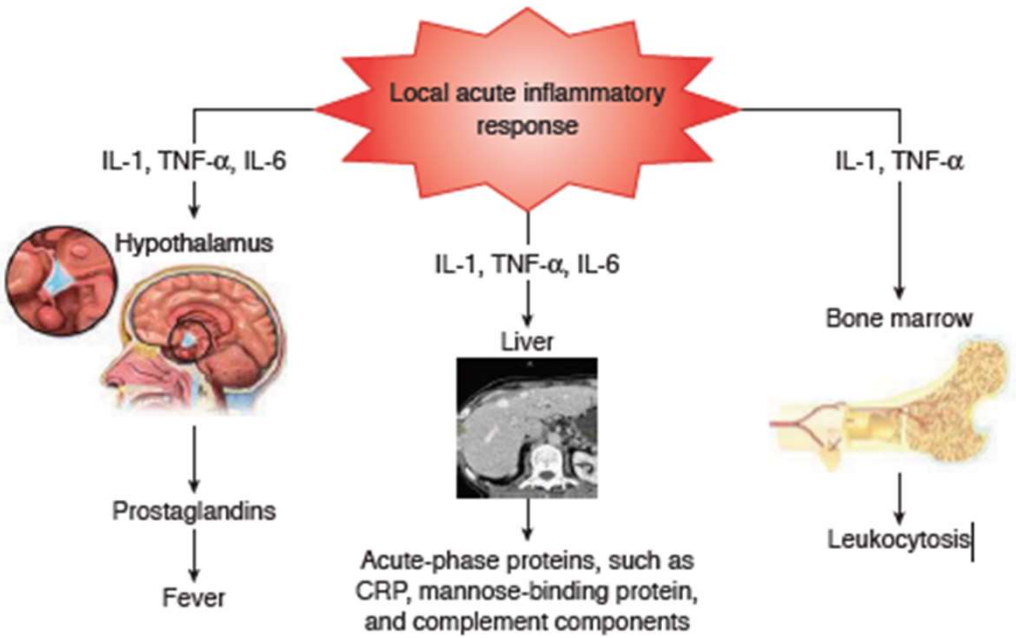
During the acute inflammatory response, pro-inflammatory cytokines such as

- IL-1,
- IL-6 and
- TNF-α are produced.

These cytokines have systemic effects on the tissues, including fever, production of acute phase proteins, and leucocytosis.

PERIPHERY: INNATE IMMUNE RESPONSE

Systemic Inflammatory Response



PERIPHERY: INNATE IMMUNE RESPONSE

Clinical Correlate

When defects prevent phagocytes from performing their critical functions as fi st responders and intracellular destroyers of invading antigens, clinically important pathologic processes ensue. Such defects tend to make the patient susceptible to severe infections with extracellular bacteria and fungi.

PERIPHERY: INNATE IMMUNE RESPONSE

Chronic granulomatous disease (CGD)

Inherited deficiency in the production of one of several subunits of NADPH oxidase. This defect eliminates the phagocyte's ability to produce many critical oxygen-dependent intracellular metabolites (·O2–, .OH, 1O2, and H2O2). The 2 other intracellular killing mechanisms remain intact (myeloperoxidase + H2O2 → HOCl and lysosomal contents).

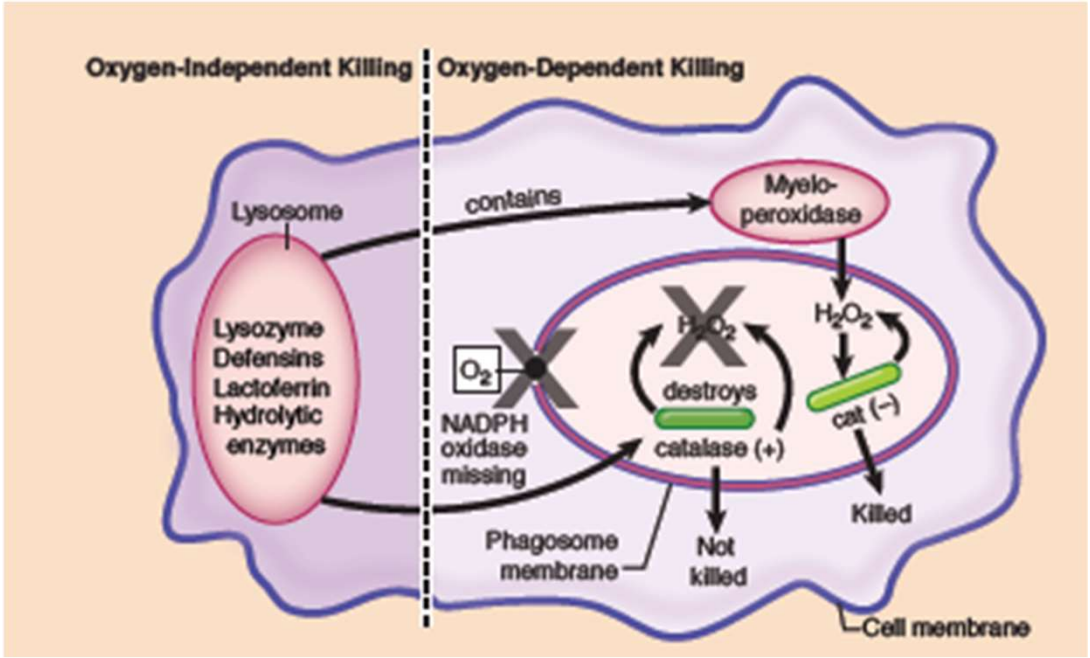
PERIPHERY: INNATE IMMUNE RESPONSE

- If the patient is infected with a catalase-negative organism, the H2O2 waste product produced by the bacterium can be used as a substrate for myeloperoxidase, and the bacterium is killed.

- If the patient is infected with a catalase-positive organism (e.g.,*Staphylococcus, Klebsiella, Serratia, Aspergillus*), the myeloperoxidase system lacks its substrate (because these organisms destroy H2O2), and the patient is left with the oxygen-independent lysosomal mechanisms that prove inadequate to control rampant infections. Thus, CGD patients suffer from chronic, recurrent infections with catalase-positive organisms.

PERIPHERY: INNATE IMMUNE RESPONSE

CGD



PERIPHERY: INNATE IMMUNE RESPONSE

CGD

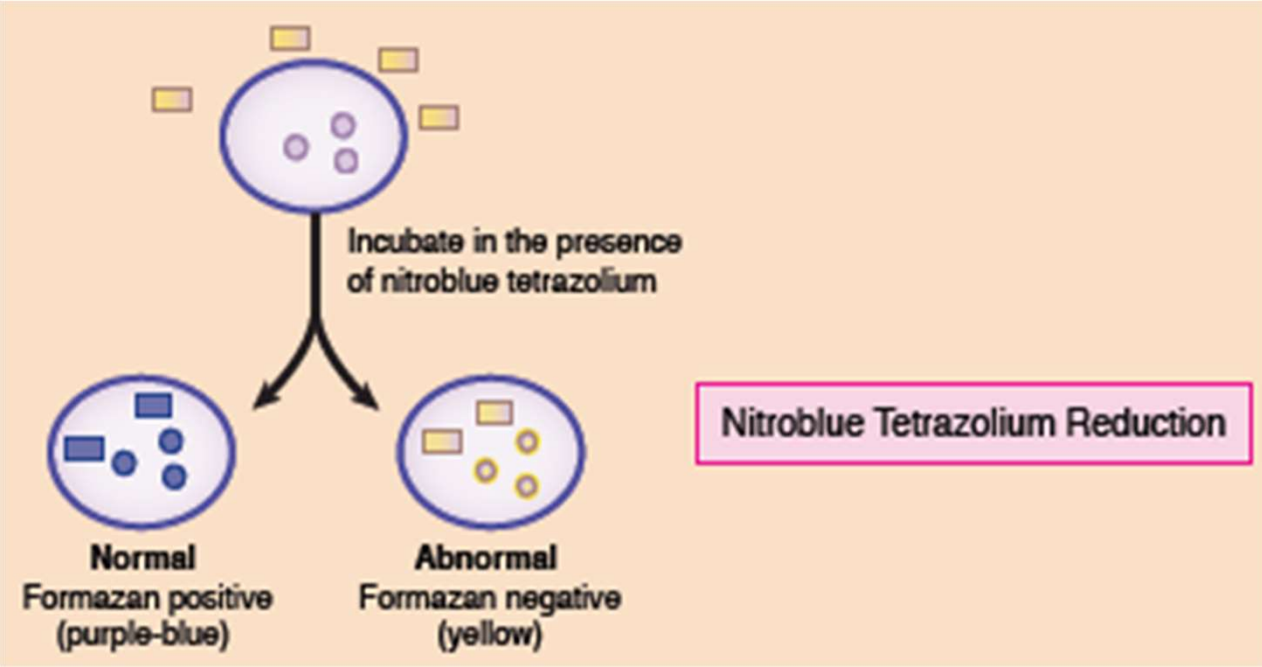
Diagnosis

- Failures of phagocytic cells to generate oxygen radicals are easily detected by the Nitroblue tetrazolium (NBT) reduction test or neutrophil oxidative index (NOI; a flow cytometric assay).
- The Dihydrorhodamine Test—a similar test using flow cytometry may also be used.

PERIPHERY: INNATE IMMUNE RESPONSE

CGD

DIAGNOSIS



PERIPHERY: INNATE IMMUNE RESPONSE

Cytokinin

Pro-Inflammatory

- IL1
- IL6
- TGF α

Chemokinin

- IL8
- IL12
- IL15
- IL18

Regulatory

- IL10

Type 1 INF α

- INF α
- IFN-β
- TGF-β

PERIPHERY: INNATE IMMUNE RESPONSE

Cytokine(s) Cell Secreted by Target Cells/Tissues Activity

Pro-inflammatory cytokines

IL-1

Macrophages

Hypothalamus: Fever

Endothelial cells: Increases expression of ICAMs

Liver: Stimulates production of acute phase proteins

PERIPHERY: INNATE IMMUNE RESPONSE

IL-6

Macrophages

Liver Synthesis of acute phase proteins

PERIPHERY: INNATE IMMUNE RESPONSE

TNF-α

Macrophages

Hypothalamus Fever

Endothelial cells Increases expression of ICAMs

Liver Stimulates production of acute phase proteins

Neutrophils Activation

Tumor cells Apoptosis

Fat, muscle Cachexia

PERIPHERY: INNATE IMMUNE RESPONSE

Chemokine

IL-8

Macrophages

Leukocytes Induces adherence to endothelium, chemotaxis, extravasation

PERIPHERY: INNATE IMMUNE RESPONSE

IL-12

Macropages, dendritic cells

NK cells IFN-γ production

IL-15

Macrophages

NK Cells proliferation

PERIPHERY: INNATE IMMUNE RESPONSE

IL-18

Macrophages

IFN-γ synthesis

PERIPHERY: INNATE IMMUNE RESPONSE

Regulatory

IL-10

Macrophages, dendritic cells

Macrophages, dendritic cells Inhibition of IL-12 production, decreased expression of co-stimulatory molecules, decreased class II MHC expression

PERIPHERY: INNATE IMMUNE RESPONSE

Type I IFNs

IFN-α

Dendritic cells, macrophages

All cells Transient inhibition of protein synthesis, increased class I MHC expression NK cells Activation

PERIPHERY: INNATE IMMUNE RESPONSE

IFN-β

Fibroblasts

All cells Transient inhibition of protein synthesis, increased class I MHC expression NK cells Activation

PERIPHERY: INNATE IMMUNE RESPONSE

TGF-β

Macrophages, lymphocytes, etc.

- Anti-inflammatory

PERIPHERY: INNATE IMMUNE RESPONSE

Innate Response to Viruses

- The innate response to viruses is unique in that it is geared toward eliminating these intracellular pathogens. The 2 major mechanisms for dealing with viral infections are IFN-a/b and NK cells.

PERIPHERY: INNATE IMMUNE RESPONSE

Interferons

- Interferons (IFNs) are a family of eukaryotic cell proteins classified according to the cell of origin. IFN-a and IFN-b are produced by a variety of virus-infected cells. They do the following:
- Act on target cells to inhibit viral replication, not the virus
- Are not virus-specific

PERIPHERY: INNATE IMMUNE RESPONSE

Interferon inhibits viral protein synthesis:

- Activation of an RNA endonuclease, which digests viral RNA
- Phosphorylation of protein kinase, which inactivates eIF2, inhibiting viral protein synthesis.

PERIPHERY: INNATE IMMUNE RESPONSE

Interferon Production

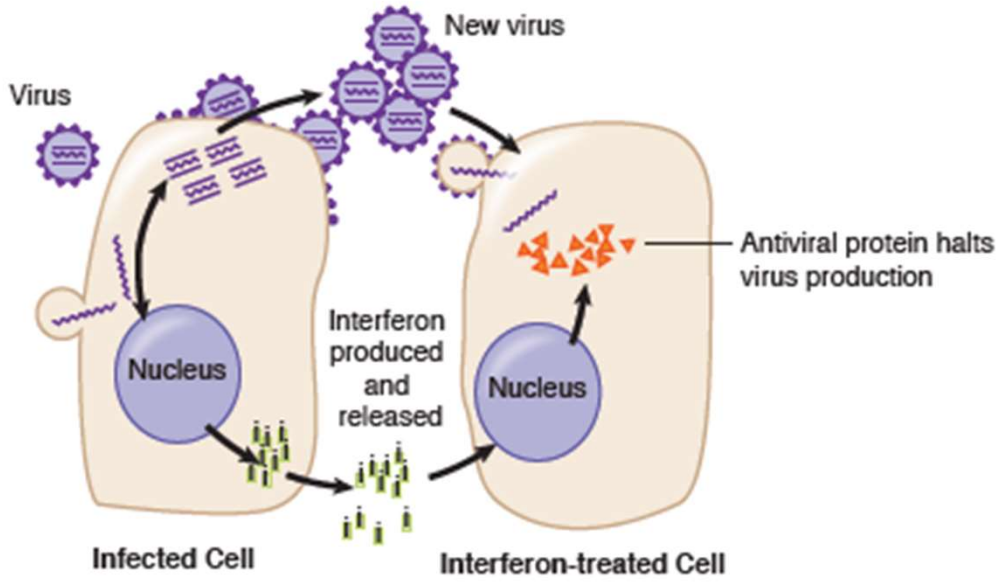


Figure I-4-13. Interferon Production

PERIPHERY: INNATE IMMUNE RESPONSE

Clinical Correlate

Therapeutic Use of Interferons

Since the fi st description of interferons (IFN) almost 50 years ago, a multitude of dramatic immunomodulatory roles have been discovered for this group of proteins. As a group, IFNs induce increases in the expression of class I and II MHC molecules and augment NK cell activity. They increase the efficiency of presentation of antigens to both cytotoxic and helper cell populations. Cloning of the genes that encode IFNs α, β, and γ has made it possible to produce sufficient amounts to make their use clinically practical.

PERIPHERY: INNATE IMMUNE RESPONSE

Interferon-a has well-known antiviral activity and has been used in the treatment of hepatitis B and C infections.

Within cancer therapy, IFN-α has shown promise in treatment of

Hairy B-cell Leukaemia,

Chronic myelogenous Leukaemia,

Kaposi sarcoma.

PERIPHERY: INNATE IMMUNE RESPONSE

Interferon-β was the first drug shown to have a positive effect on young adults with Multiple Sclerosis. Patients treated with IFN-β enjoy longer periods of remission and reduced severity of relapses.

PERIPHERY: INNATE IMMUNE RESPONSE

Interferon-γ

Used in the treatment of Chronic Granulomatous Disease (CGD). This molecule is a potent inducer of macrophage activation and a promoter of inflammatory responses. Its application appears to significantly reverse the CGD patient's inability to generate toxic oxygen metabolites inside phagocytic cells.

Rxed

- The side effects of IFN therapy are fortunately mild and can be managed with acetaminophen. They include headache, fever, chills, and fatigue, and they diminish with continued treatment.

PERIPHERY: INNATE IMMUNE RESPONSE

NK Cells

- NK cells are members of the innate branch of the immune response. They exhibit the capacity to kill virally infected cells and tumor cells. They kill via the same mechanisms of inducing apoptosis observed with CTLs (granzymes, perforin).
- NK activity is increased in the presence of interferons (IFNs) α and β, and IL-12.

PERIPHERY: INNATE IMMUNE RESPONSE

- NK cells share a common early progenitor with T cells, but they do not develop in the thymus. They do not express antigen-specific receptors or CD3. The markers used clinically to enumerate NK cells include CD16 (FcRg) and CD56 (CAM). Their recognition of targets is not MHC-restricted, and their activity does not generate immunologic memory.

PERIPHERY: INNATE IMMUNE RESPONSE

NK receptor

NK cells employ 2 categories of receptor:

- **killer activating receptor (KAR)** and
- **killer inhibitory receptor (KIR)**.

If only KARs are engaged, the target cells will be killed. If both the KIRs and the KARs are ligated, the target cell lives. Therefore the inhibitory signals trump the activation signals.

PERIPHERY: INNATE IMMUNE RESPONSE

NKG2D is the major KAR expressed by NK cells. There are many ligands for KARs; the MIC glycoproteins are one type. MIC proteins are stress proteins that are expressed only when cells are infected or undergoing transformation. Upon the binding of KAR to a MIC protein, NK cells become cytotoxic, resulting in death of the target cell.

PERIPHERY: INNATE IMMUNE RESPONSE

- The KIRs activate protein tyrosine phosphatases which inhibit intracellular signalling and activation by removing tyrosine residues from various signalling molecules.
- The KIRs on the NK cell bind to a specialized type of MHC class I antigens called HLA-E. HLA-E has a ubiquitous tissue distribution, as do the other class I HLA molecules. The HLA-E molecules bind to peptides derived from the leader sequence of HLA-A, -B and –C. HLA-E requires a bound peptide for proper expression within a cell. Therefore, the amount of HLA-E expression on a cell is indicative of the overall well-being of the cell. During viral infections or in transformed cells, the amount of class I HLA expression may be decreased, which would prevent the leader sequences from binding to HLA-E.
- This would decrease the expression of HLA-E, and make cells susceptible to NK mediated killing.

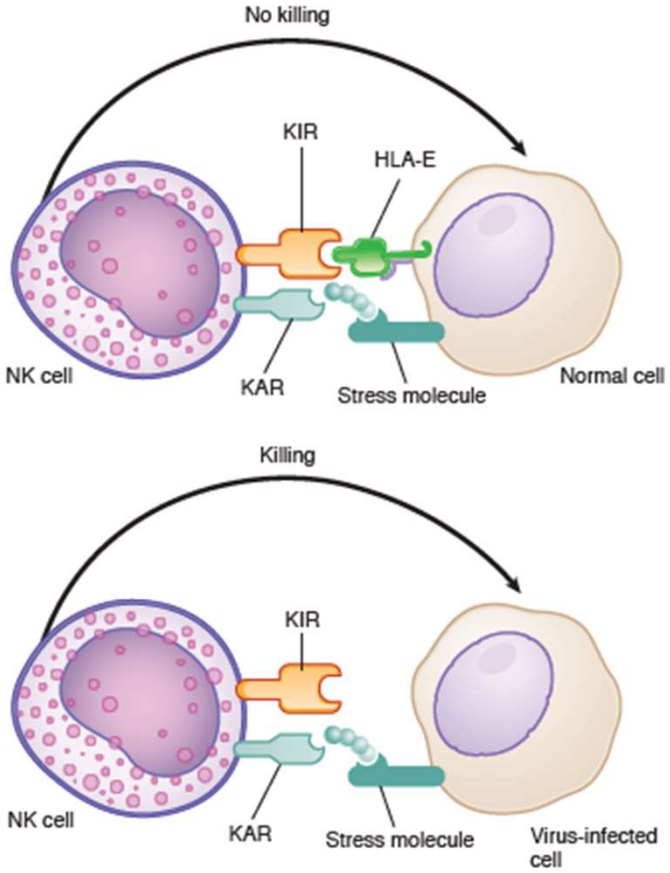
PERIPHERY: INNATE IMMUNE RESPONSE

ADCC- Antibodies dependent Cell Mediated Toxixcity

- Interestingly, when NK cells are activated through the FcR (CD16), only one signal is required because the antibody signals that there is an active infection.
- This occurs through a mechanism called antibody-dependent cell-mediated cytotoxicity (ADCC)

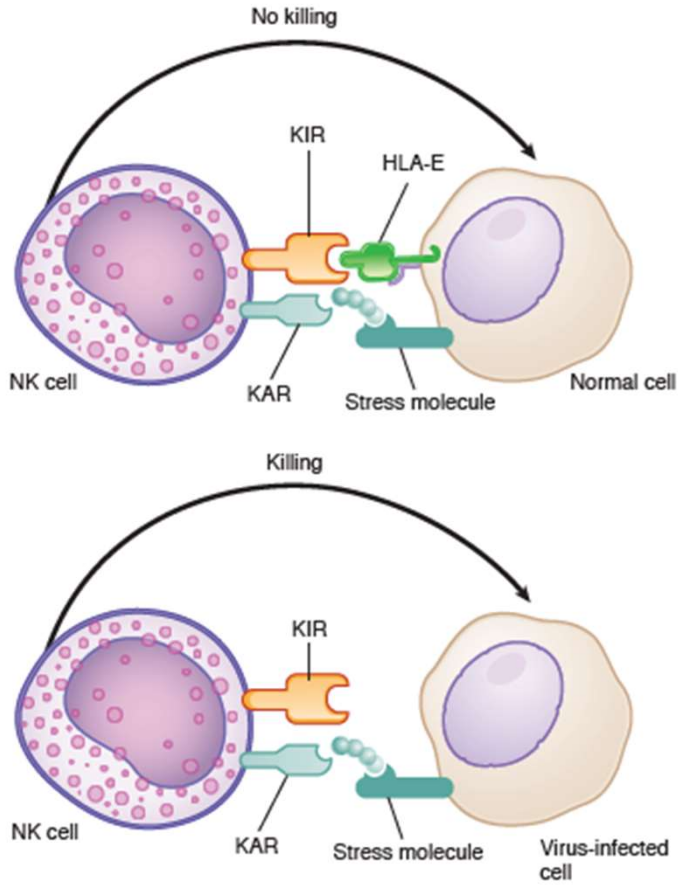
PERIPHERY: INNATE IMMUNE RESPONSE

ADCC



PERIPHERY: INNATE IMMUNE RESPONSE

Activation of NK CELLS



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