Acute Inflammation 2
Figure 7. Overview of the immune response to injury and infection. These responses are divided into innate and acquired immunity as described in the text. NK, natural killer; ROS, reactive oxygen species; CD, cluster of differentiation; Ig, immunoglobulin; Th, T helper.
Recognition of Microbes and Dead Tissues

Once leukocytes (neutrophils and monocytes) have been recruited to a site of infection or cell death, they must be activated to perform their functions.

The responses of leukocytes consist of two sequential sets of events:

(1) Recognition of the offending agents

(2) Activation to ingest and destroy the offending agents and amplify the inflammatory reaction
FIGURE 2–7C Nature of leukocyte infiltrates in inflammatory reactions. The photomicrographs are representative of the early (neutrophilic) (A) and later (mononuclear) cellular infiltrates (B) seen in an inflammatory reaction in the myocardium following ischemic necrosis (infarction). The kinetics of edema and cellular infiltration (C) are approximations.

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FIGURE 2–8 Leukocyte receptors and responses. Different classes of cell surface receptors of leukocytes recognize different stimuli. The receptors initiate responses that mediate the functions of the leukocytes. Only some receptors are depicted. IFN-γ, interferon-γ; LPS, lipopolysaccharide(s).

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Receptors for microbial products:

Toll-like receptors (TLRs) recognize components of different types of microbes. Thus far 10 mammalian TLRs have been identified, and each seems to be required for responses to different classes of infectious pathogens.

Different TLRs play essential roles in cellular responses to bacterial lipopolysaccharide (LPS, or endotoxin), other bacterial proteoglycans and lipids, and unmethylated CpG nucleotides, all of which are abundant in bacteria, as well as double-stranded RNA, which is produced by some viruses.

TLRs are present on the cell surface and in the endosomal vesicles of leukocytes (and many other cell types), so they are able to sense products of extracellular and ingested microbes.

These receptors function through receptor-associated kinases to stimulate the production of microbicidal substances and cytokines by the leukocytes.
**FPR** is a G protein–coupled receptor found on neutrophils, macrophages, and most other types of leukocytes recognize **short bacterial peptides containing N-formylmethionyl residues**.

Because all bacterial proteins and few mammalian proteins (only those synthesized within mitochondria) are initiated by N-formylmethionine, this receptor enables neutrophils to detect and respond to bacterial proteins.

Other G protein–coupled receptors recognize chemokines, breakdown products of complement such as C5a, and lipid mediators, including platelet activating factor, prostaglandins, and leukotrienes, all of which are produced in response to microbes and cell injury.

Binding of ligands, such as microbial products and mediators, to the G protein–coupled receptors induces migration of the cells from the blood through the endothelium and production of microbicidal substances by activation of the respiratory burst.
Receptors for Opsonins:

Leukocytes express receptors for proteins that coat microbes.

The process of coating a particle, such as a microbe, to target it for ingestion (phagocytosis) is called opsonization, and substances that do this are opsonins. These substances include antibodies, complement proteins, and lectins.

One of the most efficient ways of enhancing the phagocytosis of particles is coating the particles with IgG antibodies specific for the particles, which are then recognized by the high-affinity Fcγ receptor of phagocytes, called.

Components of the complement system, especially fragments of the complement protein C3, are also potent opsonins, because these fragments bind to microbes and phagocytes express a receptor, called the type 1 complement receptor (CR1), that recognizes breakdown products of C3 (discussed later). Plasma lectins, mainly mannan-binding lectin, also bind to bacteria and deliver them to leukocytes. The binding of opsonized particles to leukocyte Fc or C3 receptors promotes phagocytosis of the particles and activates the cells.
FIGURE 2-14 The activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins, and by the membrane attack complex (MAC).

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FIGURE 2–15 Interrelationships between the four plasma mediator systems triggered by activation of factor XII (Hageman factor). Note that thrombin induces inflammation by binding to protease-activated receptors (principally PAR-1) on platelets, endothelium, smooth muscle cells, and other cells. HMWK, high molecular weight kininogen.

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Removal of the Offending Agents

Recognition of microbes or dead cells by the receptors described above induces several responses in leukocytes that are referred to under the rubric of leukocyte activation.

Activation results from signaling pathways that are triggered in leukocytes, resulting in increases in cytosolic Ca\(_2+\) and activation of enzymes such as protein kinase C and phospholipase A\(_2\).

The functional responses that are most important for destruction of microbes and other offenders are phagocytosis and intracellular killing.
Phagocytosis.

Phagocytosis involves three sequential steps (Fig. 2-9):

1. **Recognition and attachment** of the particle to be ingested by the leukocyte

2. **Its engulfment**, with subsequent formation of a phagocytic vacuole

3. **Killing or degradation** of the ingested material
Mannose receptors, scavenger receptors, and receptors for various opsonins all function to bind and ingest microbes.

The macrophage mannose receptor is a lectin that binds terminal mannose and fucose residues of glycoproteins and glycolipids. These sugars are typically part of molecules found on microbial cell walls, whereas mammalian glycoproteins and glycolipids contain terminal sialic acid or N-acetylgalactosamine.
Scavenger receptors were originally defined as molecules that bind and mediate endocytosis of oxidized or acetylated low-density lipoprotein (LDL) particles that can no longer interact with the conventional LDL receptor. Macrophage scavenger receptors bind a variety of microbes in addition to modified LDL particles. Macrophage integrins, notably Mac-1 (CD11b/CD18), may also bind microbes for phagocytosis.
Killing and Degradation

Microbial killing is accomplished largely by reactive oxygen species (ROS, also called reactive oxygen intermediates) and reactive nitrogen species, mainly derived from NO.

The generation of ROS is due to the rapid assembly and activation of a multicomponent oxidase (NADPH oxidase, also called phagocyte oxidase), which oxidizes NADPH (reduced nicotinamide-adenine dinucleotide phosphate) and, in the process, reduces oxygen to superoxide anion.

In neutrophils, this rapid oxidative reaction is triggered by activating signals and accompanies phagocytosis, and is called the respiratory burst.

http://physiologyonline.physiology.org/content/25/1/27/F4.large.jpg
Phagocyte oxidase is an enzyme complex consisting of at least seven proteins. In resting neutrophils, different components of the enzyme are located in the plasma membrane and the cytoplasm. In response to activating stimuli, the cytosolic protein components translocate to the phagosomal membrane, where they assemble and form the functional enzyme complex. Thus, the ROS are produced within the lysosome where the ingested substances are segregated, and the cell's own organelles are protected from the harmful effects of the ROS.

Superoxide is then converted into hydrogen peroxide (H2O2), mostly by spontaneous dismutation.

**H2O2 is not able to efficiently kill microbes by itself.**

However, the azurophilic granules of neutrophils contain the enzyme myeloperoxidase (MPO), which, in the presence of a halide such as Cl\(^-\), converts H2O2 to hypochlorite (OCl\(^-\), the active ingredient in household bleach). The latter is a potent antimicrobial agent that destroys microbes by halogenation (in which the halide is bound covalently to cellular constituents) or by oxidation of proteins and lipids (lipid peroxidation).

**The H2O2-MPO-halide system is the most efficient bactericidal system of neutrophils.** H2O2 is also converted to hydroxyl radical (•OH), another powerful destructive agent.
NO, produced from arginine by the action of nitric oxide synthase (NOS), also participates in microbial killing. NO reacts with superoxide to generate the highly reactive free radical peroxynitrite (ONOO$\cdot$). These oxygen- and nitrogen-derived free radicals attack and damage the lipids, proteins, and nucleic acids of microbes as they do with host macromolecule.

NO has dual actions in inflammation: it relaxes vascular smooth muscle and promotes vasodilation, thus contributing to the vascular reaction, but it is also an inhibitor of the cellular component of inflammatory responses. NO reduces platelet aggregation and adhesion, inhibits several features of mast cell–induced inflammation, and inhibits leukocyte recruitment. Because of these inhibitory actions, production of NO is thought to be an endogenous mechanism for controlling inflammatory responses.
FIGURE 2-12 Functions of nitric oxide (NO) in blood vessels and macrophages. NO is produced by two NO synthase (NOS) enzymes. It causes vasodilation, and NO-derived free radicals are toxic to microbial and mammalian cells.

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FIGURE 2–10 Subsets of activated macrophages. Different stimuli activate monocytes/macrophages to develop into functionally distinct populations. Classically activated macrophages are induced by microbial products and cytokines, particularly IFN-γ, and are microbicidal and involved in potentially harmful inflammation. Alternatively activated macrophages are induced by other cytokines and in response to helminths (not shown), and are important in tissue repair and the resolution of inflammation (and may play a role in defense against helminthic parasites, also not shown).

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Macrophages make me sick: How macrophage activation states influence sickness behavior
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### Macrophage Marker Associated functions

<table>
<thead>
<tr>
<th>Macrophage</th>
<th>Marker</th>
<th>Associated functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>iNOS</td>
<td>Produces microbicidal NO from arginine</td>
</tr>
<tr>
<td></td>
<td>↑ IL-1β, TNF</td>
<td>↑ Inflammatory activity</td>
</tr>
<tr>
<td>Alternative</td>
<td>↓ IL-1β, TNF, IL-1ra</td>
<td>↓ Inflammatory activity</td>
</tr>
<tr>
<td></td>
<td>Insulin-like growth factor 1</td>
<td>Antagonizes IL-1 signaling</td>
</tr>
<tr>
<td></td>
<td>Arginase 1</td>
<td>Tissue proliferation/repair</td>
</tr>
<tr>
<td></td>
<td>Mannose receptor</td>
<td>Produces wound-healing compounds from arginine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uptake of mannosylated antigens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pathogen recognition</td>
</tr>
<tr>
<td>Deactivated</td>
<td>IL-10</td>
<td>Inhibit proinflammatory cytokine production/action</td>
</tr>
<tr>
<td></td>
<td>↓ IL-12</td>
<td>↓ cytotoxic lymphocyte generation/activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ IFN-γ production</td>
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Macrophages make me sick: How macrophage activation states influence sickness behavior

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Figure 2-13: Principal local and systemic actions of tumor necrosis factor (TNF) and interleukin-1 (IL-1).

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Histamine and Serotonin are the two major vasoactive amines, so named because they have important actions on blood. They are stored as preformed molecules in cells and are therefore among the first mediators to be released during inflammation.

The richest sources of histamine are the mast cells that are normally present in the connective tissue adjacent to blood vessels. It is also found in blood basophils and platelets. Histamine is present in mast cell granules and is released by mast cell degranulation in response to a variety of stimuli, including:

1. physical injury such as trauma, cold, or heat;
2. binding of antibodies to mast cells, which underlies allergic reactions;
3. fragments of complement called anaphylatoxins (C3a and C5a);
4. histamine-releasing proteins derived from leukocytes;
5. neuropeptides (e.g., substance P);
6. cytokines (IL-1, IL-8).

Histamine causes dilation of arterioles and increases the permeability of venules. It is considered to be the principal mediator of the immediate transient phase of increased vascular permeability, producing interendothelial gaps in venules, as we have seen. Its vasoactive effects are mediated mainly via binding to H1 receptors on microvascular endothelial cells.
Mast-cell activation and granule release

- **Gastrointestinal tract**
  - Increased fluid secretion, increased peristalsis
  - Expulsion of gastrointestinal tract contents (diarrhea, vomiting)

- **Eyes, nasal passages, and airways**
  - Decreased diameter, increased mucus secretion
  - Congestion and blockage of airways (wheezing, coughing, phlegm)
  - Swelling and mucus secretion in nasal passages

- **Blood vessels**
  - Increased blood flow, increased permeability
  - Increased fluid in tissues causing increased flow of lymph to lymph nodes, increased cells and protein in tissues, increased effector response in tissues
  - Hypotension potentially leading to anaphylactic shock

http://o.quizlet.com/1eh-bKUqeKwpXoB8jyMjnA.png
Serotonin (5-hydroxytryptamine) is a preformed vasoactive mediator with actions similar to those of histamine.

It is present in platelets and certain neuroendocrine cells, e.g. in the gastrointestinal tract, and in mast cells in rodents but not humans.

Release of serotonin from platelets is stimulated when platelets aggregate after contact with collagen, thrombin, adenosine diphosphate, and antigen-antibody complexes.

Thus, the platelet release reaction, which is a key component of coagulation, also results in increased vascular permeability. This is one of several links between clotting and inflammation.
Arachidonic Acid (AA) Metabolites: Prostaglandins, Leukotrienes, and Lipoxins

When cells are activated by diverse stimuli, such as microbial products and various mediators of inflammation, membrane AA is rapidly converted by the actions of enzymes to produce prostaglandins and leukotrienes. These biologically active lipid mediators serve as intracellular or extracellular signals to affect a variety of biologic processes, including inflammation and hemostasis.

![Arachidonic Acid Structure](http://upload.wikimedia.org/wikipedia/commons/thumb/7/74/Arachidonic_acid_structure.svg/620px-Arachidonic_acid_structure.svg.png)
FIGURE 2-11 Generation of arachidonic acid metabolites and their roles in inflammation. The molecular targets of action of some anti-inflammatory drugs are indicated by a red X. Not shown are agents that inhibit leukotriene production by inhibition of 5-lipoxygenase (e.g., Zileuton) or block leukotriene receptors (e.g., Montelukast). COX, cyclooxygenase; HETE, hydroxyeicosatetraenoic acid; HPETE, hydroperoxyeicosatetraenoic acid.

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Platelet-Activating Factor (PAF)

PAF is a phospholipid-derived mediator. Its name comes from its discovery as a factor that causes platelet aggregation, but it is now known to have multiple inflammatory effects. A variety of cell types, including platelets themselves, basophils, mast cells, neutrophils, macrophages, and endothelial cells, can elaborate PAF, in both secreted and cell-bound forms.

In addition to platelet aggregation, PAF causes vasoconstriction and bronchoconstriction, and at extremely low concentrations it induces vasodilation and increased venular permeability with a potency 100 to 10,000 times greater than that of histamine. PAF also causes increased leukocyte adhesion to endothelium (by enhancing integrin-mediated leukocyte binding), chemotaxis, degranulation, and the oxidative burst. Thus, PAF can elicit most of the vascular and cellular reactions of inflammation. PAF also boosts the synthesis of other mediators, particularly eicosanoids, by leukocytes and other cells. A role for PAF in vivo is supported by the ability of synthetic PAF receptor antagonists to inhibit inflammation in some experimental models.
Fig. 3 The PAF Signaling System Mediates Activation Responses in Inflammation and Thrombosis. A, the PAF signaling system includes a cell surface receptor that is constitutively present on the plasma membranes of platelets and various other cell types. Upon activation of these cells, PAF are released into the extracellular environment. B, PAF are released from activated cells and bind to their receptors on target cells and other cell types. This results in the activation of various intracellular signaling pathways, including the production of inflammatory mediators and the recruitment of leukocytes. C, PAF also mediate the activation of platelets and other blood cells, leading to aggregation and thrombus formation. See text and cited references for details.
Chemokines are a family of small (8 to 10 kD) proteins that act primarily as chemoattractants for specific types of leukocytes.

About 40 different chemokines and 20 different receptors for chemokines have been identified. They are classified into four major groups, according to the arrangement of the conserved cysteine (C) residues in the mature proteins.
Chemokines have two main functions

Stimulate leukocyte recruitment in inflammation and control the normal migration of cells through various tissues. Some chemokines are produced transiently in response to inflammatory stimuli and promote the recruitment of leukocytes to the sites of inflammation. Other chemokines are produced constitutively in tissues and function to organize different cell types in different anatomic regions of the tissues.

In both situations, chemokines may be displayed at high concentrations attached to proteoglycans on the surface of endothelial cells and in the extracellular matrix.
Neuropeptides

Neuropeptides are secreted by sensory nerves and various leukocytes, and play a role in the initiation and propagation of an inflammatory response. The small peptides, such as substance P and neurokinin A, belong to a family of tachykinin neuropeptides produced in the central and peripheral nervous systems. Nerve fibers containing substance P are prominent in the lung and gastrointestinal tract. Substance P has many biologic functions, including the transmission of pain signals, regulation of blood pressure, stimulation of secretion by endocrine cells, and increasing vascular permeability. Sensory neurons can also produce other pro-inflammatory molecules, such as calcitonin-related gene product, which are thought to link the sensing of painful stimuli to the development of protective host responses.
**FIGURE 2–17A** The characteristic histopathology of acute inflammation. **A,** Normal lung shows thin (virtually invisible) blood vessels in the alveolar walls and no cells in the alveoli. **B,** The vascular component of acute inflammation is manifested by congested blood vessels (packed with erythrocytes), resulting from stasis. **C,** The cellular component of the response is manifested by large numbers of leukocytes (neutrophils) in the alveoli.
Vascular congestion and stasis

FIGURE 2–17B The characteristic histopathology of acute inflammation. A, Normal lung shows thin (virtually invisible) blood vessels in the alveolar walls and no cells in the alveoli. B, The vascular component of acute inflammation is manifested by congested blood vessels (packed with erythrocytes), resulting from stasis. C, The cellular component of the response is manifested by large numbers of leukocytes (neutrophils) in the alveoli.

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FIGURE 2–17C The characteristic histopathology of acute inflammation. 

A, Normal lung shows thin (virtually invisible) blood vessels in the alveolar walls and no cells in the alveoli. 

B, The vascular component of acute inflammation is manifested by congested blood vessels (packed with erythrocytes), resulting from stasis. 

C, The cellular component of the response is manifested by large numbers of leukocytes (neutrophils) in the alveoli.

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Systemic Effects of Inflammation

The systemic changes associated with acute inflammation are collectively called the acute-phase response, or the systemic inflammatory response syndrome.

These changes are reactions to cytokines whose production is stimulated by bacterial products such as LPS and by other inflammatory stimuli.
Malarial antigens from schizogony
Phagocytosis of malarial parasites

Dendritic cells

Pattern-recognition-receptor ligation

Macrophages

IL-6, IL-1, TNF-α secretion

Brain

Hypothalamus
Pituitary gland
Hippocampus
Cerebral cortex

Increased cytokine receptor expression

Altered thermoregulation

Liver

Acute-phase protein production
e.g. C-reactive protein, mannan-binding lectin

Altered appetite

Pathogen opsonisation

The acute-phase reaction

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Fever

Characterized by an elevation of body temperature, usually by 1° to 4°C. One of the most prominent manifestations of the acute-phase response, especially when inflammation is associated with infection.

Fever is produced in response to substances called pyrogens that act by stimulating prostaglandin synthesis in the vascular and perivascular cells of the hypothalamus.

Bacterial products, such as LPS (called exogenous pyrogens), stimulate leukocytes to release cytokines such as IL-1 and TNF (called endogenous pyrogens) that increase the enzymes (cyclooxygenases) that convert AA into prostaglandins.

In the hypothalamus, the prostaglandins, especially PGE2, stimulate the production of neurotransmitters such as cyclic adenosine monophosphate, which function to reset the temperature set point at a higher level.
NSAIDs, including aspirin, reduce fever by inhibiting prostaglandin synthesis.

An elevated body temperature has been shown to help amphibians ward off microbial infections, and it is assumed that fever does the same for mammals, although the mechanism is unknown. One hypothesis is that fever may induce heat shock proteins that enhance lymphocyte responses to microbial antigens.
Acute-phase proteins are plasma proteins, mostly synthesized in the liver, whose plasma concentrations may increase several hundred-fold as part of the response to inflammatory stimuli.

Three of the best-known of these proteins are C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA) protein.

Synthesis of these molecules by hepatocytes is up-regulated by cytokines, especially IL-6 (for CRP and fibrinogen) and IL-1 or TNF (for SAA). Many acute-phase proteins, such as CRP and SAA, bind to microbial cell walls, and they may act as opsonins and fix complement.
Leukocytosis is a common feature of inflammatory reactions, especially those induced by bacterial infections. The leukocyte count usually climbs to 15,000 or 20,000 cells/μL, but sometimes it may reach extraordinarily high levels of 40,000 to 100,000 cells/μL.

The leukocytosis occurs initially because of accelerated release of cells from the bone marrow post-mitotic reserve pool (caused by cytokines, including TNF and IL-1) and is therefore associated with a rise in the number of more immature neutrophils in the blood (shift to the left).

Prolonged infection also induces proliferation of precursors in the bone marrow, caused by increased production of colony-stimulating factors. Thus, the bone marrow output of leukocytes is increased to compensate for the loss of these cells in the inflammatory reaction.

Most bacterial infections induce an increase in the blood neutrophil count, called neutrophilia. Viral infections, such as infectious mononucleosis, mumps, and German measles, cause an absolute increase in the number of lymphocytes (lymphocytosis). In bronchial asthma, allergy, and parasitic infestations, there is an increase in the absolute number of eosinophils, creating an eosinophilia. Certain infections (typhoid fever and infections caused by some viruses, rickettsiae, and certain protozoa) are associated with a decreased number of circulating white cells (leukopenia). Leukopenia is also encountered in infections that overwhelm patients debilitated by disseminated cancer, rampant tuberculosis, or severe alcoholism.
FIGURE 2–16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic inflammation. The components of the various reactions and their functional outcomes are listed.

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