

PART I. THE INFLAMMATORY RESPONSE – AN OVERVIEW

1 Acute and Chronic Inflammation

Peter A. Ward

INTRODUCTION

The inflammatory response consists of an innate system of cellular and humoral responses following injury (such as after heat or cold exposure, ischemia/reperfusion, blunt trauma, etc.), in which the body attempts to restore the tissue to its preinjury state. In the *acute inflammatory response*, there is a complex orchestration of events involving leakage of water, salt, and proteins from the vascular compartment; activation of endothelial cells; adhesive interactions between leukocytes and the vascular endothelium; recruitment of leukocytes; activation of tissue macrophages; activation of platelets and their aggregation; activation of the complement; clotting and fibrinolytic systems; and release of proteases and oxidants from phagocytic cells, all of which may assist in coping with the state of injury. Whether due to physical or chemical causes, infectious organisms, or any number of other reasons that damage tissues, the earliest in vivo hallmark of the acute inflammatory response is the adhesion of neutrophils (polymorphonuclear leukocytes, PMNs) to the vascular endothelium (“margination”) (Figure 1.1). The *chronic inflammatory response* is defined according to the nature of the inflammatory cells appearing in tissues. The definition of chronic inflammation is *not* related to the duration of the inflammatory response. Reversal or *resolution* of the inflammatory response implies that leukocytes will be removed either via lymphatics or by apoptosis (programmed cell suicide) and that the ongoing acute inflammatory response is terminated. As a consequence, during resolution increased vascular permeability is reversed due to closure of the open tight junctions and PMN emigration from the blood compartment ceases. In both the vascular and extravascular compartments, fibrin deposits are removed by pathways that lead to activation of plasminogen (to plasmin), which degrades fibrin (see section on “Intercommunications between Inflammatory

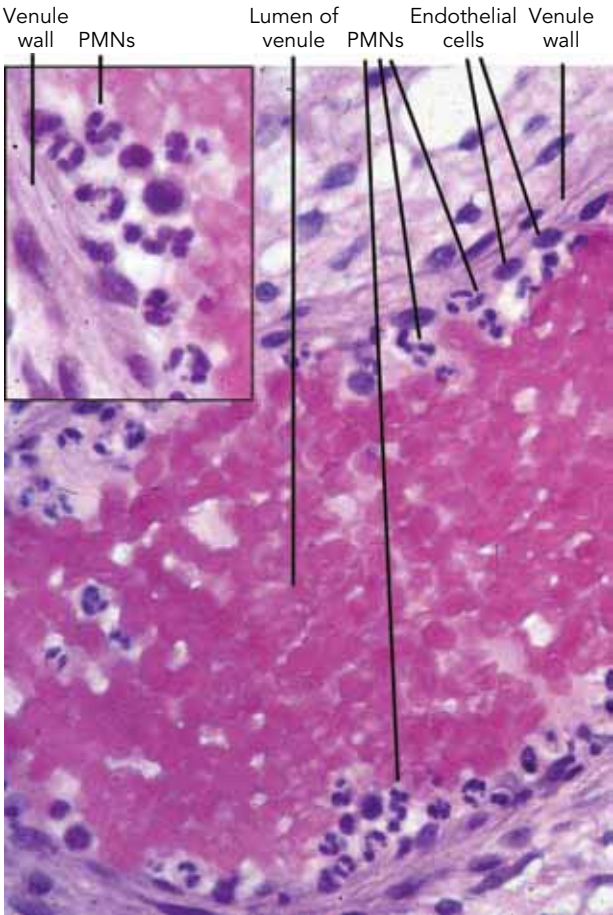


Figure 1.1. Early changes in a human venule involved in an acute inflammatory response. PMNs are “marginating” along the endothelial surface of a venule preparatory to their migrating into the extravascular space due to their adhesion to endothelial surfaces.

Cascades and the Coagulation Cascade”). Cell debris and red blood cells (RBCs) in the extravascular compartment are removed by phagocytosis involving tissue macrophages. There are many situations in which

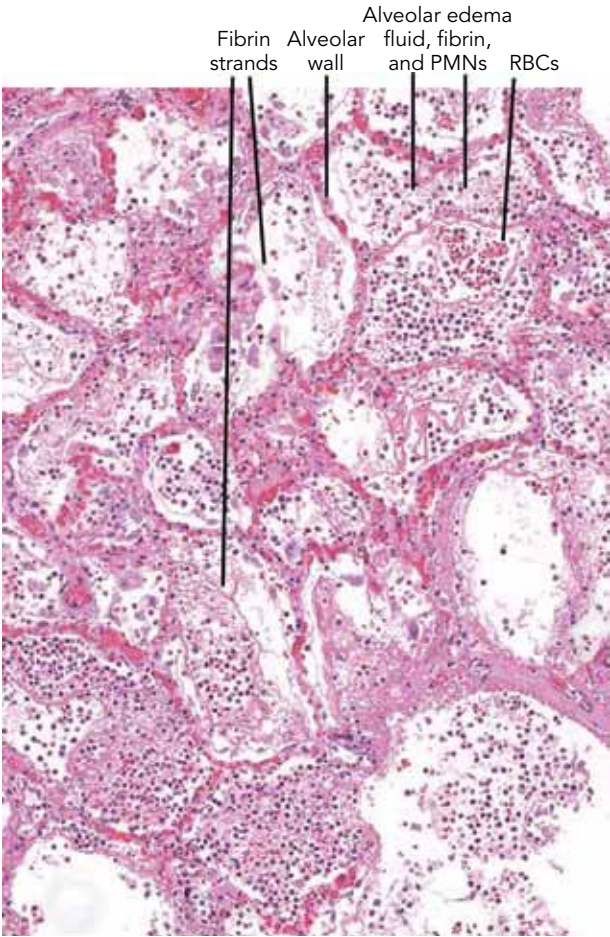


Figure 1.2. Acute bacterial pneumonia (*Streptococcus pneumoniae*) in human lung. Most alveolar spaces are filled with PMNs, fibrin strands, edema fluid, and RBCs, which clinically results in serious interference with gas exchange between the air spaces and vascular compartment.

the acute inflammatory response becomes excessive or prolonged, leading to serious damage of tissues and organs. Examples of unremitting acute inflammatory responses resulting in injury are discussed in the following section. Presented subsequently are concepts regarding acute and chronic inflammation. These are designed to provide the reader with a conceptual framework for an understanding of the inflammatory responses, their causation, and the outcomes.

THE ACUTE INFLAMMATORY RESPONSE

The acute inflammatory response is defined as a series of tissue responses that can occur within the first few hours following injury. In cases of bacterial pneumonia (Figure 1.2), bacterial meningitis (Figure 1.3), or ischemic myocardial injury (Figure 1.4), the inflammatory response is exuberant within the first few hours or days and then gradually declines unless the offending agent (such as bacteria-inducing pneumonia) cannot be

cleared by phagocytosis. Resolution of the inflammatory response requires killing of bacteria and removal of their debris. When tissue injury occurs in various organs, the resolution of the inflammatory response may, to an extent, involve regeneration in which an organ can rapidly replace damaged or destroyed cells with an architectural outcome that resembles the original uninjured tissue. A good example of this is acute injury (chemical, viral, etc.) in the liver in which the inflammatory response resolves via regeneration of liver cells (hepatocytes, Kupffer cells, endothelial cells, etc.), reconstituting the damaged or destroyed liver, with the end result being tissue that is virtually identical to that before injury. In other situations, such as in the myocardium, ischemic destruction of cardiomyocytes results in an intense acute inflammatory response with a heavy build-up of PMNs (Figure 1.4). The regenerative abilities of the myocardium are extremely limited, if at all, and the destroyed myocardium must be quickly replaced with a fibrous (collagenous) scar. If scar formation is insufficient, the clinical outcome may be fatal due to cardiac rupture and a filling of the pericardial cavity with blood (hemopericardium). In the central nervous system, the commonly held belief is that vital cells such as neurons are largely unable

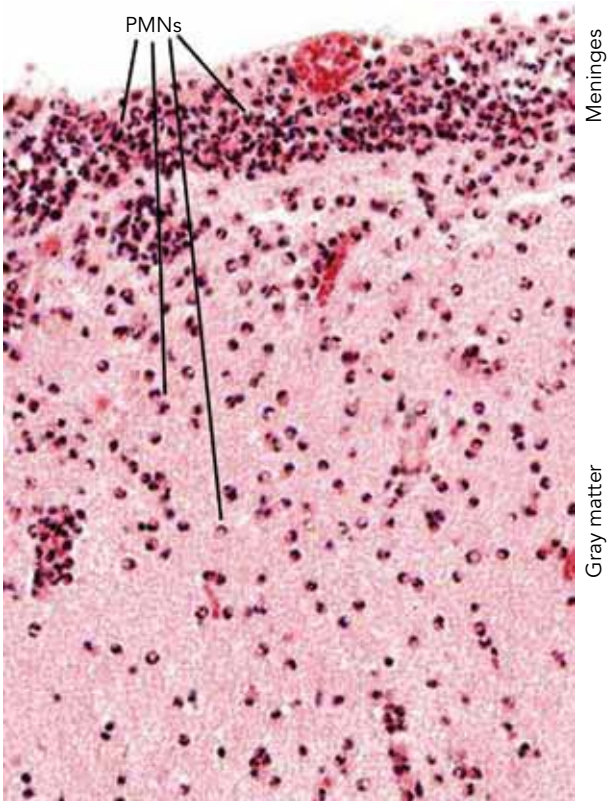


Figure 1.3. Acute bacterial meningitis (*Neisseria meningitidis*) with an intense accumulation of PMNs in the brain covering (meninges) and scattered accumulations of PMNs in the gray matter of the brain.

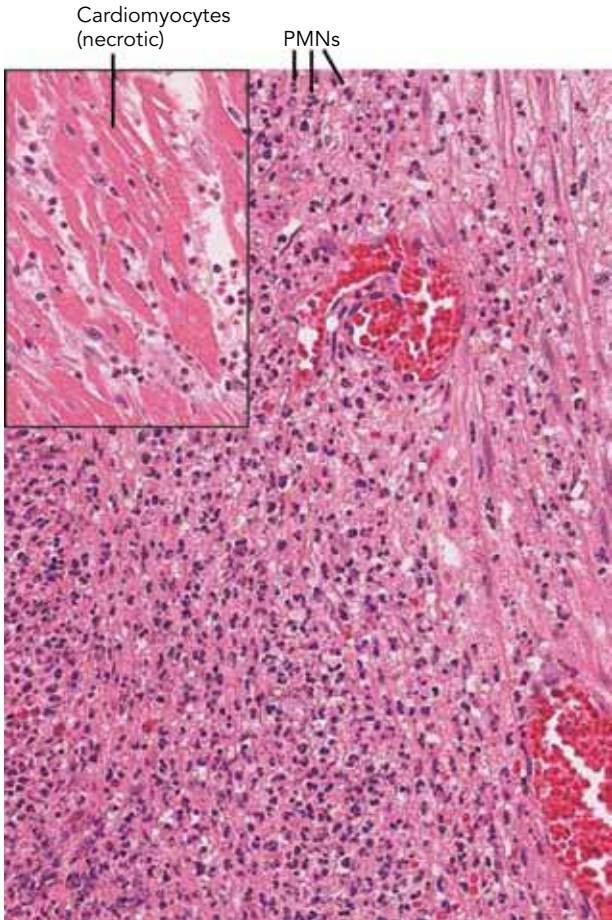


Figure 1.4. An acute inflammatory response in the myocardium 48 h after clinical onset of acute ischemic injury. The main frame shows an intense PMN infiltrate. The inset shows the edge of the infarct area with a necrotic area of myocardium and interstitial accumulation of PMNs.

to regenerate so that, once lost, replacement cannot occur. Most of the theories about cellular regeneration are undergoing reconsideration in the face of extensive stem cell work, which raises the question as to whether locally present or circulating stem cells may become actively involved in replacing cells similar to those that have been destroyed. This is an intensely debated topic that requires much additional investigation.

Figure 1.5 describes changes in tissues related to induction of the acute inflammatory response regardless of what has incited this rejection. There are numerous changes within the vascular compartment that trigger the acute inflammatory response, involving at least six intravascular events. The first change is *activation of endothelial cells*, during which these cells begin to express on their surfaces adhesion molecules for leukocytes (see Chapter 18 for detailed information about these molecules and their “counter-receptors” on leukocytes). Activated endothelial cells also engage in the generation and release of proinflammatory cytokines and chemokines (Chapter 13),

which will chemotactically attract and activate PMNs as these cells adhere to the endothelium before their transmigration into the extravascular compartment. Activated endothelial cells often also express tissue factor (TF, aka Factor III) on their luminal surfaces. The complement activation product, C5a, can cause upregulation of TF on endothelial cells. TF is a potent procoagulant that can lead to thrombus formation on the vascular surface. A second event is *reversible opening of endothelial cells tight junctions*, which allows for the leak of protein and fluids from the vascular compartment into the extravascular compartment. When extensive edema develops in closed compartments, such as in the central nervous system (during bacterial meningitis) or in articular joints (after trauma), this can result in increased hydrostatic pressure that can seriously impair organ function. In the lung, extensive edema formation in the alveolar compartment (also known as “alveolar flooding”) can seriously compromise air exchange between the alveolar and vascular compartments. Examples of this problem occur in acute high-altitude sickness, during bacterial pneumonia, and during Hanta virus infection of the lung. An inability for adequate gas exchange between

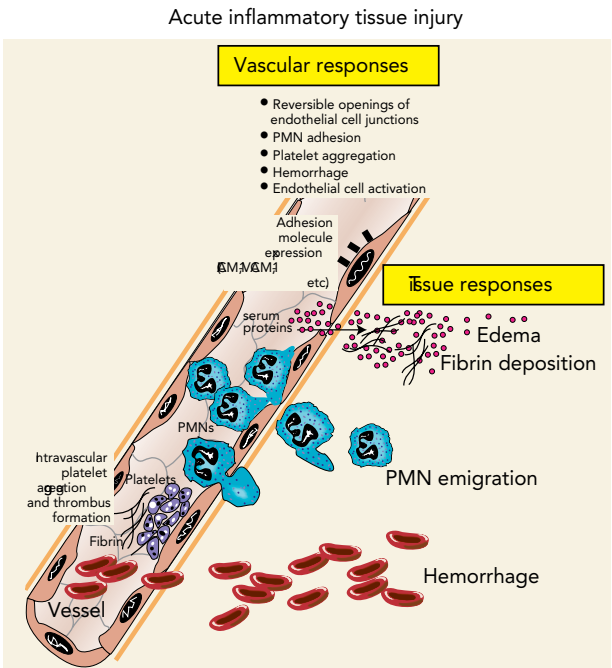


Figure 1.5. Mechanisms of acute inflammatory responses, featuring the initial intravascular events that lead to increased permeability changes, activation of endothelial cells (increased expression of adhesion molecules for neutrophils [PMNs]), adhesion of PMNs to the endothelial surfaces, and platelet activation (resulting in their aggregation and adhesion to one another as well as to endothelial surfaces). Platelets are often present in areas of fibrin deposition. Tissue responses (in extravascular compartment) feature edema, transmigration of PMNs, fibrin deposition, and hemorrhage if the structural integrity of the vascular barrier has been compromised.

TABLE 1.1. Factors affecting vascular integrity		
	Events	Factors responsible
Edema	Reversible opening of endothelial tight junctions	Histamine, serotonin, kinins (bradykinin), C3a, C5a, •NO, PAF, prostaglandins
PMN emigration	Movement beyond vascular barrier	Chemoattractants: C5a, cytokines (IL-1β, TNFα), CXC, chemokines: collagen and bacterial peptides, metabolites of arachidonic acid
Hemorrhage	RBCs in extravascular compartment	Physical forces (heat, cold), bacterial products, proteins and oxidants from phagocytes
Platelets	Intravascular aggregation and fibrin formation	PAF, ADP, thrombin activation, etc.

the alveolar and vascular compartments can lead to a life-threatening state of hypoxia requiring intensive resuscitative support. Reversibility of the junctional changes in the vascular endothelium implies that open endothelial junctions can close to contain the amount of edema fluid accumulating in the extravascular compartment. Agents such as histamine are well known to interact with the vascular wall to bring about reversible opening of the tight endothelial junctions (Table 11.1 of Chapter 11). Whether vasopermeability mediators directly affect vascular endothelial cells (resulting in their contractility that opens tight junctions) or whether there are periendothelial cells which are tethered to endothelial cells (that respond by contraction to factors such as histamine, pulling the tight junctions open) is a matter of considerable debate. Another key factor in the acute inflammatory response is adhesive interactions between PMNs and endothelial cells (Chapters 4 and 11). Ordinarily, PMNs and other leukocytes are carried in the center in the blood stream without making contact with endothelial surfaces. PMNs undergo activation responses such as upregulation of CD11b/CD18 on their cell membranes (Chapter 4), while endothelial cells undergo activation most commonly with gene expression, leading to appearance of adhesion molecules on the laminar faces of endothelial cells. Examples of these molecules are P-selectin, E-selectin, and ICAM-1 (Chapter 18). The sequence of intermittent PMN adhesion to the endothelium (described as PMN rolling) followed by tight adhesion and eventual transmigration of PMNs through endothelial cell junctions is described in detail (Chapter 18). It should be pointed out that studies featuring intermittent (“rolling”) followed by firm adhesion have been focused on changes in postcapillary venules. In the case of the lung, PMN transmigration occurs in capillaries that would not permit the rolling phenomenon described above because of physical constraints (inadequate space, since PMNs have a diameter equivalent to the diameter of a capillary). Furthermore, as the inflammatory response commences, PMNs become activated and stiff and cannot undergo deformity to

adjust to the tight confines of capillaries. Nevertheless, vascular adhesion molecules play an important role in the transmigration of PMNs in the lung, since the absence or blockade of adhesion molecules clearly diminishes the build-up of PMNs in the extravascular space. Another feature of the acute inflammatory response is platelet activation, which is usually associated with the conversion of prothrombin to thrombin. Platelets can also be directly activated by various other agents (Table 1.1). The end result is platelet adhesion to one another (resulting in platelet aggregates) as well as to endothelial cells. This is the forerunner of intravascular thrombosis in which fibrin deposition develops in and around aggregated platelets. Finally, the acute inflammatory response may be associated with hemorrhage because of direct structural damage (reversible or irreversible) to the endothelial barrier. The development of hemorrhage implies that the vasculature has been severely damaged, since RBCs have no intrinsic mobility and are passively carried out of the vasculature if there has been sufficient loss of vascular integrity. Hemorrhage occurs after thermal or cold trauma, in situations of severe platelet dysfunction or platelet deficiency, after infections due to the release of toxins (as from Streptococcal A bacteria), and in patients undergoing excessive anticoagulant therapy, to cite a few examples. As indicated earlier, all of these changes of the acute inflammatory response are reversible. Edema fluid is cleared from the distal airway (alveolar compartment) by uptake of these fluids together with inflammatory cells into the draining lymphatics, with return to the blood compartment. Thus, what comes from the blood compartment often returns to the blood compartment. PMN clearance in tissues may also occur by apoptosis of these cells and their phagocytosis by tissue macrophages. Thrombosis within vessels can be cleared by activation of the fibrinolytic system, involving tissue plasminogen activator (TPA) and other factors that will activate the fibrinolytic enzyme, plasmin (Figure 1.6).

Table 1.1 lists factors that affect the vascular integrity and lead to changes in the endothelium, resulting

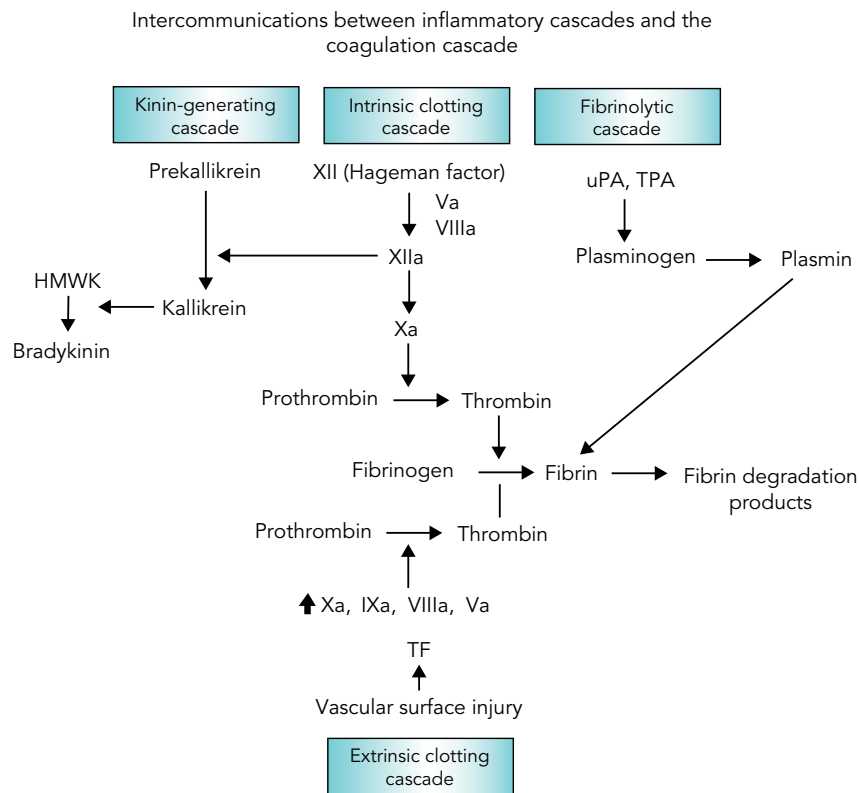


Figure 1.6. The coagulation cascades (intrinsic and extrinsic) and intercommunications with kinin generating and fibrinolytic cascades.

in edema formation, PMN accumulation, platelet activation, and development of hemorrhage. Edema due to reversible openings of endothelial cell tight junctions can be induced by histamine; serotonin; kinins (such as bradykinin); the complement anaphylatoxins (C3a and C5a), which act on mast cells to release histamine; nitric oxide; platelet activating factor (PAF); and certain prostaglandins (Chapter 12). As indicated earlier, these responses resulting in edema fluid accumulation outside the vascular compartment are usually reversible and transient. PMN emigration is preceded by adhesive interactions between these cells and endothelial cells via engagement of adhesion molecules on both cell types (e.g., E- and P-selectins on endothelial cells; CD11b/CD18 on PMNs, etc.) (as described earlier and in Chapter 18). Ordinarily, adhesion molecules are present in low quantities on endothelial and PMN surfaces but activation of either cell type can dramatically and rapidly or slowly increase the levels of adhesion molecules that appear either following fusion of cytosolic granules to the cell membrane in the case of PMNs (the rapid response occurring within minutes) or following transcriptional upregulation (a slow response requiring hours). Adhesion molecules on endothelial cells include ICAM-1 and E-selectin, although in the case of P-selectin, this adhesion molecule can be upregulated either via transcriptionally dependent responses

or via transcriptionally independent responses. Rapid expression is due to P-selectin addition to the cell membrane via fusion of cytosolic granules (Weibel–Palade granules). Rapid upregulation of adhesion molecule is found in PMNs, platelets, and endothelial cells. In the case of PMNs, increased expression of cell membrane adhesion molecules (CD11b/CD18) is usually rapid due to fusion of secondary granules in the cytosol (which contain adhesion molecules on their inner surfaces) to the cell membranes of PMNs. Chemoattractants for PMNs responsible for their extravascular migration (emigration) include C5a, cytokines (such as IL-1 β and TNF α), CXC chemokines, collagen and bacterial peptides, as well as metabolites of arachidonic acid, all of which are described in Chapters 4, 12, and 13. Proteases and oxidants from activated phagocytic cells cause damage to the endothelial barrier, as well as to cells and connective tissue matrix, resulting in widespread damage of both the vascular and extravascular compartments (Chapter 17). Platelets can be activated by a variety of factors (Chapters 5, 8, 12, and 15), such as PAF, ADP, and thrombin, which is activated when the clotting cascade has been triggered (see section on “Intercommunications between Inflammatory Cascades and the Coagulation Cascade”).

As suggested in the earlier comments, the acute inflammatory response is a protective shield against

TABLE 1.2. Regulation of the acute inflammatory response: natural anti-inflammatory factors		
	Factors	Targets
Cytokines	IL-4, IL-10, IL-12	• Stabilization of IκB and reduced NF-κB activation
Protease inhibitors	SLPI, TIMP-1, α ₁ PI, etc.	• Inhibition of serine proteases and nonserine proteases
Antioxidant enzymes	Superoxide dismutase Catalase, Glutathione peroxidase	• Converts •O ₂ to H ₂ O ₂ • Destroys H ₂ O ₂ • Catalyzes the breakdown of H ₂ O ₂ to H ₂ O
Lipoxins		see Chapter 12
Glucocorticoids		• Diverse
Kinases	Hydrolysis of kinins	• Bradykinin, etc.
Phosphatases	Removal of phosphates from proteins	• Transcriptional factors
Transcriptional factors	STAT3, SOCS3	• Blockade of gene activation for proinflammatory mediators

tissue that has been damaged. The purpose of the response is to return the tissue to its predamaged state. In some cases, the response is excessive due to persistence of the damage-causing agent (e.g., bacteria) or the offending trigger (e.g., immune complexes in autoimmune diseases). As will be discussed later, excessive or unregulated inflammatory responses can themselves cause tissue damage. In 1972, Lewis Thomas said “Our arsenals for fighting off bacteria are so powerful, and involve so many different defense mechanisms, that we are more in danger from them than the invaders. We live in the midst of explosive devices; we are mined.” (*Germes, N Engl J Med*, 1972, 287:553–555.)

Regulation of the Acute Inflammatory Response

How is the acute inflammatory response kept in check? It is clear that the response is subject to very tight regulation to contain the cascades before they lead to extensive tissue or organ injury. There are numerous, naturally occurring anti-inflammatory factors (Table 1.2). Cytokines such as IL-4, IL-10, and IL-12 in very low concentrations are inducible and are powerful anti-inflammatory factors that contain the acute inflammatory response by stabilizing IκBα, which blocks NF-κB activation. As a result, these regulatory cytokines have greatly diminished the production of proinflammatory mediators and reduced numbers of PMNs accumulating in tissues. There are several protease inhibitors that also contain the response by inhibiting serine proteases, many of which are released from phagocytic cells. The secreted leukocyte protease inhibitor (SLPI) was described as trypsin-like inhibitor that was largely confined to upper airway secretions, produced by and released from nearby epithelial cells of the lung. It is now known that SLPI reduces activation

of NF-κB via stabilization of IκBβ. Hydrolysis of the IκB proteins is required for activation of NF-κB. In addition, there are nonserine protease inhibitors such as inhibitors of metalloproteases (MMPs). MMP3 and MMP9 may be the most important MMPs, with targets being elastin, collagen, and altered (denatured) collagens. Tissue inhibitor of MMP2 (TIMP-2) is a common and inducible TIMP and has broad inhibitory activity for MMPs. α1 Protease inhibitor (α₁PI) is abundantly present in plasma and in lung tissue. It is a powerful serine protease inhibitor of trypsin-like enzymes. If α₁PI is absent or present in a functionally defective manner, this is almost always associated with the development of progressive and often fatal pulmonary emphysema in humans. Such individuals may also develop hepatic cirrhosis for reasons that are poorly understood. There are many other naturally occurring protease inhibitors that suppress tissue damaging proteases associated with the induction of acute inflammatory response.

Antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase, are abundant in a variety of tissues and can be upregulated in the course of the inflammatory response such as those occurring after hyperoxia, bacterial infection, ischemia–reperfusion, and in various other situations. Upregulation of antioxidant enzymes is especially well documented in the lung, in the case of Gram-negative bacteria (e.g., *Escherichia coli*) lipopolysaccharide (LPS) can rapidly and powerfully upregulate these antioxidant enzymes. Superoxide dismutase converts superoxide anion (•O₂) to H₂O₂, while catalase destroys H₂O₂, reducing it to water and molecular oxygen (Table 1.2). Glutathione peroxidase in the presence of glutathione (GSH) catalyzes the conversion of H₂O₂ to H₂O. If GSH levels are very low in an organ or tissue, it leads to “redox stress” in which the tissue has impaired ability to deal with oxidants

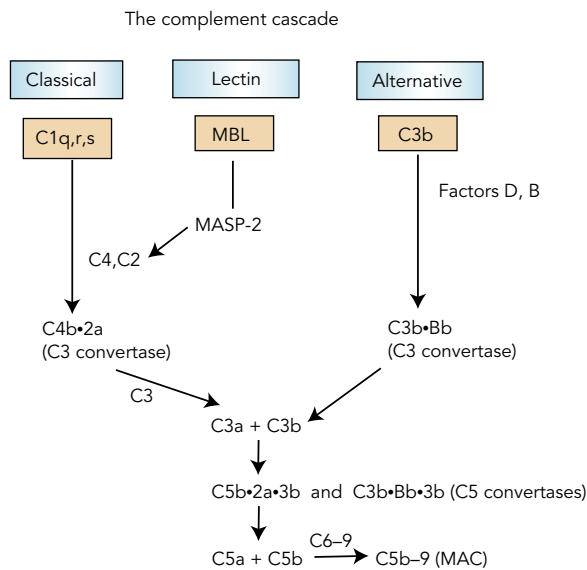


Figure 1.7. The complement cascade, including the three pathways of activation, the C3 and C5 convertases, and the chief complement activation products.

(Chapter 17). Lipoxins represent another source of natural anti-inflammatory factors (Chapter 12). Glucocorticoids are well known to be naturally occurring anti-inflammatory factors. Kininases hydrolyze kinins such as bradykinin and lysyl-bradykinin, leading to their functional inactivation. These enzymes are present in most tissues. The lung vasculature is lined with kininases, such that one pass of blood through the lung can result in complete inactivation of kinins. Phosphatases, such as PTEN, remove phosphates from proteins such as transcriptional and signaling factors, leading to their termination as functionally active moieties. Such regulation can greatly reduce the production of proinflammatory molecules (e.g., adhesion molecules, cytokines, chemokines, etc.). Similar to all other cascades of the inflammatory system, these phosphatases control the production of proinflammatory mediators. Finally, there are several transcriptional regulatory factors such as suppressor of cytokine signaling 3 (SOCS3) and STAT3 that block the activation of proinflammatory genes, resulting in greatly reduced levels of proinflammatory mediators. Obviously, all of these factors are aligned to bring about tightly regulated inflammatory responses before they unleash serious damage to tissues.

THE COMPLEMENT CASCADE

The complement system is an important part of the innate immune system conferring protection especially against invading infectious agents, such as bacteria, viruses, and protozoa. Its role in innate immunity is to generate biologically active products

from the pathways of complement activation, resulting in proinflammatory mediators that will call in PMNs as well as the production of opsonic (phagocytosis promoting) and lytic factors for bacteria (C5b-9, membrane attack complex [MAC]) and nucleated cells. The three pathways of complement activation are shown in Figure 1.7. The *classical pathway* is traditionally activated by the presence of IgG or IgM immune complexes. Activation of the first complement component (C1q,r,s) leads to activation of the subunits to active enzymes, with targets being C4 and C2, resulting in fragmentation products (C4a, C4b, C2a, C2b), some of which form the C4b•2a complex, which is a C3 convertase that cleaves C3 into C3a and C3b. C3b can be adducted to the C4b•2a complex to form the complex, C4b•2a•3b, which is a C5 convertase that can convert C5 into C5a and C5b. The second pathway of complement activation is the *lectin pathway* which involves the mannose-binding lectin (MBL), a plasma “collectin,” that binds to mannose-related carbohydrates present on surfaces of viruses and bacteria. This leads to the activation of mannose-associated serine protease-2 (MASP-2), a serine protease that has the ability (like C1q,r,s) to interact with C4 and C2 to form the C3 convertase (C4b•2a). The third pathway of activation is the *alternative complement pathway* that can be activated by the presence of C3b which, when interacting with factors B and D, forms a complex, C3b•Bb, which has C3 convertase activity that generates C3a and C3b. Adduction of another molecule of C3b generates the C5 convertase of the alternative pathway, C3b•Bb•3b. The C5a convertases cleave C5 into C5a and C5b. C5b can interact with the terminal complement proteins, C6–9, to form the C5b–9 complex (MAC). In addition to these traditional pathways of complement activation, other serine proteases unrelated to the complement system can interact directly with C3 or C5 to form complement activation products (C3a, C3b, C5a, C5b). For instance, plasmin can interact with C3 to generate C3a and C3b. There are several serine proteases (such as the elastase present in neutrophils and a neutral protease present in macrophages) that will then interact directly with C5 to generate C5a and C5b. In addition, thrombin has the ability to interact with C5 to produce the same activation products. The complement activation pathways are under very rigid and tight control, based on “complement regulatory proteins” (CRPs) that are present both in plasma and on cell surfaces. These CRPs tightly regulate the complement system to either limit the formation of complement activation products or form a protective shield to prevent the activation products from bringing about cell damage. Some complement-mediated human disorders, such as paroxysmal nocturnal hemoglobinemia, result in intensive hemolysis of

RBCs because of a defect in two of the CRPs (decay accelerating factor and CD59).

The complement anaphylatoxins are small peptides (<10 kDa) and consist of C3a, C4a, and C5a. The most abundant of these is C3a since C3 is the complement protein present in highest concentration in plasma. C3a appears to have its major biological activity as induction of histamine release from mast cells, which then leads to greatly increased vasopermeability in the local area. C3b is the major opsonic product generated by the complement system and reacts with receptors on a variety of different cells and microorganisms to bring about greatly enhanced phagocytosis and intracellular killing of microbes. There are relatively few humans with complete C3 deficiency and, as such, they are highly susceptible to life-threatening bacterial infections. The role of C4a is not well understood. C5a is an extremely potent anaphylatoxin which, in very low nanomolar concentrations, can interact with receptors on phagocytic cells, especially neutrophils, either to bring about their priming for enhanced subsequent responses in the presence of a co-stimulus or to bring about direct activation of phagocytic cells by inducing chemotaxis, an intracellular calcium response, generation of reactive oxygen species ($\bullet\text{O}_2$, H_2O_2), enzyme release, and a variety of other responses, all of which tend to function as a protective shield in a local setting and bring about accumulation of neutrophils at inflammatory sites. A major function is to contain and kill microorganisms. In some instances, excessive amounts of C5a are generated as in sepsis and in autoimmune diseases (such as rheumatoid arthritis and systemic lupus erythematosus [SLE]). In these cases, major problems can arise such as the signaling paralysis of neutrophils due to excessive generation of C5a and the priming of macrophages for accentuated and excessive inflammatory responses during sepsis. The final product of the complement activation sequence, C5b–9 (MAC), attaches to surfaces of antibody-coated bacteria, leading to their cytolytic destruction. In certain autoimmune disorders in which there are antibodies that can react with epitopes on surfaces of nucleated cells, cell lysis can occur. Soluble C5b–9 has the ability to interact with endothelial cells to bring about their activation with the formation of proinflammatory cytokines and chemokines. Finally, C5b–9 is an important protective factor leading to lysis of Gram-negative bacteria. Details on the biochemistry and functions of the complement system and its role in human diseases are discussed elsewhere.

Intercommunications between Inflammatory Cascades and the Coagulation Cascade

Figure 1.7 demonstrates the intricate intercommunications between three different proinflammatory

cascades: the kinin-generating cascade, the clotting cascades, and the fibrinolytic cascade. Central to these intercommunications is the clotting system which involves two activation pathways, the intrinsic and the extrinsic cascades. The intrinsic cascade occurs with the engagement and activation of Hageman factor (Factor XII) which interacts with Factors Va and VIIIa to convert Factor XII to XIIa (“a” signifies the active form of the protein). In turn, this leads to the activation of Factor X, which then directly converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin, which is the major product involved in *in vivo* clot formation. Following vascular injury, the extrinsic clotting cascade is activated resulting in the expression of endothelial cells on the surfaces of TF and in the copresence of other clot activating factors (Xa, IXa, VIIIa, Va), there is also conversion of prothrombin to thrombin and generation of fibrin from fibrinogen. The fibrinolytic cascade is activated by urinary plasminogen activator (uPA) and TPA which cause conversion of plasminogen to plasmin. Plasmin directly interacts with fibrin to bring about fibrin degradation products resulting in the breakdown of fibrin clots as they are formed within the intravascular compartment or elsewhere. TPA is used in patients with acute myocardial ischemia to try to bring about lysis of intracoronary arterial clots to allow perfusion to occur. The kinin-generating cascade is also linked to the clotting cascades by the fact that Factor XIIa will convert prekallikrein to kallikrein. Kallikrein interacts with high-molecular-weight kininogen (HMWK) to bring about its hydrolysis and release of bradykinin, which is a powerful vasopermeability agent. Bradykinin also has the ability to slow the heart rate (bradycardia). All of these cascades as well as the complement cascade have, as a common theme, activation of proteins by their limited hydrolysis, after which the split products directly interact with cell receptors to trigger cell responses (e.g., C5a interacting with receptors on PMNs [see earlier]) or the split products can assemble to form an active enzyme (such as C4b•2a, the substrate of which is C3). As with the complement system, the clotting, generating, and fibrolytic systems are each subject to very tight regulation by a series of inhibitors designed to prevent excessive product formation when one of the cascades is activated.

OUTCOMES OF THE ACUTE INFLAMMATORY RESPONSE AND DISORDERED RESPONSES

A clinical example of an acute inflammatory response that is not adequately contained is the acute respiratory distress syndrome (ARDS) in humans where there is a sustained accumulation of PMNs within the distal airway (alveolar) compartment. ARDS occurs in adults and in infants in a variety of clinical

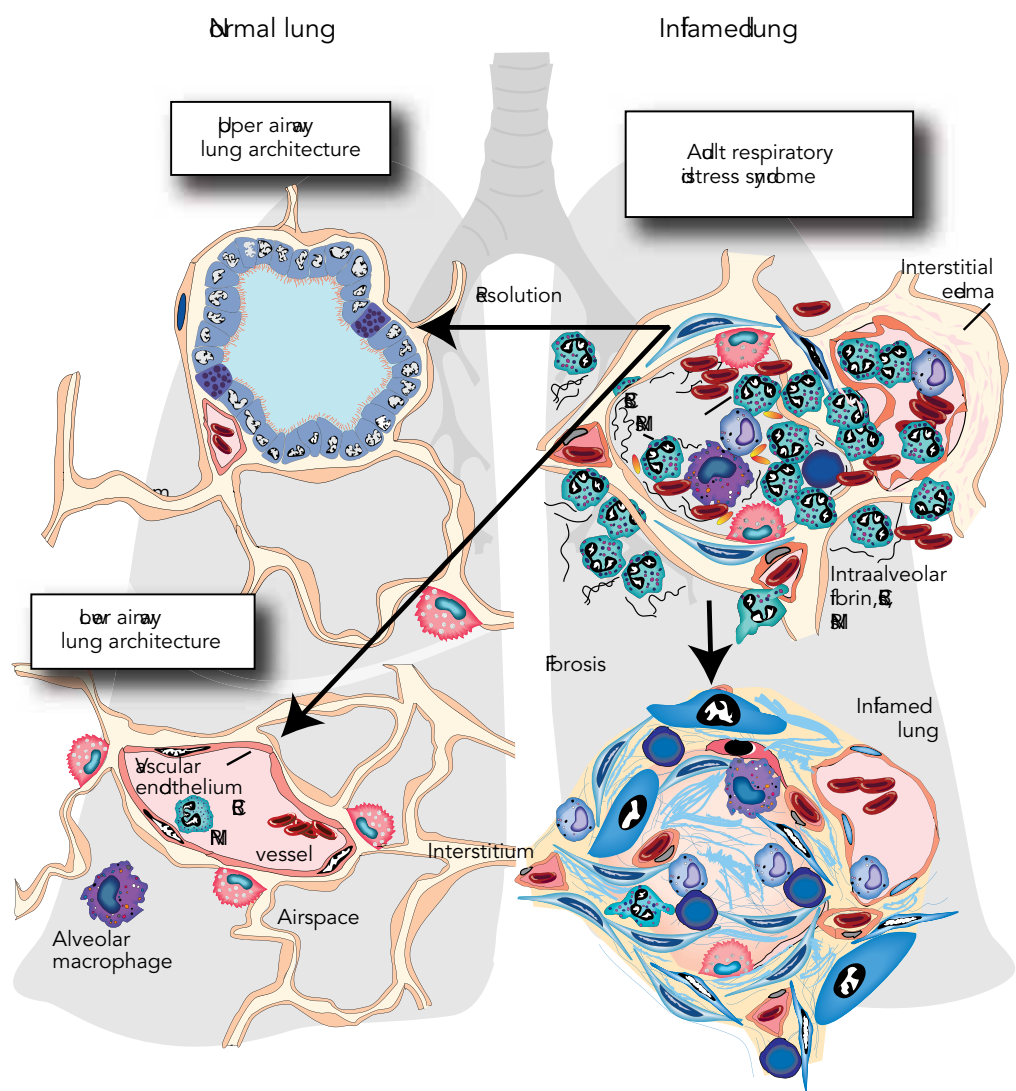


Figure 1.8. Outcomes of the acute inflammatory response in lung in ARDS in humans. In ARDS, edema fluid, fibrin, and PMNs accumulate in the alveolar compartment (upper right area). The inflammatory response can regress (undergo resolution) with return of the lung to its preinflammatory state (lower left area), or it may progress to extensive pulmonary fibrosis (lower right area).

situations, such as premature birth and polytrauma and bacterial pneumonia in adults. The mechanisms responsible for the development of ARDS are very poorly understood. ARDS can be considered to be a sustained and dangerous inflammatory condition in the lung. Bronchoalveolar fluids contain an abundance of PMNs, fibrin split products, and C5a. There is no known specific therapy for ARDS, only supportive treatment (mechanical ventilation, fluid therapy, etc.). ARDS may proceed to resolution or to pulmonary fibrosis that is often fatal (Figure 1.8). The pulmonary infiltrates in ARDS patients often lead to a radiographic “whiteout” in lungs, due to alveolar edema, PMNs accumulation, and fibrin deposition, collectively causing severely compromised gas exchange between the alveolar and vascular compartments, resulting in a high mortality rate. Why some cases of ARDS resolve completely (Figure 1.8) while

others progress to pulmonary fibrosis and pulmonary arterial hypertension (Figure 1.8, lower right frame) is entirely obscure. Another clinical example in which the acute inflammatory response is not sufficiently contained is in the setting of sepsis, following bacterial or viral pneumonia, intestinal perforation, or any number of other clinical situations. Sepsis occurs in all age groups and is age related, commonly seen in patients who are immunocompromised (postchemotherapy or age related). The death rate can be as high as 60%. Over the past decade there has been a progressive rise in the incidence of sepsis, which has been linked with bacteria, both Gram-positive (such as *Staphylococcus aureus*) and Gram-negative (such as *E. coli*), viruses, and fungi. Sepsis is clearly a condition in which there has been loss in control of the inflammatory system. For instance, there is a surge of proinflammatory mediators (e.g., $\text{TNF}\alpha$, $\text{IL-1}\beta$, IL-6 ,

etc.) in the plasma, referred to as the “cytokine storm,” although, the cause for high levels of these mediators is poorly understood. The vasculature undergoes upregulation of adhesion molecules for leukocytes. Tissue macrophages are “primed” and show excessive responses (e.g., production of oxygen free radicals, granule enzyme release, etc.). Blood PMNs express high levels of adhesion molecules such as CD11b/CD18 on their surfaces, which indicate PMN activation. In sepsis, there is extensive evidence of complement activation and consumptive coagulopathy (activation of the clotting system with depletion of the clotting factors) based on products measurable in plasma. Why the body has lost control of the inflammatory system during sepsis is entirely unknown. Currently, in addition to traditional supportive therapy (fluid resuscitation, ventilatory support, broad spectrum antibiotics, etc.), only a single drug (activated protein C, APC) has been approved for therapy in sepsis. Because APC is an anticoagulant and most septic patients have consumptive coagulopathy, APC is of limited value in sepsis.

FUNCTIONAL CONSEQUENCES OF THE ACUTE INFLAMMATORY RESPONSE

Once the acute inflammatory response has been triggered in tissues, it is important to understand the consequences. Initially, the acute inflammatory response can be triggered by the presence of infectious agents such as bacteria. The rapid build-up of plasma constituents in the lung alveolar space results in accumulation of antibodies, complement proteins, clotting factors, and other factors that may assist in containment of microorganisms. Traumatic injury triggers an acute inflammatory response in a locale, although in spite of the localized nature of this response, there are often systemic symptoms such as fever, increased numbers of circulating neutrophils (neutrophilia), increased heart rate (tachycardia), and sometimes a feeling of anxiety and apprehension. The local consequences of traumatic injury are well known. The common situation of a sprained ankle results in increased blood flow to the local area which is characterized by redness and increased local temperature. Soon, extensive edema develops, causing soft tissue swelling and pain in the joint area which prevents a full range of motion. Induration (increased thickness of soft tissue) is due to the accumulation of leukocytes and edema fluid. Occasionally, hemorrhage may develop. As described earlier, the acute inflammatory response may resolve with ultimate removal of cell debris, fibrin, red cells, and disappearance of leukocytes. Well-known therapy consists of immobilization of the joint and application of localized cold temperature to reduce blood flow to the area. (The inflammatory response absolutely requires accelerated blood flow to the area.)

Sometimes, the acute inflammatory response will not resolve for various reasons, such as the inability to clear an infectious agent whose contained presence will “fan” the flames of the inflammatory response, resulting in persistent and sometimes increasing intensity of inflammation. Ischemia–reperfusion of any organ or region will trigger an acute inflammatory response during the phase of reperfusion when sufficient blood flow is occurring to allow formation of edema and extravascular accumulation of leukocytes, primarily neutrophils. Toxic agents are well known to be able to cause tissue injury and unleash an inflammatory response. In the liver, excessive ingestion of acetaminophen, which is metabolized by liver into free radical intermediates, can result in hepatocellular toxicity (necrosis). If the dose of the ingested drug is limited, the liver can regenerate and replace the lost hepatocytes. Weeks or months later, little evidence of the cell destructive events after drug ingestion may be apparent if regeneration is successful. If the dose of

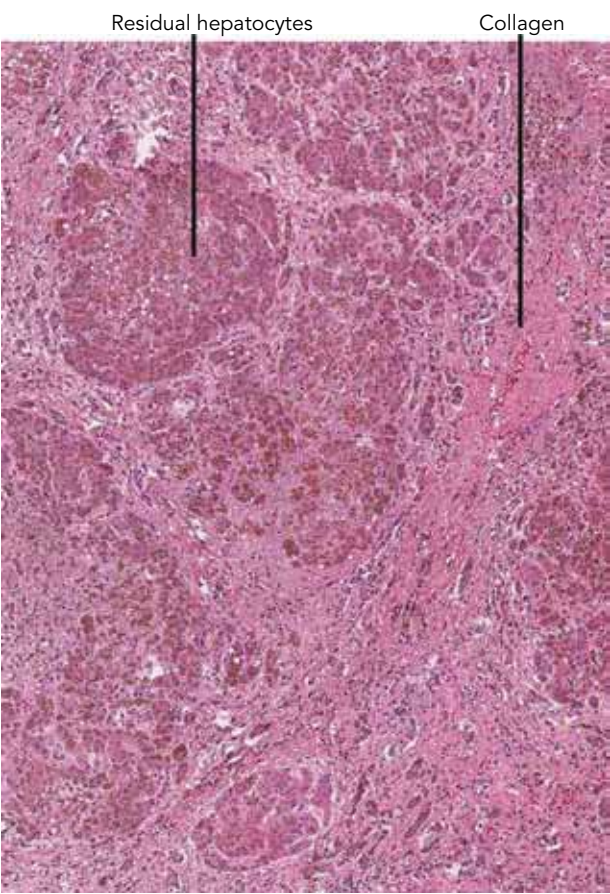


Figure 1.9. Postalcoholic cirrhotic liver. There are residual lobules of hepatocytes, with dense bands of collagenous scar surrounding some lobules and infiltrating others. The presence of dense collagenous scars interferes with the ability of residual hepatocytes to regenerate and restore damaged or destroyed hepatic lobules.