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Inflammatory Response Plays a Role in Innate Immunity: A Narrative Literature Review

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Abstract

The inflammatory response is the rapid initiation and interplay between the humoral (blood-soluble) and cellular systems designed to limit the extent of tissue damage, destroy infectious microorganisms, initiate an adaptive immune response, and initiate the healing process. This review aims to comprehensively outline the role of the inflammatory response in innate immunity. Three key plasma protein systems are important for an effective inflammatory response. These are the complement system, the fibrinolytic system, and the kinin system. Although each system has a unique role in inflammation, they also have many things in common. Each system consists of several proteins in the blood. To prevent activation in unnecessary situations, each protein is usually in an inactive form. Some proteins are enzymes that circulate in an inactive form as proenzymes. Each system contains several proteins that can be activated at the onset of inflammation. Cells of the innate and acquired immune system are recruited and activated by biochemical mediators produced at the site of cell damage. These molecules come from destroyed or damaged cells, contaminating microbes, activation of plasma protein systems, or secretion by other cells of the innate or acquired immune system. Activation may result in cells acquiring important functions for the inflammatory response or induction of the release of additional cellular products that enhance inflammation, or both. Inflammatory cells and various protein systems (complement, kinin, and clotting), together with the substances they produce, act at the site of tissue injury to limit the extent of damage, kill microorganisms, and eliminate debris in preparation for healing: tissue regeneration or repair.

Keywords: Inflammatory, Plasma Protein System, Innate Immunity

1. Introduction

The body's defense system is a series of mechanisms from the body for the elimination of various aspects of threats from the external environment, either in the form of the threat of microorganisms or various environmental stimuli both physical or chemical. The body has two main defense systems, namely innate immunity and adaptive immunity. Innate immunity is an immune response that is always ready to provide protection against various threats from outside, while adaptive immunity provides protection after first being done. The process of activating and activating adaptive immunity takes time. ¹

Natural physical, mechanical and biochemical barriers present an immediate and static innate immunity response. If this natural barrier has not been able to optimally provide protection, then the inflammatory response presents a more dynamic innate immunity response. The inflammatory response is programmed to respond to cell or tissue damage, whether the damaged tissue is septic (contaminated with microorganisms) or sterile. The inflammatory response is the rapid initiation and interplay between the humoral (blood-soluble) and cellular systems designed to limit the extent of tissue damage, destroy infectious microorganisms, initiate an adaptive immune response, and initiate the healing process. The inflammatory response has the following properties: (1) occurs in tissues with blood supply (vascularization); (2) activated quickly (within seconds) after damage occurs; (3) depending on the activity of *cellular and chemical components*, including plasma proteins; and (4) nonspecific, meaning that it occurs in approximately the same way regardless of the type of stimulus or whether exposure to the same stimulus has occurred in the past. ² This review aims to comprehensively outline the role of the inflammatory response in innate immunity.

Vascular Response

Almost any injury to the vascularized tissue will activate inflammation. Injury can occur due to a variety of causes including infection or necrosis (e.g., trauma, lack of oxygen [ischemia], nutritional deficiencies, genetic or immune defects, chemical injury, foreign bodies, temperature extremes, ionizing radiation). Classic symptoms of acute inflammation include redness (erythema), heat, swelling (edema), and pain. These tetrads represent the main sign of inflammation and were identified in the first century by a Roman writer, Celsus. The fifth sign is added later: the loss of function. Microscopically, inflammatory changes can be seen at the vascular level. Three characteristic changes in microcirculation (arterioles, capillaries, and venules) near

the injury site are as follows: 1. Vasodilation (an increase in the size of blood vessels) causes a slower blood velocity and increases blood flow to the injured site. 2. Increased vascular permeability (blood vessels become porous due to endothelial cell contraction) and leakage of fluid out of blood vessels (exudation) causing swelling (edema) at the site of injury; As plasma moves out, the blood in the microcirculation becomes thicker and flows more slowly, and the increase in blood flow and the increase in the concentration of red blood cells at the site of inflammation cause increased redness (erythema) and local warmth. 3. White blood cells attach to the inner wall of blood vessels, and they migrate through enlarged connections between endothelial cells lining blood vessels to surrounding tissues (diapedesis).³

The inflammatory effect is noticeable in seconds. First, the arterioles near the site of infection or injury briefly narrow. Vasodilation then causes a slower blood velocity and increases local blood flow to the site of injury. Increased capillary flow and permeability result in plasma leakage from blood vessels, causing edema of surrounding tissues. As the plasma moves out, the blood remaining in the microcirculation flows more slowly and becomes thicker. Increased blood flow and increased concentration of red blood cells at the site of inflammation lead to a local increase in warmth and redness. Leukocytes attach to the walls of blood vessels. At the same time, biochemical mediators (e.g., histamine, bradykinin, leukotrienes, prostaglandins) stimulate endothelial cells lining capillaries and venules to retract, creating space at the junction between cells, allowing leukocytes and plasma to enter surrounding tissues (intercellular junctions).⁴

Any characteristic changes associated with inflammation are a direct result of the activity and interaction of a number of chemicals and cellular components found in the blood and tissues. Vascular changes deliver leukocytes (especially neutrophils), plasma proteins, and other biochemical mediators to the site of injury where they work together.

Inflammatory benefits include: 1. Prevention of infection and further damage by contaminating microorganisms through the ingress of fluids to dilute toxins produced by bacteria and released from dying cells, entry and activation of plasma protein systems that help destroy and contain bacteria (e.g., complement system, fibrinolytic system), and entry of cells (e.g., neutrophils, macrophages) that phagocytose and destroys cellular debris and infectious agents. 2. Restriction and control of inflammatory processes through the inclusion of plasma protein systems (e.g., clotting system), plasma enzymes, and cells (e.g., eosinophils) that prevent the inflammatory response from spreading to healthy tissue areas. 3. Interaction with components of the adaptive

immune system to elicit a more specific response to contaminating pathogens through the entry of macrophages and lymphocytes. 4. Preparation of the injured area for healing through the removal of bacterial products, dead cells and other inflammatory products (for example, through channels through the epithelium or drainage by lymphatic vessels) and initiation of healing and repair mechanisms. ⁵

Extravascular fluid and debris that accumulate in the inflamed place are secreted by the lymphatic vessels. This process also facilitates the development of adaptive immunity because microbial antigens in the lymphatic fluid pass through the lymph nodes, where they activate B and T lymphocytes. Lymphangitis of lymph vessels and lymphadenitis of lymph nodes, which become hyperplastic, enlarged and often painful.

Inflammation and repair can be divided into several phases. The characteristics of the initial inflammatory response (i.e., acute) are different from subsequent (i.e., chronic) responses, and each phase involves different biochemical mediators and cells functioning together. The acute inflammatory response is short-lived; that is, it continues only until the immediate threat to the host is eliminated. This process usually takes 8 to 10 days from start to healing. ⁶

Plasma Protein System

Three key plasma protein systems are important for an effective inflammatory response. These are the complement system, the freezing system, and the kinin system. Although each system has a unique role in inflammation, they also have many things in common. Each system consists of several proteins in the blood. To prevent activation in unnecessary situations, each protein is usually in an inactive form. Some proteins are enzymes that circulate in an inactive form as proenzymes. Each system contains several proteins that can be activated at the onset of inflammation. Activation of the first component of a system results in sequential activation of other components, leading to biological functions that help protect the individual. This sequential activation is referred to as *a cascade*. So, we are referring to the complement cascade, freezing cascade, or kinin cascade. In some cases, activation of a protein may require it to be enzymatically cut into two pieces or fragments of different sizes. Usually larger fragments continue the cascade by activating the next component, and smaller fragments often have strong biological activity to trigger inflammation. ⁷

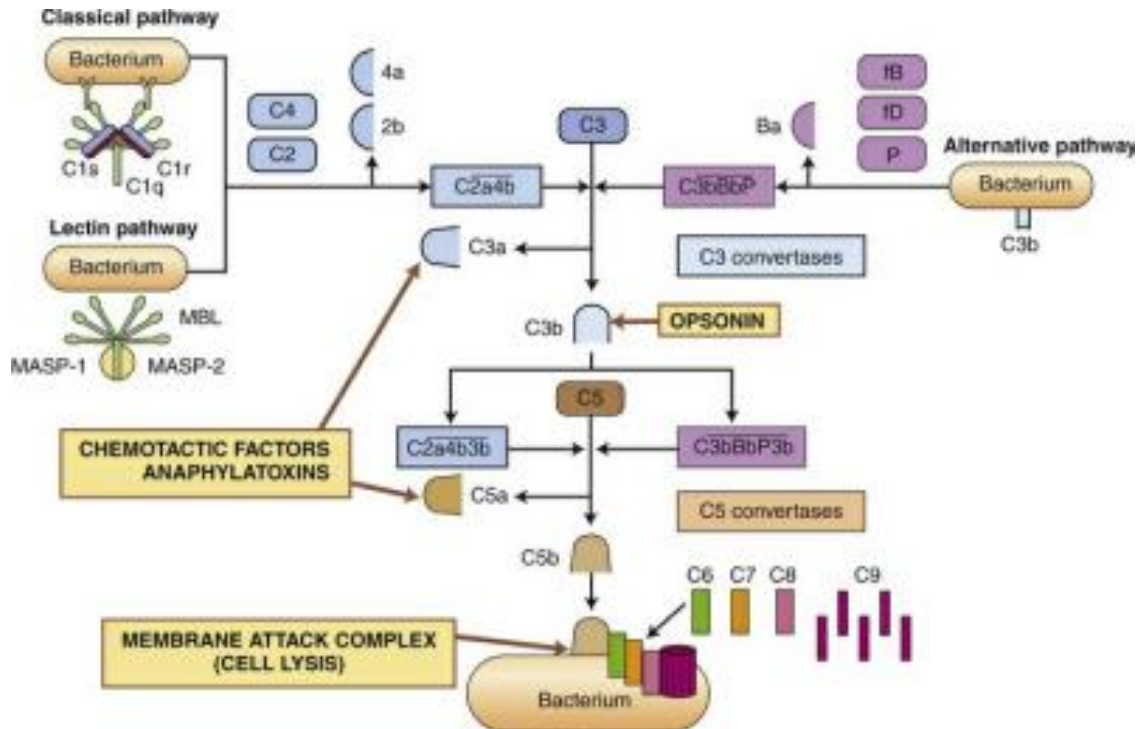


Figure 1. Complementary cascade activation path. The complement system is enabled by three paths: the classical path, the lectin path, and the alternate path. During activation, many complement components are broken down into fragments (2b, 4a, Ba, C3a, and C5a). Smaller fragments often have strong biological activity and can serve as larger activated chemotactic and anaphylatoxin factors. The fragments are usually converted into active enzymes (indicated by the bar above the name) and form complexes with additional components in the cascade. The classical pathway is usually activated by an antigen-antibody complex via the C1 component, which consists of C1q and two molecules of C1r and C1s. As shown, C1q must simultaneously bind to two antibody molecules (indicated by a Y-shaped structure). The lectin pathway is activated by mannose-binding lectin (*MBL*), which binds two mannose-rich pathogen-related molecular patterns on the bacterial surface. *MBL* contains two related enzymes, *MASP-1* and *MASP-2*, and functions in a similar way to C1. C1 and *MBL* enable the C4 and C2 complement components, respectively. Alternative pathways are activated by many agents, such as bacterial polysaccharides, which bind to and stabilize C3b, resulting from the normal breakdown of C3 in the blood. C3b forms the binding site of factor B (*fB*), which is activated by factor D (*fD*) into Bb and small fragments of Ba. Properdin (*P*) helps stabilize the complex. Each pathway produces C3 and C5

convertases, which are active complexes of enzymes that activate C3 and C5, respectively. The C3b produced by the C3 convertase can function as opsonin. C5b initiates a collection of membrane attack complexes (MACs), which produce several C9 molecules that form pores in the bacterial membrane.

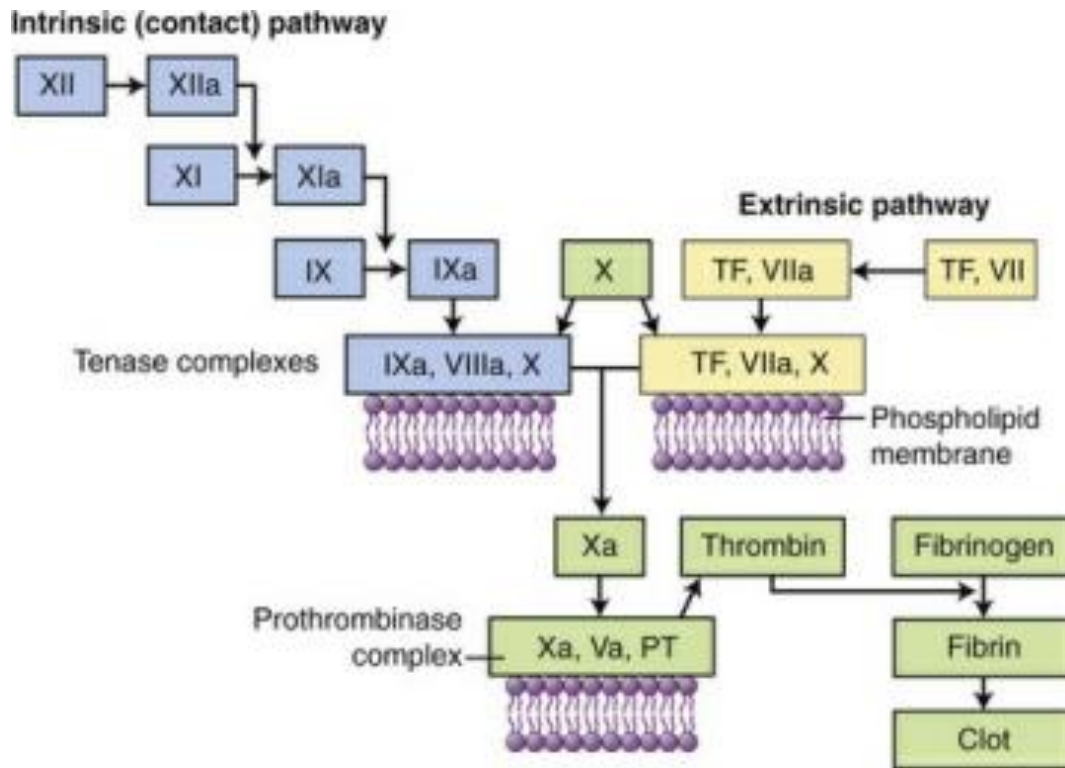


Figure 2. Coagulation Cascade. Freezing is activated through two pathways: the intrinsic (contact) pathway and the extrinsic pathway. The intrinsic pathway is initiated by the activation of Hageman factor (*XII*) to *XIIa* (the activated factor is an enzyme and is indicated by a lowercase a). Sequential activation of other components of the intrinsic pathway results in the formation of *IXa*, *VIIIa*, and *X* complexes. *TF* complexes with factor *VII*, which are activated (*VIIa*) and form complexes with factor *X* (*TF, VIIa, X*). The complex of intrinsic and extrinsic pathways are both calcium-dependent, formed on phospholipid membranes rich in phosphatidylserine, and have "tenase" activity (can activate factor *X* to *Xa*). Factor *X* initiates a general pathway in which *Xa* complexes with *Va* and prothrombin (*PT*), with calcium and phospholipid membranes, to form active prothrombinase (activating prothrombin to thrombin). Thrombin is an enzyme that cuts high molecular weight fibrinogen into fibrin molecules. Fibrin polymerizes to form clots.

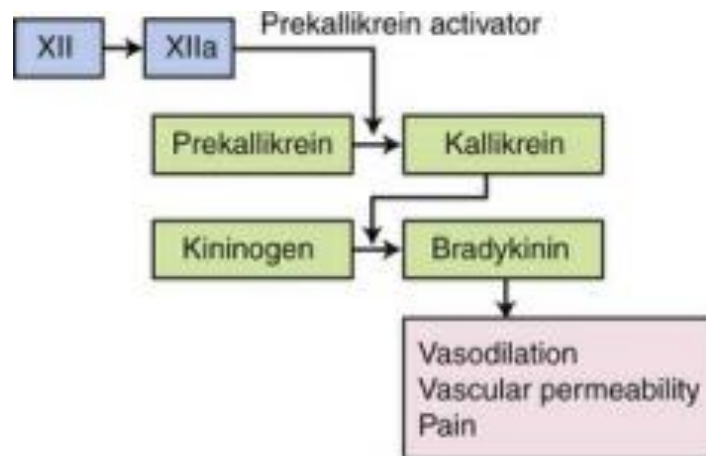


Figure 3. Kinin plasma cascade. The kinin pathway is activated by factor XIIa of the clotting system, which functions as an enzyme (prekallikrein activator) to convert prekallikrein into calicrein. Enzymatically active kallikrein converts kininogen into bradykinin.

Complement System

The complement system consists of several plasma proteins (sometimes called complement components) that together constitute about 10% of the total circulating serum proteins. Activation of the complement system produces several factors that can destroy pathogens directly and can activate or collaborate with other components of the innate and adaptive immune response. The factors produced during the activation of the complement system are one of the body's most powerful defenses, especially against bacterial infections.

Activation of the complement system can be achieved in three different pathways, all of which converge in the third component pathway (C3): 1. Classic pathway: activated by adaptive immune system proteins (antibodies) bound to their specific target (antigen). 2. Lectin pathway: activated by bacterial carbohydrates containing mannose. 3. Alternative pathway: activated by gram-negative bacteria and fungal cell wall polysaccharides. *Activation of the classical pathway* begins with activation of complement protein C1 and is preceded by the formation of complexes between antigens and antibodies to form antigen-antibody complexes (immune complexes). An antigen may be a unique chemical component of the surface of bacteria or other microorganisms. Most pathogens express many antigens; Therefore, several antibodies are usually bound in a complex. The first component of the classical complement cascade, C1, has six sites that can bind to antibodies, and efficient activation of the complement cascade usually requires simultaneous

binding of C1 to at least two antibody molecules. The complex formed by the complement bond of C1 antigen-antibodies is a macromolecular complex consisting of C1q and two molecules of C1r and C1s respectively. Conformational changes in C1 produce enzymatically active molecules whose substrates are C4 and C2. Complexes resulting from the interaction of C1, C4, and C2 use C3 as substrate, resulting in the production of C3a and C3b. Complexes that have C3 as substrate are generally referred to as C3 convertases. The addition of C3b to the complex converts the specificity of the substrate to C5, resulting in the conversion of C5 to C5a and C5b. Complexes that have C5 as a substrate are generally called C5 convertases. So C1 activation initiates sequential enzymatic activation of all other components of the classical pathway, ultimately resulting in C5 activation. The classical pathway can also be activated to a lesser extent by biological molecules other than antibodies, including heparin (a charged molecule that prevents clotting), deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), and C-reactive protein, which increases in the blood during inflammation. ^{8,9}

Even under normal conditions, small amounts of circulating C3 are spontaneously broken down into C3b and C3a by a number of natural enzymes in the blood. The level of spontaneous activation of C3 is generally very low, and C3b is readily inactivated by complement regulatory proteins in the blood (e.g., factor H and factor I). However, materials produced by some infectious microorganisms (e.g., lipopolysaccharides [endotoxins] on bacterial surfaces, yeast cell wall carbohydrates [zymosans]) can bind to naturally produced C3b and protect it from inactivation. This will initiate activation of the alternate complement path. C3b bound to bacterial products can react with another normally occurring component, factor B. The C3b and factor B complexes are recognized by an enzyme, factor D, which activates factor B, producing factor Bb. The resulting C3b/Bb complex is very unstable unless it binds to propeptidase (P). The C3b/Bb/P complex is a C3 convertase that produces further C3b, resulting in a C3b/Bb/P/C3b complex that is a C5 convertase, which activates C5.

The lectin pathway is similar to the classical pathway but does not rely on antibodies. It is activated by a plasma protein called mannose-binding lectin (MBL). MBL is similar to C1q and binds to mannose carbohydrate-containing bacterial polysaccharides and activates complement via two MBL-associated serine proteases (MASP-1 and MASP-2) that replace C1r and C1s and activate C4 and C2 to make C3 convertase. Thus, infectious agents that do not activate alternative pathways may be susceptible to supplementing via lectin pathways. After C5 activation, the

cascade continues through terminal components C6, C7, C8, and C9. C5b to C9 components come together to form complexes (*membrane attack*, or *MAC*) capable of creating pores in the cell membrane and allowing water and ions to enter and ultimately resulting in cell lysis. ¹⁰

The most important result of complement activation is the production of fragments during C4, C2, C3, and C5 activation. The C4a, C2b, C3a, and C5a fragments are soluble and low-weight molecules that contribute in other ways to the inflammatory response. C2b affects smooth muscle, causing vasodilation and increased vascular permeability. C3a and C5a, and to some extent C4a, are anaphylatoxins; That is, those that induce rapid degranulation of mast cells (release of granular contents) and release of histamine, causing vasodilation and increased capillary permeability. C5a is the primary chemotaxis factor for neutrophils. C3a is approximately 100 times stronger in chemotactic and anaphylactic activity. Chemotactic factors are biochemical substances that attract leukocytes to the site of inflammation. ¹¹

The dual function of chemotactic factor and anaphylatoxin is not required simultaneously or to the same degree. Anaphylatoxic activity is necessary at the onset of inflammation and occurs near the site of inflammation to induce local mast cell degranulation and to increase the number of dissolved mediators available to increase vascular permeability and vasodilation. Chemotactic activity, on the other hand, is necessary for a longer period and occurs in the distal part of the inflammatory site to pull leukocytes from circulation. It is therefore beneficial for an effective inflammatory response to limit the range of anaphylactic activity while allowing broad chemotactic activity. A plasma enzyme, a carboxypeptidase, removes terminal arginine on peptides C3a and C5a, thus producing "C3a desArg" and "C5a desArg," respectively, which are inactive as anaphylatoxins but retain chemotactic activity. Thus chemotactic activity is maintained, while not inducing distal mast cell degranulation that would result in a considerable enlargement of the inflammatory response detrimental to surrounding healthy tissue.

C3b adheres to the surface of pathogenic microorganisms and serves as an efficient opsonin. Opsonin is a molecule that "tags" microorganisms for destruction by cells of the inflammatory system (mainly neutrophils and macrophages). C3b on the cell surface can also be broken down by some enzymes in the blood into inactive fragments (e.g., iC3b), which maintain opsonic activity. In summary, the complement cascade can be activated by at least three different ways, and its products have four functions: (1) anaphylactic activity resulting in mast cell degranulation

(C3a, C3b), (2) leukocyte chemotaxis (C5a), (3) opsonization (C3b), and (4) cell lysis (C5b-C9, MAC).¹²

Freezing System

The clotting (coagulation) system is a group of plasma proteins that, when activated sequentially, form a blood clot at the injured or inflamed site. A blood clot is a tangle of protein strands (fibrin) that contain platelets (the main cellular initiators of clotting) and trap other cells, such as erythrocytes, phagocytes, and microorganisms. It (1) prevents the spread of infection to adjacent tissues, (2) traps microorganisms and foreign bodies at the site of inflammation for removal by infiltration cells (e.g., neutrophils and macrophages), (3) forms clots that stop bleeding, and (4) provides a framework for future repair and healing. The main substance in the interweaving of insoluble proteins called *fibrinfibrin* is which is the end product of the coagulation cascade.

The clotting system can be activated by many substances released during tissue injury and infection, including collagen, proteinase, calicrein, and plasmin, as well as by bacterial products such as endotoxins. Like the complement cascade, the coagulation cascade can be activated through different convergent pathways. The tissue factor (extrinsic) pathway is activated by tissue factor (TF) (also called *tissue thromboplastin*) which is released by damaged endothelial cells in blood vessels and reacts with activated factor VII (VIIa). The intrinsic (contact) pathway is activated when the vascular wall is damaged and the Hageman factor (factor XII) in plasma comes into contact with a negatively charged subendothelial substance. The pathway converges at factor X. Activation of factor X initiates a general pathway leading to activation of fibrin which polymerizes to form fibrin clots.

As with the complement system, activation of the clotting system produces protein fragments that enhance the inflammatory response. Two low molecular weight fibrinopeptides, A and B, are released from fibrinogen when fibrin is produced. Both fibrinopeptides (especially fibrinopeptide B) are chemotactic to neutrophils and increase the vascular permeability of endothelial cells by enhancing the effects of bradykinin (formed from the kinin system).^{13,14}

Kinin System

A third plasma protein system, the kinin system, increases inflammation in several ways. The main product of the kinin system is bradykinin, which causes dilation of blood vessels, works

with prostaglandins to stimulate nerve endings and induce pain, causes contraction of smooth muscle cells, increases vascular permeability, and can increase leukocyte chemotaxis. Bradykinin induces smooth muscle contractions more slowly than histamine and, together with E series prostaglandins, may be responsible for endothelial cell retraction and increased vascular permeability in later inflammatory phases.

The kinin system is activated by stimulation of the plasma kinin cascade. The conversion of plasma prekallikrein to calicreïn is induced by the *activator prekallikrein*, which is identical to factor XIIa (the product resulting from the activation of Hageman factor —factor XII) of the clotting cascade. Kallikrein then converts kininogen into bradykinin. Although the plasma kinin cascade is one pathway that leads to bradykinin production, tissue calcicreïn in saliva, sweat, tears, urine, and feces provides another source for these inflammatory mediators. This tissue calcicreïn converts serum kininogen into callidin, also known as Lys-bradykinin, which can be converted into *bradykinin* by plasma aminopeptidases. To limit the extent of inflammation, kinins are rapidly degraded by kininases which are enzymes present in plasma and tissues.¹⁵⁻¹⁷

Control and Interaction of Plasma Protein Systems

All three plasma protein systems are so interactive that activation of one system results in the production of a large number of very powerful biologically active substances that further activate other systems. Very tight control of this process is essential for two reasons: 1. The inflammatory process is essential for the survival of the individual; Thus, efficient activation must be guaranteed regardless of the cause of tissue injury. 2. The biochemical mediators produced during this process are very powerful and potentially detrimental to the individual, and their action should be strictly limited to injured or infected tissues.¹⁸

Various mechanisms are available to *enable* or *disable (regulate)* this plasma protein system. For example, plasma that enters tissues during inflammation (edema) contains enzymes that destroy inflammatory mediators. Carboxypeptidase inactivates the anaphylactic activity of C3a and C5a, and kininase degrades kinins. Histaminase degrades histamine and kallikrein and decreases the inflammatory response. Blood clot formation also activates the fibrinolytic system designed to limit the size of the clot and expel the clot once the bleeding stops. Thrombin activates plasminogen in the blood to form the plasmin enzyme. The main activity of plasmin is the degradation of fibrin polymers in the clot. However, plasmin can also activate the complement

cascade via components C1, C3, and C5 and the kinin cascade by activating factor XII and producing prekallikrein activators. Hageman factor activation has four effects that affect all three plasma protein systems: 1. Activation of the clotting cascade via factor XI, 2. Clotting control through conversion of plasminogen proactivator to plasminogen activator, resulting in plasmin generation, 3. Activation of the kinin system by activating Hageman factor (prekallikrein activator), 4. Activation of C1 in the complement cascade.

The activity of plasmin itself is also regulated because it is synthesized as a proenzyme, plasminogen. Plasminogen is converted into plasmin by several factors, including plasminogen activators produced from the caiccrein system, thrombin produced from the clotting system, bacterial factors such as streptokinase produced by hemolytic streptococci, plasminogen activators produced by endothelial cells, and some cellular enzymes released during tissue destruction. Another example of a common regulator is a C1-esterase inhibitor (C1-inh). C1-inh inhibits complement activation through reactivity with C1 (classical pathway), MASP-2 (lectin pathway), and C3b (alternative pathway). It is also a major inhibitor of components of clotting pathways and kinins (e.g., kalikrein, XIIa). Genetic defects in C1-inh (C1-inh deficiency) cause hereditary angioedema, which is self-healing edema of the skin and mucosal layers due to stress, disease, or relatively minor or invisible trauma. The disease is characterized by hyperactivation of all three plasma protein systems, although excessive bradykinin production appears to be the main cause of increased vascular permeability.¹⁹

Inflammatory Cellular Mediators

Inflammation is a process in the vascular network; Thus, cellular components are found in the blood and tissues around blood vessels. Blood vessels are lined with endothelial cells, which under normal conditions actively maintain normal blood flow. During inflammation, the vascular endothelium becomes the main coordinator of blood clotting and cell lines and fluid into tissues. The tissue close to the blood vessels contains mast cells, which are perhaps the most important inflammatory activators, and dendritic cells, which link innate and adaptive immune responses. Blood contains a complex mixture of cells. Blood cells are divided into erythrocytes (red blood cells), platelets, and leukocytes (white blood cells). Erythrocytes carry oxygen to tissues, and platelets are small cell fragments involved in blood clotting. Leukocytes are further divided into granulocytes (containing many cytoplasmic granules containing enzymes), monocytes, and

lymphocytes. Granulocytes are the most common leukocytes and are classified according to the type of staining required to visualize their granules (basophils, eosinophils and neutrophils). Monocytes in the blood are precursors of macrophages found in tissues. Different forms of lymphocytes participate in innate (e.g., natural killer cell [NK]) and adaptive immune responses (B and T cells).

Cells of the innate and acquired immune system are recruited and activated by biochemical mediators produced at the site of cell damage. These molecules come from destroyed or damaged cells, contaminating microbes, activation of plasma protein systems, or secretion by other cells of the innate or acquired immune system. Activation may result in cells acquiring important functions for the inflammatory response or induction of the release of additional cellular products that enhance inflammation, or both.²⁰

2. Conclusion

Inflammatory cells and various protein systems (complement, kinin, and clotting), together with the substances they produce, act at the site of tissue injury to limit the extent of damage, kill microorganisms, and eliminate debris in preparation for healing: tissue regeneration or repair.

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Submission acknowledgement

Dear author(s),

Rara Inggarsih, Rachmat Hidayat* has submitted the manuscript "Inflammatory Response Plays a Role in Innate Immunity: A Narrative Literature Review" to Open Access Indonesian Journal of Medical Reviews. The paper will be screened by editor and reviewed by peer review.

Cordially,

A handwritten signature in black ink, appearing to be "P. Magnano", is positioned to the left of the editor's name.

Prof. Paula Magnano, PhD

Editor



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Peer Review Results

Dear author(s),

Rara Inggarsih, Rachmat Hidayat* has submitted the manuscript
"Inflammatory Response Plays a Role in Innate Immunity: A Narrative
Literature Review" to Open Access Indonesian Journal of Medical
Reviews. The decision : Revision Required.

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Prof. Paula Magnano, PhD

Editor



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Inflammatory Response Plays a Role in Innate Immunity: A Narrative Literature

Review→1

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Abstract→3

The inflammatory response is the rapid initiation and interplay between the humoral (blood-soluble) and cellular systems designed to limit the extent of tissue damage, destroy infectious microorganisms, initiate an adaptive immune response, and initiate the healing process. This review aims to comprehensively outline the role of the inflammatory response in innate immunity. Three key plasma protein systems are important for an effective inflammatory response. These are the complement system, the fibrinolytic system, and the kinin system. Although each system has a unique role in inflammation, they also have many things in common. Each system consists of several proteins in the blood. To prevent activation in unnecessary situations, each protein is usually in an inactive form. Some proteins are enzymes that circulate in an inactive form as proenzymes. Each system contains several proteins that can be activated at the onset of inflammation. Cells of the innate and acquired immune system are recruited and activated by biochemical mediators produced at the site of cell damage. These molecules come from destroyed or damaged cells, contaminating microbes, activation of plasma protein systems, or secretion by other cells of the innate or acquired immune system. Activation may result in cells acquiring important functions for the inflammatory response or induction of the release of additional cellular products that enhance inflammation, or both. Inflammatory cells and various protein systems (complement, kinin, and clotting), together with the substances they produce, act at the site of tissue injury to limit the extent of damage, kill microorganisms, and eliminate debris in preparation for healing: tissue regeneration or repair.

Keywords: Inflammatory, Plasma Protein System, Innate Immunity→2

1.Introduction→4

The body's defense system is a series of mechanisms from the body for the elimination of various aspects of threats from the external environment, either in the form of the threat of microorganisms or various environmental stimuli both physical or chemical. The body has two main defense systems, namely innate immunity and adaptive immunity. Innate immunity is an immune response that is always ready to provide protection against various threats from outside, while adaptive immunity provides protection after first being done. The process of activating and activating adaptive immunity takes time. ¹

Natural physical, mechanical and biochemical barriers present an immediate and static innate immunity response. If this natural barrier has not been able to optimally provide protection, then the inflammatory response presents a more dynamic innate immunity response. The inflammatory response is programmed to respond to cell or tissue damage, whether the damaged tissue is septic (contaminated with microorganisms) or sterile. The inflammatory response is the rapid initiation and interplay between the humoral (blood-soluble) and cellular systems designed to limit the extent of tissue damage, destroy infectious microorganisms, initiate an adaptive immune response, and initiate the healing process. The inflammatory response has the following properties: (1) occurs in tissues with blood supply (vascularization); (2) activated quickly (within seconds) after damage occurs; (3) depending on the activity of *cellular and chemical components*, including plasma proteins; and (4) nonspecific, meaning that it occurs in approximately the same way regardless of the type of stimulus or whether exposure to the same stimulus has occurred in the past. ² This review aims to comprehensively outline the role of the inflammatory response in innate immunity.

Vascular Response

Almost any injury to the vascularized tissue will activate inflammation. Injury can occur due to a variety of causes including infection or necrosis (e.g., trauma, lack of oxygen [ischemia], nutritional deficiencies, genetic or immune defects, chemical injury, foreign bodies, temperature extremes, ionizing radiation). Classic symptoms of acute inflammation include redness (erythema), heat, swelling (edema), and pain. These tetrads represent the main sign of inflammation and were identified in the first century by a Roman writer, Celsus. The fifth sign is added later: the loss of function. Microscopically, inflammatory changes can be seen at the vascular level. Three characteristic changes in microcirculation (arterioles, capillaries, and venules) near

the injury site are as follows: 1. Vasodilation (an increase in the size of blood vessels) causes a slower blood velocity and increases blood flow to the injured site. 2. Increased vascular permeability (blood vessels become porous due to endothelial cell contraction) and leakage of fluid out of blood vessels (exudation) causing swelling (edema) at the site of injury; As plasma moves out, the blood in the microcirculation becomes thicker and flows more slowly, and the increase in blood flow and the increase in the concentration of red blood cells at the site of inflammation cause increased redness (erythema) and local warmth. 3. White blood cells attach to the inner wall of blood vessels, and they migrate through enlarged connections between endothelial cells lining blood vessels to surrounding tissues (diapedesis).³

The inflammatory effect is noticeable in seconds. First, the arterioles near the site of infection or injury briefly narrow. Vasodilation then causes a slower blood velocity and increases local blood flow to the site of injury. Increased capillary flow and permeability result in plasma leakage from blood vessels, causing edema of surrounding tissues. As the plasma moves out, the blood remaining in the microcirculation flows more slowly and becomes thicker. Increased blood flow and increased concentration of red blood cells at the site of inflammation lead to a local increase in warmth and redness. Leukocytes attach to the walls of blood vessels. At the same time, biochemical mediators (e.g., histamine, bradykinin, leukotrienes, prostaglandins) stimulate endothelial cells lining capillaries and venules to retract, creating space at the junction between cells, allowing leukocytes and plasma to enter surrounding tissues (intercellular junctions).⁴

Any characteristic changes associated with inflammation are a direct result of the activity and interaction of a number of chemicals and cellular components found in the blood and tissues. Vascular changes deliver leukocytes (especially neutrophils), plasma proteins, and other biochemical mediators to the site of injury where they work together.

Inflammatory benefits include: 1. Prevention of infection and further damage by contaminating microorganisms through the ingress of fluids to dilute toxins produced by bacteria and released from dying cells, entry and activation of plasma protein systems that help destroy and contain bacteria (e.g., complement system, fibrinolytic system), and entry of cells (e.g., neutrophils, macrophages) that phagocytose and destroys cellular debris and infectious agents. 2. Restriction and control of inflammatory processes through the inclusion of plasma protein systems (e.g., clotting system), plasma enzymes, and cells (e.g., eosinophils) that prevent the inflammatory response from spreading to healthy tissue areas. 3. Interaction with components of the adaptive

immune system to elicit a more specific response to contaminating pathogens through the entry of macrophages and lymphocytes. 4. Preparation of the injured area for healing through the removal of bacterial products, dead cells and other inflammatory products (for example, through channels through the epithelium or drainage by lymphatic vessels) and initiation of healing and repair mechanisms. ⁵

Extravascular fluid and debris that accumulate in the inflamed place are secreted by the lymphatic vessels. This process also facilitates the development of adaptive immunity because microbial antigens in the lymphatic fluid pass through the lymph nodes, where they activate B and T lymphocytes. Lymphangitis of lymph vessels and lymphadenitis of lymph nodes, which become hyperplastic, enlarged and often painful.

Inflammation and repair can be divided into several phases. The characteristics of the initial inflammatory response (i.e., acute) are different from subsequent (i.e., chronic) responses, and each phase involves different biochemical mediators and cells functioning together. The acute inflammatory response is short-lived; that is, it continues only until the immediate threat to the host is eliminated. This process usually takes 8 to 10 days from start to healing. ⁶

Plasma Protein System

Three key plasma protein systems are important for an effective inflammatory response. These are the complement system, the fibrinolytic system, and the kinin system. Although each system has a unique role in inflammation, they also have many things in common. Each system consists of several proteins in the blood. To prevent activation in unnecessary situations, each protein is usually in an inactive form. Some proteins are enzymes that circulate in an inactive form as proenzymes. Each system contains several proteins that can be activated at the onset of inflammation. Activation of the first component of a system results in sequential activation of other components, leading to biological functions that help protect the individual. This sequential activation is referred to as *a cascade*. So, we are referring to the complement cascade, fibrinolytic cascade, or kinin cascade. In some cases, activation of a protein may require it to be enzymatically cut into two pieces or fragments of different sizes. Usually larger fragments continue the cascade by activating the next component, and smaller fragments often have strong biological activity to trigger inflammation. ⁷

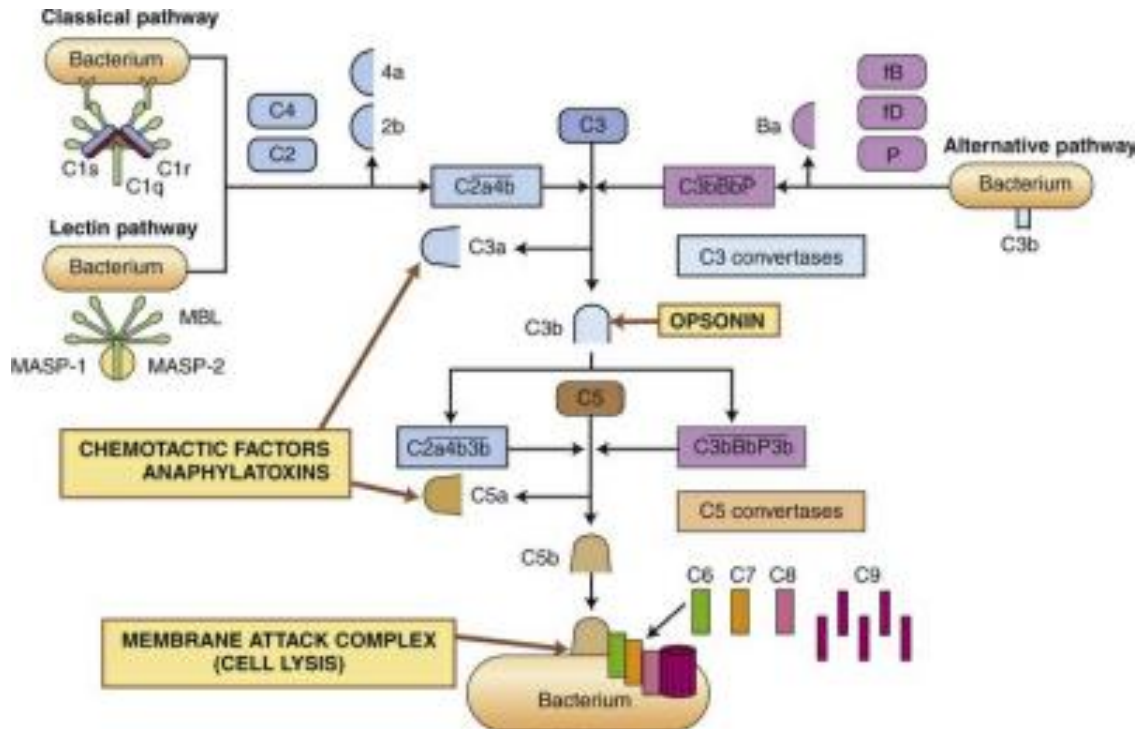


Figure 1. Complementary cascade activation path. The complement system is enabled by three paths: the classical path, the lectin path, and the alternate path. During activation, many complement components are broken down into fragments (2b, 4a, Ba, C3a, and C5a). Smaller fragments often have strong biological activity and can serve as larger activated chemotactic and anaphylatoxin factors. The fragments are usually converted into active enzymes (indicated by the bar above the name) and form complexes with additional components in the cascade. The classical pathway is usually activated by an antigen-antibody complex via the C1 component, which consists of C1q and two molecules of C1r and C1s. As shown, C1q must simultaneously bind to two antibody molecules (indicated by a Y-shaped structure). The lectin pathway is activated by mannose-binding lectin (MBL), which binds two mannose-rich pathogen-related molecular patterns on the bacterial surface. MBL contains two related enzymes, MASP-1 and MASP-2, and functions in a similar way to C1. C1 and MBL enable the C4 and C2 complement components, respectively. Alternative pathways are activated by many agents, such as bacterial polysaccharides, which bind to and stabilize C3b, resulting from the normal breakdown of C3 in the blood. C3b forms the binding site of factor B (fB), which is activated by factor D (fD) into Bb and small fragments of Ba. Properdin (P) helps stabilize the complex. Each pathway produces C3 and C5

convertases, which are active complexes of enzymes that activate C3 and C5, respectively. The C3b produced by the C3 convertase can function as opsonin. C5b initiates a collection of membrane attack complexes (MACs), which produce several C9 molecules that form pores in the bacterial membrane.

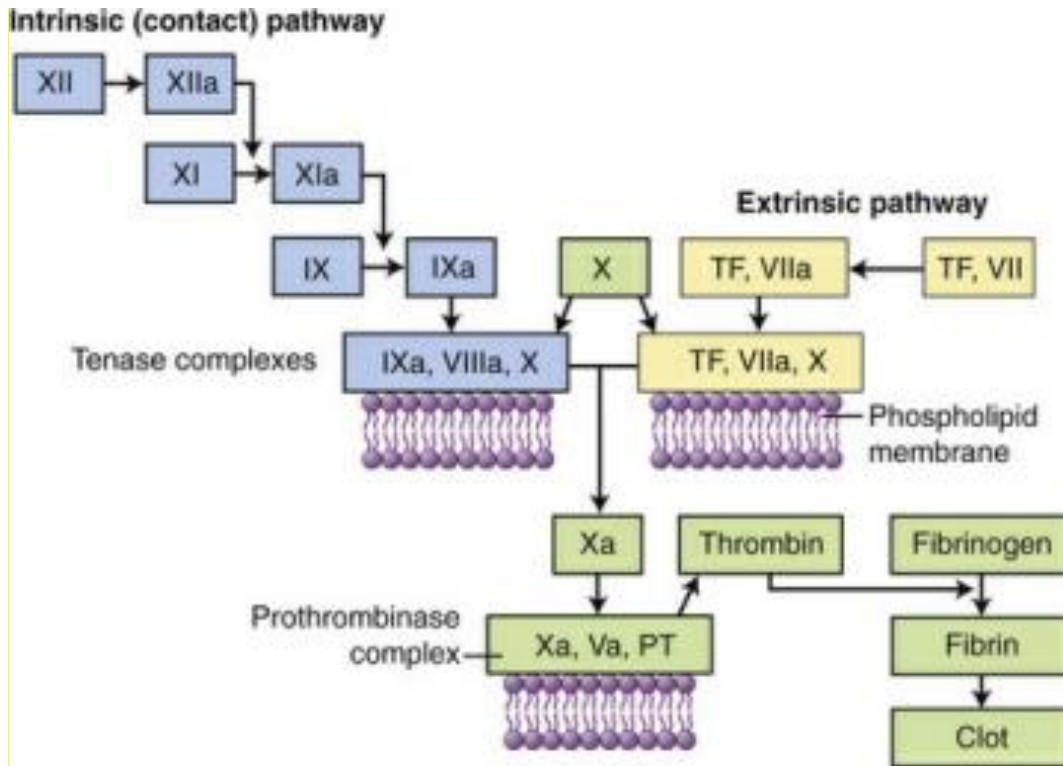


Figure 2. Coagulation Cascade. Freezing is activated through two pathways: the intrinsic (contact) pathway and the extrinsic pathway. The intrinsic pathway is initiated by the activation of Hageman factor (*XII*) to *XIIa* (the activated factor is an enzyme and is indicated by a lowercase a). Sequential activation of other components of the intrinsic pathway results in the formation of *IXa*, *VIIIa*, and *X* complexes. TF complexes with factor VII, which are activated (*VIIa*) and form complexes with factor X (*TF, VIIa, X*). The complex of intrinsic and extrinsic pathways are both calcium-dependent, formed on phospholipid membranes rich in phosphatidylserine, and have "tenase" activity (can activate factor X to *Xa*). Factor X initiates a general pathway in which *Xa* complexes with *Va* and prothrombin (*PT*), with calcium and phospholipid membranes, to form active prothrombinase (activating prothrombin to thrombin). Thrombin is an enzyme that cuts high molecular weight fibrinogen into fibrin molecules. Fibrin polymerizes to form clots.

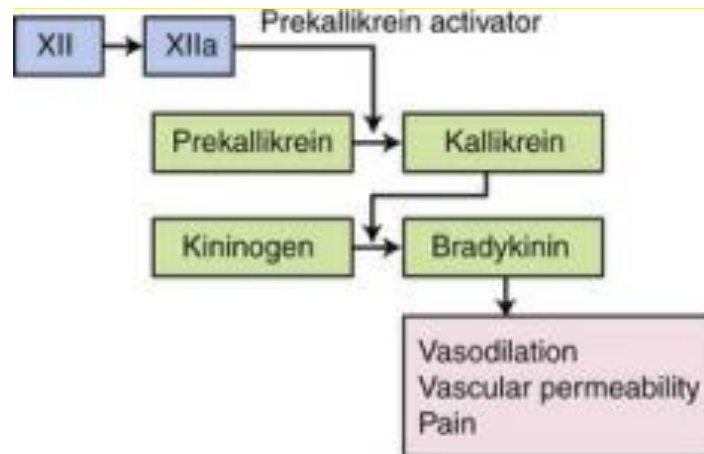


Figure 3. Kinin plasma cascade. The kinin pathway is activated by factor XIIa of the clotting system, which functions as an enzyme (prekallikrein activator) to convert prekallikrein into calicrein. Enzymatically active kallikrein converts kininogen into bradykinin.

Complement System

The complement system consists of several plasma proteins (sometimes called complement components) that together constitute about 10% of the total circulating serum proteins. Activation of the complement system produces several factors that can destroy pathogens directly and can activate or collaborate with other components of the innate and adaptive immune response. The factors produced during the activation of the complement system are one of the body's most powerful defenses, especially against bacterial infections.

Activation of the complement system can be achieved in three different pathways, all of which converge in the third component pathway (C3): 1. Classic pathway: activated by adaptive immune system proteins (antibodies) bound to their specific target (antigen). 2. Lectin pathway: activated by bacterial carbohydrates containing mannose. 3. Alternative pathway: activated by gram-negative bacteria and fungal cell wall polysaccharides. *Activation of the classical pathway* begins with activation of complement protein C1 and is preceded by the formation of complexes between antigens and antibodies to form antigen-antibody complexes (immune complexes). An antigen may be a unique chemical component of the surface of bacteria or other microorganisms. Most pathogens express many antigens; Therefore, several antibodies are usually bound in a complex. The first component of the classical complement cascade, C1, has six sites that can bind to antibodies, and efficient activation of the complement cascade usually requires simultaneous

binding of C1 to at least two antibody molecules. The complex formed by the complement bond of C1 antigen-antibodies is a macromolecular complex consisting of C1q and two molecules of C1r and C1s respectively. Conformational changes in C1 produce enzymatically active molecules whose substrates are C4 and C2. Complexes resulting from the interaction of C1, C4, and C2 use C3 as substrate, resulting in the production of C3a and C3b. Complexes that have C3 as substrate are generally referred to as C3 convertases. The addition of C3b to the complex converts the specificity of the substrate to C5, resulting in the conversion of C5 to C5a and C5b. Complexes that have C5 as a substrate are generally called C5 convertases. So C1 activation initiates sequential enzymatic activation of all other components of the classical pathway, ultimately resulting in C5 activation. The classical pathway can also be activated to a lesser extent by biological molecules other than antibodies, including heparin (a charged molecule that prevents clotting), deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), and C-reactive protein, which increases in the blood during inflammation.^{8,9}

Even under normal conditions, small amounts of circulating C3 are spontaneously broken down into C3b and C3a by a number of natural enzymes in the blood. The level of spontaneous activation of C3 is generally very low, and C3b is readily inactivated by complement regulatory proteins in the blood (e.g., factor H and factor I). However, materials produced by some infectious microorganisms (e.g., lipopolysaccharides [endotoxins] on bacterial surfaces, yeast cell wall carbohydrates [zymosans]) can bind to naturally produced C3b and protect it from inactivation. This will initiate activation of the alternate complement path. C3b bound to bacterial products can react with another normally occurring component, factor B. The C3b and factor B complexes are recognized by an enzyme, factor D, which activates factor B, producing factor Bb. The resulting C3b/Bb complex is very unstable unless it binds to propeptidase (P). The C3b/Bb/P complex is a C3 convertase that produces further C3b, resulting in a C3b/Bb/P/C3b complex that is a C5 convertase, which activates C5.

The lectin pathway is similar to the classical pathway but does not rely on antibodies. It is activated by a plasma protein called mannose-binding lectin (MBL). MBL is similar to C1q and binds to mannose carbohydrate-containing bacterial polysaccharides and activates complement via two MBL-associated serine proteases (MASP-1 and MASP-2) that replace C1r and C1s and activate C4 and C2 to make C3 convertase. Thus, infectious agents that do not activate alternative pathways may be susceptible to supplementing via lectin pathways. After C5 activation, the

cascade continues through terminal components C6, C7, C8, and C9. C5b to C9 components come together to form complexes (*membrane attack*, or *MAC*) capable of creating pores in the cell membrane and allowing water and ions to enter and ultimately resulting in cell lysis. ¹⁰

The most important result of complement activation is the production of fragments during C4, C2, C3, and C5 activation. The C4a, C2b, C3a, and C5a fragments are soluble and low-weight molecules that contribute in other ways to the inflammatory response. C2b affects smooth muscle, causing vasodilation and increased vascular permeability. C3a and C5a, and to some extent C4a, are anaphylatoxins; That is, those that induce rapid degranulation of mast cells (release of granular contents) and release of histamine, causing vasodilation and increased capillary permeability. C5a is the primary chemotaxis factor for neutrophils. C3a is approximately 100 times stronger in chemotactic and anaphylactic activity. Chemotactic factors are biochemical substances that attract leukocytes to the site of inflammation. ¹¹

The dual function of chemotactic factor and anaphylatoxin is not required simultaneously or to the same degree. Anaphylatoxic activity is necessary at the onset of inflammation and occurs near the site of inflammation to induce local mast cell degranulation and to increase the number of dissolved mediators available to increase vascular permeability and vasodilation. Chemotactic activity, on the other hand, is necessary for a longer period and occurs in the distal part of the inflammatory site to pull leukocytes from circulation. It is therefore beneficial for an effective inflammatory response to limit the range of anaphylactic activity while allowing broad chemotactic activity. A plasma enzyme, a carboxypeptidase, removes terminal arginine on peptides C3a and C5a, thus producing "C3a desArg" and "C5a desArg," respectively, which are inactive as anaphylatoxins but retain chemotactic activity. Thus chemotactic activity is maintained, while not inducing distal mast cell degranulation that would result in a considerable enlargement of the inflammatory response detrimental to surrounding healthy tissue.

C3b adheres to the surface of pathogenic microorganisms and serves as an efficient opsonin. Opsonin is a molecule that "tags" microorganisms for destruction by cells of the inflammatory system (mainly neutrophils and macrophages). C3b on the cell surface can also be broken down by some enzymes in the blood into inactive fragments (e.g., iC3b), which maintain opsonic activity. In summary, the complement cascade can be activated by at least three different ways, and its products have four functions: (1) anaphylactic activity resulting in mast cell degranulation

(C3a, C3b), (2) leukocyte chemotaxis (C5a), (3) opsonization (C3b), and (4) cell lysis (C5b-C9, MAC).¹²

Freezing System

The clotting (coagulation) system is a group of plasma proteins that, when activated sequentially, form a blood clot at the injured or inflamed site. A blood clot is a tangle of protein strands (fibrin) that contain platelets (the main cellular initiators of clotting) and trap other cells, such as erythrocytes, phagocytes, and microorganisms. It (1) prevents the spread of infection to adjacent tissues, (2) traps microorganisms and foreign bodies at the site of inflammation for removal by infiltration cells (e.g., neutrophils and macrophages), (3) forms clots that stop bleeding, and (4) provides a framework for future repair and healing. The main substance in the interweaving of insoluble proteins called *fibrin* is which is the end product of the coagulation cascade.

The clotting system can be activated by many substances released during tissue injury and infection, including collagen, proteinase, calicrein, and plasmin, as well as by bacterial products such as endotoxins. Like the complement cascade, the coagulation cascade can be activated through different convergent pathways. The tissue factor (extrinsic) pathway is activated by tissue factor (TF) (also called *tissue thromboplastin*) which is released by damaged endothelial cells in blood vessels and reacts with activated factor VII (VIIa). The intrinsic (contact) pathway is activated when the vascular wall is damaged and the Hageman factor (factor XII) in plasma comes into contact with a negatively charged subendothelial substance. The pathway converges at factor X. Activation of factor X initiates a general pathway leading to activation of fibrin which polymerizes to form fibrin clots.

As with the complement system, activation of the clotting system produces protein fragments that enhance the inflammatory response. Two low molecular weight fibrinopeptides, A and B, are released from fibrinogen when fibrin is produced. Both fibrinopeptides (especially fibrinopeptide B) are chemotactic to neutrophils and increase the vascular permeability of endothelial cells by enhancing the effects of bradykinin (formed from the kinin system).^{13,14}

Kinin System

A third plasma protein system, the kinin system, increases inflammation in several ways. The main product of the kinin system is bradykinin, which causes dilation of blood vessels, works

with prostaglandins to stimulate nerve endings and induce pain, causes contraction of smooth muscle cells, increases vascular permeability, and can increase leukocyte chemotaxis. Bradykinin induces smooth muscle contractions more slowly than histamine and, together with E series prostaglandins, may be responsible for endothelial cell retraction and increased vascular permeability in later inflammatory phases.

The kinin system is activated by stimulation of the plasma kinin cascade. The conversion of plasma prekallikrein to kallikrein is induced by the *activator prekallikrein*, which is identical to factor XIIa (the product resulting from the activation of Hageman factor —factor XII) of the clotting cascade. Kallikrein then converts kininogen into bradykinin. Although the plasma kinin cascade is one pathway that leads to bradykinin production, tissue kallikrein in saliva, sweat, tears, urine, and feces provides another source for these inflammatory mediators. This tissue kallikrein converts serum kininogen into kallidin, also known as Lys-bradykinin, which can be converted into *bradykinin* by plasma aminopeptidases. To limit the extent of inflammation, kinins are rapidly degraded by kininases which are enzymes present in plasma and tissues.¹⁵⁻¹⁷

Control and Interaction of Plasma Protein Systems

All three plasma protein systems are so interactive that activation of one system results in the production of a large number of very powerful biologically active substances that further activate other systems. Very tight control of this process is essential for two reasons: 1. The inflammatory process is essential for the survival of the individual; Thus, efficient activation must be guaranteed regardless of the cause of tissue injury. 2. The biochemical mediators produced during this process are very powerful and potentially detrimental to the individual, and their action should be strictly limited to injured or infected tissues.¹⁸

Various mechanisms are available to *enable* or *disable (regulate)* this plasma protein system. For example, plasma that enters tissues during inflammation (edema) contains enzymes that destroy inflammatory mediators. Carboxypeptidase inactivates the anaphylactic activity of C3a and C5a, and kininase degrades kinins. Histaminase degrades histamine and kallikrein and decreases the inflammatory response. Blood clot formation also activates the fibrinolytic system designed to limit the size of the clot and expel the clot once the bleeding stops. Thrombin activates plasminogen in the blood to form the plasmin enzyme. The main activity of plasmin is the degradation of fibrin polymers in the clot. However, plasmin can also activate the complement

cascade via components C1, C3, and C5 and the kinin cascade by activating factor XII and producing prekallikrein activators. Hageman factor activation has four effects that affect all three plasma protein systems: 1. Activation of the clotting cascade via factor XI, 2. Clotting control through conversion of plasminogen proactivator to plasminogen activator, resulting in plasmin generation, 3. Activation of the kinin system by activating Hageman factor (prekallikrein activator), 4. Activation of C1 in the complement cascade.

The activity of plasmin itself is also regulated because it is synthesized as a proenzyme, plasminogen. Plasminogen is converted into plasmin by several factors, including plasminogen activators produced from the caiccrein system, thrombin produced from the clotting system, bacterial factors such as streptokinase produced by hemolytic streptococci, plasminogen activators produced by endothelial cells, and some cellular enzymes released during tissue destruction. Another example of a common regulator is a C1-esterase inhibitor (C1-inh). C1-inh inhibits complement activation through reactivity with C1 (classical pathway), MASP-2 (lectin pathway), and C3b (alternative pathway). It is also a major inhibitor of components of clotting pathways and kinins (e.g., kalikrein, XIIa). Genetic defects in C1-inh (C1-inh deficiency) cause hereditary angioedema, which is self-healing edema of the skin and mucosal layers due to stress, disease, or relatively minor or invisible trauma. The disease is characterized by hyperactivation of all three plasma protein systems, although excessive bradykinin production appears to be the main cause of increased vascular permeability.¹⁹

Inflammatory Cellular Mediators

Inflammation is a process in the vascular network; Thus, cellular components are found in the blood and tissues around blood vessels. Blood vessels are lined with endothelial cells, which under normal conditions actively maintain normal blood flow. During inflammation, the vascular endothelium becomes the main coordinator of blood clotting and cell lines and fluid into tissues. The tissue close to the blood vessels contains mast cells, which are perhaps the most important inflammatory activators, and dendritic cells, which link innate and adaptive immune responses. Blood contains a complex mixture of cells. Blood cells are divided into erythrocytes (red blood cells), platelets, and leukocytes (white blood cells). Erythrocytes carry oxygen to tissues, and platelets are small cell fragments involved in blood clotting. Leukocytes are further divided into granulocytes (containing many cytoplasmic granules containing enzymes), monocytes, and

lymphocytes. Granulocytes are the most common leukocytes and are classified according to the type of staining required to visualize their granules (basophils, eosinophils and neutrophils). Monocytes in the blood are precursors of macrophages found in tissues. Different forms of lymphocytes participate in innate (e.g., natural killer cell [NK]) and adaptive immune responses (B and T cells).

Cells of the innate and acquired immune system are recruited and activated by biochemical mediators produced at the site of cell damage. These molecules come from destroyed or damaged cells, contaminating microbes, activation of plasma protein systems, or secretion by other cells of the innate or acquired immune system. Activation may result in cells acquiring important functions for the inflammatory response or induction of the release of additional cellular products that enhance inflammation, or both. ²⁰

2. Conclusion →5

Inflammatory cells and various protein systems (complement, kinin, and clotting), together with the substances they produce, act at the site of tissue injury to limit the extent of damage, kill microorganisms, and eliminate debris in preparation for healing: tissue regeneration or repair.

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Reviewer Comment:

1 → Title of Manuscripts should be explained main review and declared type of literature review: narrative or systematic review.

2 → Keywords should be showed the main words of the study, the authors can use MeSH to develop keywords.

3 → Abstract should be showed the main of background, main of review and conclusion of study.

4 → Introduction should be showed the urgency of study (epidemiology data), biological plausibility concept, and lack of knowledge in the study.

5 → Conclusion should more specific and not more showed more review.

6→ Authors must check the references for make update references. References should no more than 10 years.

Reviewer 2: Revision required

Inflammatory Response Plays a Role in Innate Immunity: A Narrative Literature

Review→1

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Abstract→3

The inflammatory response is the rapid initiation and interplay between the humoral (blood-soluble) and cellular systems designed to limit the extent of tissue damage, destroy infectious microorganisms, initiate an adaptive immune response, and initiate the healing process. This review aims to comprehensively outline the role of the inflammatory response in innate immunity. Three key plasma protein systems are important for an effective inflammatory response. These are the complement system, the fibrinolytic system, and the kinin system. Although each system has a unique role in inflammation, they also have many things in common. Each system consists of several proteins in the blood. To prevent activation in unnecessary situations, each protein is usually in an inactive form. Some proteins are enzymes that circulate in an inactive form as proenzymes. Each system contains several proteins that can be activated at the onset of inflammation. Cells of the innate and acquired immune system are recruited and activated by biochemical mediators produced at the site of cell damage. These molecules come from destroyed or damaged cells, contaminating microbes, activation of plasma protein systems, or secretion by other cells of the innate or acquired immune system. Activation may result in cells acquiring important functions for the inflammatory response or induction of the release of additional cellular products that enhance inflammation, or both. Inflammatory cells and various protein systems (complement, kinin, and clotting), together with the substances they produce, act at the site of tissue injury to limit the extent of damage, kill microorganisms, and eliminate debris in preparation for healing: tissue regeneration or repair.

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1.Introduction→4

The body's defense system is a series of mechanisms from the body for the elimination of various aspects of threats from the external environment, either in the form of the threat of microorganisms or various environmental stimuli both physical or chemical. The body has two main defense systems, namely innate immunity and adaptive immunity. Innate immunity is an immune response that is always ready to provide protection against various threats from outside, while adaptive immunity provides protection after first being done. The process of activating and activating adaptive immunity takes time. ¹

Natural physical, mechanical and biochemical barriers present an immediate and static innate immunity response. If this natural barrier has not been able to optimally provide protection, then the inflammatory response presents a more dynamic innate immunity response. The inflammatory response is programmed to respond to cell or tissue damage, whether the damaged tissue is septic (contaminated with microorganisms) or sterile. The inflammatory response is the rapid initiation and interplay between the humoral (blood-soluble) and cellular systems designed to limit the extent of tissue damage, destroy infectious microorganisms, initiate an adaptive immune response, and initiate the healing process. The inflammatory response has the following properties: (1) occurs in tissues with blood supply (vascularization); (2) activated quickly (within seconds) after damage occurs; (3) depending on the activity of *cellular and chemical components*, including plasma proteins; and (4) nonspecific, meaning that it occurs in approximately the same way regardless of the type of stimulus or whether exposure to the same stimulus has occurred in the past. ² This review aims to comprehensively outline the role of the inflammatory response in innate immunity.

Vascular Response

Almost any injury to the vascularized tissue will activate inflammation. Injury can occur due to a variety of causes including infection or necrosis (e.g., trauma, lack of oxygen [ischemia], nutritional deficiencies, genetic or immune defects, chemical injury, foreign bodies, temperature extremes, ionizing radiation). Classic symptoms of acute inflammation include redness (erythema), heat, swelling (edema), and pain. These tetrads represent the main sign of inflammation and were identified in the first century by a Roman writer, Celsus. The fifth sign is added later: the loss of function. Microscopically, inflammatory changes can be seen at the vascular level. Three characteristic changes in microcirculation (arterioles, capillaries, and venules) near

the injury site are as follows: 1. Vasodilation (an increase in the size of blood vessels) causes a slower blood velocity and increases blood flow to the injured site. 2. Increased vascular permeability (blood vessels become porous due to endothelial cell contraction) and leakage of fluid out of blood vessels (exudation) causing swelling (edema) at the site of injury; As plasma moves out, the blood in the microcirculation becomes thicker and flows more slowly, and the increase in blood flow and the increase in the concentration of red blood cells at the site of inflammation cause increased redness (erythema) and local warmth. 3. White blood cells attach to the inner wall of blood vessels, and they migrate through enlarged connections between endothelial cells lining blood vessels to surrounding tissues (diapedesis).³

The inflammatory effect is noticeable in seconds. First, the arterioles near the site of infection or injury briefly narrow. Vasodilation then causes a slower blood velocity and increases local blood flow to the site of injury. Increased capillary flow and permeability result in plasma leakage from blood vessels, causing edema of surrounding tissues. As the plasma moves out, the blood remaining in the microcirculation flows more slowly and becomes thicker. Increased blood flow and increased concentration of red blood cells at the site of inflammation lead to a local increase in warmth and redness. Leukocytes attach to the walls of blood vessels. At the same time, biochemical mediators (e.g., histamine, bradykinin, leukotrienes, prostaglandins) stimulate endothelial cells lining capillaries and venules to retract, creating space at the junction between cells, allowing leukocytes and plasma to enter surrounding tissues (intercellular junctions).⁴

Any characteristic changes associated with inflammation are a direct result of the activity and interaction of a number of chemicals and cellular components found in the blood and tissues. Vascular changes deliver leukocytes (especially neutrophils), plasma proteins, and other biochemical mediators to the site of injury where they work together.

Inflammatory benefits include: 1. Prevention of infection and further damage by contaminating microorganisms through the ingress of fluids to dilute toxins produced by bacteria and released from dying cells, entry and activation of plasma protein systems that help destroy and contain bacteria (e.g., complement system, fibrinolytic system), and entry of cells (e.g., neutrophils, macrophages) that phagocytose and destroys cellular debris and infectious agents. 2. Restriction and control of inflammatory processes through the inclusion of plasma protein systems (e.g., clotting system), plasma enzymes, and cells (e.g., eosinophils) that prevent the inflammatory response from spreading to healthy tissue areas. 3. Interaction with components of the adaptive

immune system to elicit a more specific response to contaminating pathogens through the entry of macrophages and lymphocytes. 4. Preparation of the injured area for healing through the removal of bacterial products, dead cells and other inflammatory products (for example, through channels through the epithelium or drainage by lymphatic vessels) and initiation of healing and repair mechanisms. ⁵

Extravascular fluid and debris that accumulate in the inflamed place are secreted by the lymphatic vessels. This process also facilitates the development of adaptive immunity because microbial antigens in the lymphatic fluid pass through the lymph nodes, where they activate B and T lymphocytes. Lymphangitis of lymph vessels and lymphadenitis of lymph nodes, which become hyperplastic, enlarged and often painful.

Inflammation and repair can be divided into several phases. The characteristics of the initial inflammatory response (i.e., acute) are different from subsequent (i.e., chronic) responses, and each phase involves different biochemical mediators and cells functioning together. The acute inflammatory response is short-lived; that is, it continues only until the immediate threat to the host is eliminated. This process usually takes 8 to 10 days from start to healing. ⁶

Plasma Protein System

Three key plasma protein systems are important for an effective inflammatory response. These are the complement system, the freezing system, and the kinin system. Although each system has a unique role in inflammation, they also have many things in common. Each system consists of several proteins in the blood. To prevent activation in unnecessary situations, each protein is usually in an inactive form. Some proteins are enzymes that circulate in an inactive form as proenzymes. Each system contains several proteins that can be activated at the onset of inflammation. Activation of the first component of a system results in sequential activation of other components, leading to biological functions that help protect the individual. This sequential activation is referred to as *a cascade*. So, we are referring to the complement cascade, freezing cascade, or kinin cascade. In some cases, activation of a protein may require it to be enzymatically cut into two pieces or fragments of different sizes. Usually larger fragments continue the cascade by activating the next component, and smaller fragments often have strong biological activity to trigger inflammation. ⁷

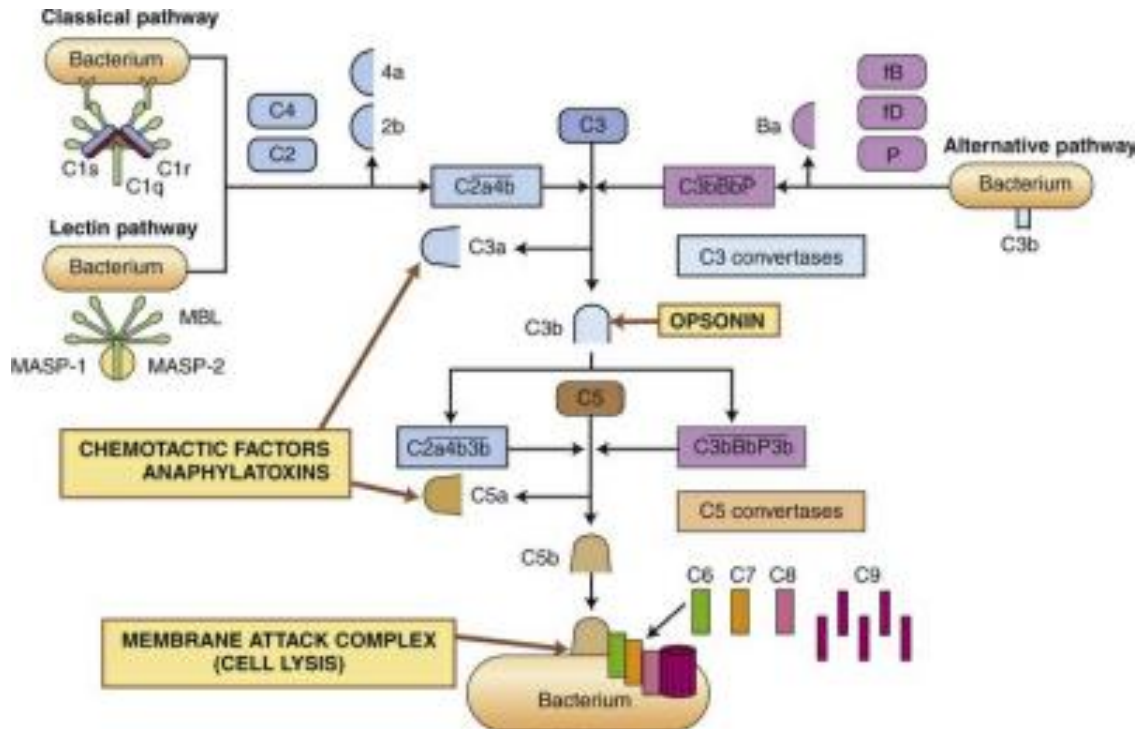


Figure 1. Complementary cascade activation path. The complement system is enabled by three paths: the classical path, the lectin path, and the alternate path. During activation, many complement components are broken down into fragments (2b, 4a, Ba, C3a, and C5a). Smaller fragments often have strong biological activity and can serve as larger activated chemotactic and anaphylatoxin factors. The fragments are usually converted into active enzymes (indicated by the bar above the name) and form complexes with additional components in the cascade. The classical pathway is usually activated by an antigen-antibody complex via the C1 component, which consists of C1q and two molecules of C1r and C1s. As shown, C1q must simultaneously bind to two antibody molecules (indicated by a Y-shaped structure). The lectin pathway is activated by mannose-binding lectin (*MBL*), which binds two mannose-rich pathogen-related molecular patterns on the bacterial surface. *MBL* contains two related enzymes, *MASP-1* and *MASP-2*, and functions in a similar way to C1. C1 and *MBL* enable the C4 and C2 complement components, respectively. Alternative pathways are activated by many agents, such as bacterial polysaccharides, which bind to and stabilize C3b, resulting from the normal breakdown of C3 in the blood. C3b forms the binding site of factor B (*fB*), which is activated by factor D (*fD*) into Bb and small fragments of Ba. Properdin (*P*) helps stabilize the complex. Each pathway produces C3 and C5

convertases, which are active complexes of enzymes that activate C3 and C5, respectively. The C3b produced by the C3 convertase can function as opsonin. C5b initiates a collection of membrane attack complexes (MACs), which produce several C9 molecules that form pores in the bacterial membrane.

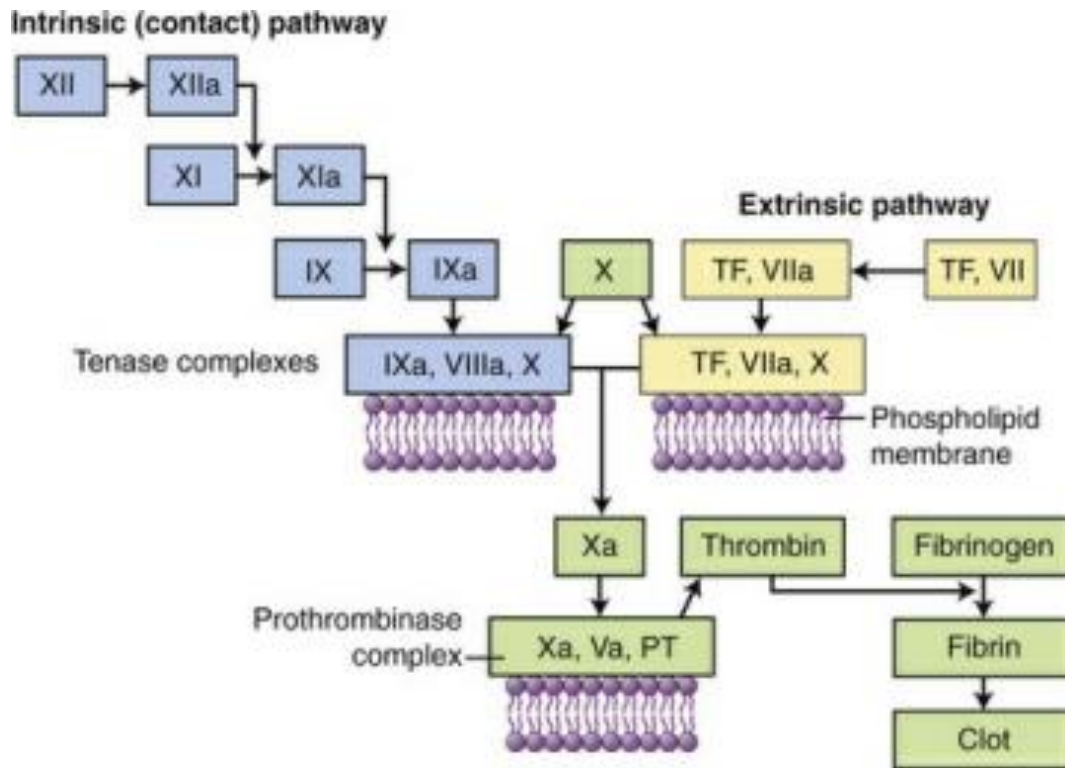


Figure 2. Coagulation Cascade. Freezing is activated through two pathways: the intrinsic (contact) pathway and the extrinsic pathway. The intrinsic pathway is initiated by the activation of Hageman factor (*XII*) to XIIa (the activated factor is an enzyme and is indicated by a lowercase a). Sequential activation of other components of the intrinsic pathway results in the formation of IXa, VIIIa, and X complexes. TF complexes with factor VII, which are activated (VIIa) and form complexes with factor X (*TF, VIIa, X*). The complex of intrinsic and extrinsic pathways are both calcium-dependent, formed on phospholipid membranes rich in phosphatidylserine, and have "tenase" activity (can activate factor X to Xa). Factor X initiates a general pathway in which Xa complexes with Va and prothrombin (*PT*), with calcium and phospholipid membranes, to form active prothrombinase (activating prothrombin to thrombin). Thrombin is an enzyme that cuts high molecular weight fibrinogen into fibrin molecules. Fibrin polymerizes to form clots.

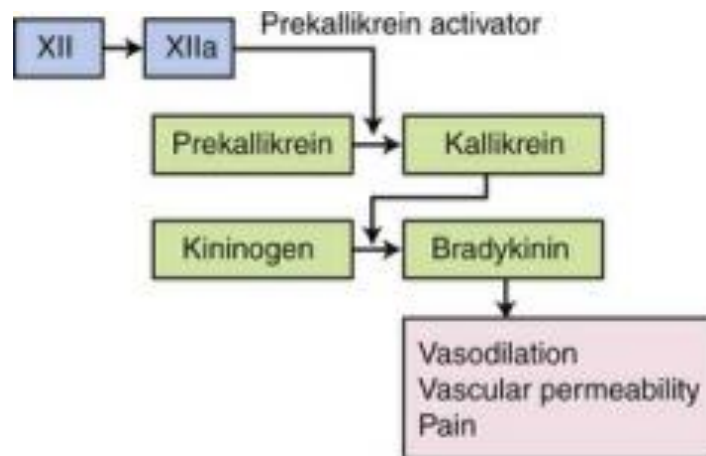


Figure 3. Kinin plasma cascade. The kinin pathway is activated by factor XIIa of the clotting system, which functions as an enzyme (prekallikrein activator) to convert prekallikrein into calicrein. Enzymatically active kallikrein converts kininogen into bradykinin.

Complement System

The complement system consists of several plasma proteins (sometimes called complement components) that together constitute about 10% of the total circulating serum proteins. Activation of the complement system produces several factors that can destroy pathogens directly and can activate or collaborate with other components of the innate and adaptive immune response. The factors produced during the activation of the complement system are one of the body's most powerful defenses, especially against bacterial infections.

Activation of the complement system can be achieved in three different pathways, all of which converge in the third component pathway (C3): 1. Classic pathway: activated by adaptive immune system proteins (antibodies) bound to their specific target (antigen). 2. Lectin pathway: activated by bacterial carbohydrates containing mannose. 3. Alternative pathway: activated by gram-negative bacteria and fungal cell wall polysaccharides. *Activation of the classical pathway* begins with activation of complement protein C1 and is preceded by the formation of complexes between antigens and antibodies to form antigen-antibody complexes (immune complexes). An antigen may be a unique chemical component of the surface of bacteria or other microorganisms. Most pathogens express many antigens; Therefore, several antibodies are usually bound in a complex. The first component of the classical complement cascade, C1, has six sites that can bind to antibodies, and efficient activation of the complement cascade usually requires simultaneous

binding of C1 to at least two antibody molecules. The complex formed by the complement bond of C1 antigen-antibodies is a macromolecular complex consisting of C1q and two molecules of C1r and C1s respectively. Conformational changes in C1 produce enzymatically active molecules whose substrates are C4 and C2. Complexes resulting from the interaction of C1, C4, and C2 use C3 as substrate, resulting in the production of C3a and C3b. Complexes that have C3 as substrate are generally referred to as C3 convertases. The addition of C3b to the complex converts the specificity of the substrate to C5, resulting in the conversion of C5 to C5a and C5b. Complexes that have C5 as a substrate are generally called C5 convertases. So C1 activation initiates sequential enzymatic activation of all other components of the classical pathway, ultimately resulting in C5 activation. The classical pathway can also be activated to a lesser extent by biological molecules other than antibodies, including heparin (a charged molecule that prevents clotting), deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), and C-reactive protein, which increases in the blood during inflammation.^{8,9}

Even under normal conditions, small amounts of circulating C3 are spontaneously broken down into C3b and C3a by a number of natural enzymes in the blood. The level of spontaneous activation of C3 is generally very low, and C3b is readily inactivated by complement regulatory proteins in the blood (e.g., factor H and factor I). However, materials produced by some infectious microorganisms (e.g., lipopolysaccharides [endotoxins] on bacterial surfaces, yeast cell wall carbohydrates [zymosans]) can bind to naturally produced C3b and protect it from inactivation. This will initiate activation of the alternate complement path. C3b bound to bacterial products can react with another normally occurring component, factor B. The C3b and factor B complexes are recognized by an enzyme, factor D, which activates factor B, producing factor Bb. The resulting C3b/Bb complex is very unstable unless it binds to propeptidase (P). The C3b/Bb/P complex is a C3 convertase that produces further C3b, resulting in a C3b/Bb/P/C3b complex that is a C5 convertase, which activates C5.

The lectin pathway is similar to the classical pathway but does not rely on antibodies. It is activated by a plasma protein called mannose-binding lectin (MBL). MBL is similar to C1q and binds to mannose carbohydrate-containing bacterial polysaccharides and activates complement via two MBL-associated serine proteases (MASP-1 and MASP-2) that replace C1r and C1s and activate C4 and C2 to make C3 convertase. Thus, infectious agents that do not activate alternative pathways may be susceptible to supplementing via lectin pathways. After C5 activation, the

cascade continues through terminal components C6, C7, C8, and C9. C5b to C9 components come together to form complexes (*membrane attack*, or *MAC*) capable of creating pores in the cell membrane and allowing water and ions to enter and ultimately resulting in cell lysis. ¹⁰

The most important result of complement activation is the production of fragments during C4, C2, C3, and C5 activation. The C4a, C2b, C3a, and C5a fragments are soluble and low-weight molecules that contribute in other ways to the inflammatory response. C2b affects smooth muscle, causing vasodilation and increased vascular permeability. C3a and C5a, and to some extent C4a, are anaphylatoxins; That is, those that induce rapid degranulation of mast cells (release of granular contents) and release of histamine, causing vasodilation and increased capillary permeability. C5a is the primary chemotaxis factor for neutrophils. C3a is approximately 100 times stronger in chemotactic and anaphylactic activity. Chemotactic factors are biochemical substances that attract leukocytes to the site of inflammation. ¹¹

The dual function of chemotactic factor and anaphylatoxin is not required simultaneously or to the same degree. Anaphylatoxic activity is necessary at the onset of inflammation and occurs near the site of inflammation to induce local mast cell degranulation and to increase the number of dissolved mediators available to increase vascular permeability and vasodilation. Chemotactic activity, on the other hand, is necessary for a longer period and occurs in the distal part of the inflammatory site to pull leukocytes from circulation. It is therefore beneficial for an effective inflammatory response to limit the range of anaphylactic activity while allowing broad chemotactic activity. A plasma enzyme, a carboxypeptidase, removes terminal arginine on peptides C3a and C5a, thus producing "C3a desArg" and "C5a desArg," respectively, which are inactive as anaphylatoxins but retain chemotactic activity. Thus chemotactic activity is maintained, while not inducing distal mast cell degranulation that would result in a considerable enlargement of the inflammatory response detrimental to surrounding healthy tissue.

C3b adheres to the surface of pathogenic microorganisms and serves as an efficient opsonin. Opsonin is a molecule that "tags" microorganisms for destruction by cells of the inflammatory system (mainly neutrophils and macrophages). C3b on the cell surface can also be broken down by some enzymes in the blood into inactive fragments (e.g., iC3b), which maintain opsonic activity. In summary, the complement cascade can be activated by at least three different ways, and its products have four functions: (1) anaphylactic activity resulting in mast cell degranulation

(C3a, C3b), (2) leukocyte chemotaxis (C5a), (3) opsonization (C3b), and (4) cell lysis (C5b-C9, MAC).¹²

Freezing System

The clotting (coagulation) system is a group of plasma proteins that, when activated sequentially, form a blood clot at the injured or inflamed site. A blood clot is a tangle of protein strands (fibrin) that contain platelets (the main cellular initiators of clotting) and trap other cells, such as erythrocytes, phagocytes, and microorganisms. It (1) prevents the spread of infection to adjacent tissues, (2) traps microorganisms and foreign bodies at the site of inflammation for removal by infiltration cells (e.g., neutrophils and macrophages), (3) forms clots that stop bleeding, and (4) provides a framework for future repair and healing. The main substance in the interweaving of insoluble proteins called *fibrinfibrin* is which is the end product of the coagulation cascade.

The clotting system can be activated by many substances released during tissue injury and infection, including collagen, proteinase, calicrein, and plasmin, as well as by bacterial products such as endotoxins. Like the complement cascade, the coagulation cascade can be activated through different convergent pathways. The tissue factor (extrinsic) pathway is activated by tissue factor (TF) (also called *tissue thromboplastin*) which is released by damaged endothelial cells in blood vessels and reacts with activated factor VII (VIIa). The intrinsic (contact) pathway is activated when the vascular wall is damaged and the Hageman factor (factor XII) in plasma comes into contact with a negatively charged subendothelial substance. The pathway converges at factor X. Activation of factor X initiates a general pathway leading to activation of fibrin which polymerizes to form fibrin clots.

As with the complement system, activation of the clotting system produces protein fragments that enhance the inflammatory response. Two low molecular weight fibrinopeptides, A and B, are released from fibrinogen when fibrin is produced. Both fibrinopeptides (especially fibrinopeptide B) are chemotactic to neutrophils and increase the vascular permeability of endothelial cells by enhancing the effects of bradykinin (formed from the kinin system).^{13,14}

Kinin System

A third plasma protein system, the kinin system, increases inflammation in several ways. The main product of the kinin system is bradykinin, which causes dilation of blood vessels, works

with prostaglandins to stimulate nerve endings and induce pain, causes contraction of smooth muscle cells, increases vascular permeability, and can increase leukocyte chemotaxis. Bradykinin induces smooth muscle contractions more slowly than histamine and, together with E series prostaglandins, may be responsible for endothelial cell retraction and increased vascular permeability in later inflammatory phases.

The kinin system is activated by stimulation of the plasma kinin cascade. The conversion of plasma prekallikrein to calcicrein is induced by the *activator prekallikrein*, which is identical to factor XIIa (the product resulting from the activation of Hageman factor —factor XII) of the clotting cascade. Kallikrein then converts kininogen into bradykinin. Although the plasma kinin cascade is one pathway that leads to bradykinin production, tissue calcicrein in saliva, sweat, tears, urine, and feces provides another source for these inflammatory mediators. This tissue calcicrein converts serum kininogen into callidin, also known as Lys-bradykinin, which can be converted into *bradykinin* by plasma aminopeptidases. To limit the extent of inflammation, kinins are rapidly degraded by kininases which are enzymes present in plasma and tissues.¹⁵⁻¹⁷

Control and Interaction of Plasma Protein Systems

All three plasma protein systems are so interactive that activation of one system results in the production of a large number of very powerful biologically active substances that further activate other systems. Very tight control of this process is essential for two reasons: 1. The inflammatory process is essential for the survival of the individual; Thus, efficient activation must be guaranteed regardless of the cause of tissue injury. 2. The biochemical mediators produced during this process are very powerful and potentially detrimental to the individual, and their action should be strictly limited to injured or infected tissues.¹⁸

Various mechanisms are available to *enable* or *disable (regulate)* this plasma protein system. For example, plasma that enters tissues during inflammation (edema) contains enzymes that destroy inflammatory mediators. Carboxypeptidase inactivates the anaphylactic activity of C3a and C5a, and kininase degrades kinins. Histaminase degrades histamine and kallikrein and decreases the inflammatory response. Blood clot formation also activates the fibrinolytic system designed to limit the size of the clot and expel the clot once the bleeding stops. Thrombin activates plasminogen in the blood to form the plasmin enzyme. The main activity of plasmin is the degradation of fibrin polymers in the clot. However, plasmin can also activate the complement

cascade via components C1, C3, and C5 and the kinin cascade by activating factor XII and producing prekallikrein activators. Hageman factor activation has four effects that affect all three plasma protein systems: 1. Activation of the clotting cascade via factor XI, 2. Clotting control through conversion of plasminogen proactivator to plasminogen activator, resulting in plasmin generation, 3. Activation of the kinin system by activating Hageman factor (prekallikrein activator), 4. Activation of C1 in the complement cascade.

The activity of plasmin itself is also regulated because it is synthesized as a proenzyme, plasminogen. Plasminogen is converted into plasmin by several factors, including plasminogen activators produced from the kallikrein system, thrombin produced from the clotting system, bacterial factors such as streptokinase produced by hemolytic streptococci, plasminogen activators produced by endothelial cells, and some cellular enzymes released during tissue destruction. Another example of a common regulator is a C1-esterase inhibitor (C1-inh). C1-inh inhibits complement activation through reactivity with C1 (classical pathway), MASP-2 (lectin pathway), and C3b (alternative pathway). It is also a major inhibitor of components of clotting pathways and kinins (e.g., kallikrein, XIIa). Genetic defects in C1-inh (C1-inh deficiency) cause hereditary angioedema, which is self-healing edema of the skin and mucosal layers due to stress, disease, or relatively minor or invisible trauma. The disease is characterized by hyperactivation of all three plasma protein systems, although excessive bradykinin production appears to be the main cause of increased vascular permeability.¹⁹

Inflammatory Cellular Mediators

Inflammation is a process in the vascular network; Thus, cellular components are found in the blood and tissues around blood vessels. Blood vessels are lined with endothelial cells, which under normal conditions actively maintain normal blood flow. During inflammation, the vascular endothelium becomes the main coordinator of blood clotting and cell lines and fluid into tissues. The tissue close to the blood vessels contains mast cells, which are perhaps the most important inflammatory activators, and dendritic cells, which link innate and adaptive immune responses. Blood contains a complex mixture of cells. Blood cells are divided into erythrocytes (red blood cells), platelets, and leukocytes (white blood cells). Erythrocytes carry oxygen to tissues, and platelets are small cell fragments involved in blood clotting. Leukocytes are further divided into granulocytes (containing many cytoplasmic granules containing enzymes), monocytes, and

lymphocytes. Granulocytes are the most common leukocytes and are classified according to the type of staining required to visualize their granules (basophils, eosinophils and neutrophils). Monocytes in the blood are precursors of macrophages found in tissues. Different forms of lymphocytes participate in innate (e.g., natural killer cell [NK]) and adaptive immune responses (B and T cells).

Cells of the innate and acquired immune system are recruited and activated by biochemical mediators produced at the site of cell damage. These molecules come from destroyed or damaged cells, contaminating microbes, activation of plasma protein systems, or secretion by other cells of the innate or acquired immune system. Activation may result in cells acquiring important functions for the inflammatory response or induction of the release of additional cellular products that enhance inflammation, or both. ²⁰

2. Conclusion →5

Inflammatory cells and various protein systems (complement, kinin, and clotting), together with the substances they produce, act at the site of tissue injury to limit the extent of damage, kill microorganisms, and eliminate debris in preparation for healing: tissue regeneration or repair.

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Reviewer Comment:

1→ Title of Manuscripts should be explained main review and declared type of literature review: narrative or systematic review.

2→ Keywords should be showed the main words of the study, the authors can use MeSH to develop keywords.

3→ Abstract should be showed the main of background, main of review and conclusion of study.

4→ Introduction should be showed the urgency of study (epidemiology data), biological plausibility concept, and lack of knowledge in the study.

5→ Conclusion should more specific and not more showed more review.

6→ Authors must check the references for make update references. References should no more than 10 years.

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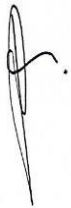
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Letter of Acceptance

Manuscript “Inflammatory Response Plays a Role in Innate Immunity: A Narrative Literature Review“ by Rara Inggarsih, Rachmat Hidayat*, has been accepted to publish in Open Access Indonesian Journal of Medical Reviews Vol 3 issue 2 in April 2023.

Cordially,



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Inflammatory Response Plays a Role in Innate Immunity: A Narrative Literature Review

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ABSTRACT

The inflammatory response is the rapid initiation and interplay of humoral (dissolved in the blood) and cellular systems designed to limit the degree of tissue damage, destroy infectious microorganisms, initiate an adaptive immune response, and initiate the healing process. This review aimed to comprehensively describe the role of the inflammatory response in innate immunity. Three key plasma protein systems are essential for an effective inflammatory response. These are the complement system, clotting system, and kinin system. Although each system has a unique role in inflammation, they also share many similarities. Each system consists of several proteins in the blood. To prevent activation in unnecessary situations, each protein is normally in an inactive form. Some proteins are enzymes that circulate in an inactive form as proenzymes. Each system contains several proteins that can be activated at the start of inflammation. Cells of the innate and acquired immune systems are recruited and activated by biochemical mediators produced at sites of cell damage. These molecules originate from destroyed or damaged cells, contaminating microbes, activation of plasma protein systems, or secretion by other cells of the innate or acquired immune system. Activation may result in the cell acquiring a function essential for the inflammatory response or inducing the release of additional cellular products that promote inflammation, or both. In conclusion, inflammatory cells and various protein systems (complement, kinin, and clotting), together with the substances they produce, act at the site of tissue injury to limit the extent of damage, kill microorganisms, and remove debris in preparation for healing: tissue regeneration or repair.

1. Introduction

The body's defense system is a series of mechanisms the body to eliminate various aspects of threats from the external environment, whether in the form of threats from microorganisms or various environmental stimuli, both physical and chemical. The body has two main defense systems, namely innate immunity and adaptive immunity. Innate immunity is an immune response that is always ready to provide protection against various external threats, whereas Adaptive immunity provides protection after the activation process is first carried out, and adaptive immunity activation takes time.¹

Natural physical, mechanical, and biochemical barriers provide an immediate and static innate

immune response. If these natural barriers are not optimally able to provide protection, then the inflammatory response presents a more dynamic innate immunity response. The inflammatory response is programmed to respond to cell or tissue damage, whether the damaged tissue is septic (contaminated with microorganisms) or sterile. The inflammatory response is the rapid initiation and interplay of humoral (dissolved in the blood) and cellular systems designed to limit the degree of tissue damage, destroy infectious microorganisms, initiate an adaptive immune response, and initiate the healing process. The inflammatory response has the following properties: (1) occurs in tissues with blood supply (vascularization); (2) activates quickly (within seconds)

after the damage was done; (3) depending on the activity cellular and chemical components, including plasma proteins; and (4) nonspecific, meaning it occurs in more or less the same way regardless of the type of stimulus or whether exposure to the same stimulus has occurred in the past.² This review aimed to comprehensively describe the role of the inflammatory response in innate immunity.

Vascular response

Almost any injury to the vascularized tissue will activate inflammation. Injury can occur from a variety of causes, including infection or necrosis (eg, trauma, oxygen deprivation [ischemia], nutritional deficiencies, genetic or immune defects, chemical injury, foreign bodies, temperature extremes, and ionizing radiation). The classic symptoms of acute inflammation include redness (erythema), heat, swelling (edema), and pain. This tetrad represented the cardinal sign of inflammation and was identified in the first century by the Roman writer Celsus. A fifth sign was added later: loss of function. Microscopically, inflammatory changes can be seen at the vascular level. Three characteristic changes in the microcirculation (arterioles, capillaries, and venules) near the site of injury are as follows: (1). Vasodilation (increased size of blood vessels) causes slower blood velocity and increases blood flow to the injured site. (2). Increased permeability of blood vessels (blood vessels become porous due to contraction of endothelial cells) and leakage of fluid out of blood vessels (exudation) causes swelling (edema) at the site of injury; as the plasma moves outward, the blood in the microcirculation becomes more viscous and flows more slowly, and the increased blood flow and increased concentration of red blood cells in the inflammation causes increased redness (erythema) and local warmth. (3). White blood cells attach to the inner walls of blood vessels, and they migrate through the enlarged junctions between the endothelial cells lining the blood vessels to the surrounding tissues (diapedesis).³

Inflammatory effects are visible within seconds. First, the arterioles near the site of infection or injury

narrow briefly. Vasodilation then causes slower blood velocity and increases local blood flow to the injury site. The increased capillary flow and permeability result in leakage of plasma from the vessels, causing edema of the surrounding tissues. As the plasma moves out, the blood remaining in the microcirculation flows more slowly and becomes more viscous. Increased blood flow and increased concentration of red blood cells in place of inflammation cause a local increase in warmth and redness. Leukocytes stick to the walls of blood vessels. At the same time, biochemical mediators (e.g., histamine, bradykinin, leukotrienes, prostaglandins) stimulate the endothelial cells lining the capillaries and venules to retract, creating spaces at the junctions between cells, allowing leukocytes and plasma to enter the surrounding tissues (intercellular junctions).⁴

Each of the characteristic changes associated with inflammation is a direct result of the activity and interactions of a number of chemical substances and cellular components found in blood and tissues. Vascular changes deliver leukocytes (mainly neutrophils), plasma proteins, and other biochemical mediators to the site of injury, where they work together.

The benefits of inflammation include (1). Prevention of infection and further damage by contaminating microorganisms through ingress of fluids to dilute toxins produced by bacteria and released from dying cells, entry and activation of plasma protein systems that help destroy and contain bacteria (e.g., the complement, coagulation systems), and the influx of cells (e.g., neutrophils, macrophages) that phagocytize and destroy cellular debris and infectious agents. (2). Limitation and control of the inflammatory process through the inclusion of plasma protein systems (e.g., clotting systems), plasma enzymes, and cells (e.g., eosinophils) that prevent the inflammatory response from spreading to areas of healthy tissue. (3). Interaction with components of the adaptive immune system to obtain a more specific response to contaminating pathogens through the influx of macrophages and lymphocytes. (4). Preparation of the

injured area for healing through the removal of bacterial products, dead cells, and other inflammatory products (for example, through a passage through the epithelium or drainage by lymphatic vessels) and initiation of healing and repair mechanisms.⁵

Extravascular fluid and debris that has accumulated in the inflamed area are removed by lymphatic vessels. This process also facilitates the development of adaptive immunity because microbial antigens in the lymphatic fluid pass through the lymph nodes, where they activate B and T lymphocytes. Lymphatic vessels may undergo secondary inflammation. Lymphangitis of the lymph vessels and lymphadenitis of the lymph nodes, which become hyperplastic, enlarged, and often painful.

Inflammation and repair can be divided into several phases. The characteristics of the initial (i.e., acute) inflammatory response differ from those of later (i.e., chronic) responses, and each phase involves different biochemical mediators and cells that function together. The acute inflammatory response is brief; that is, it continues only until the immediate threat to the host is eliminated. This process usually takes 8 to 10 days from onset to healing.⁶

Plasma protein system

Three key plasma protein systems are essential for an effective inflammatory response. These are the complement system, coagulation system, and kinin system. Although each system has a unique role in inflammation, they also share many similarities. Each system consists of several proteins in the blood. To prevent activation in unnecessary situations, each protein is normally in an inactive form. Some proteins are enzymes that circulate in an inactive form as proenzymes. Each system contains several proteins that can be activated at the start of inflammation. Activation of the first component of a system results in the sequential activation of other components, leading to biological functions that help protect the individual. This sequential activation is referred to as a cascade. Thus, we refer to the complement cascade, the coagulation cascade, or the kinin cascade. In some

cases, protein activation may require that it be enzymatically cleaved into two parts or fragments of different sizes. Usually, the larger fragments continue the cascade by activating the next component, and the smaller fragments often have a strong biologic activity to promote inflammation.⁷

Complement system

The complement system is composed of several plasma proteins (sometimes called complement components), which together constitute about 10% of the total circulating serum protein. Activation of the complement system produces several factors that can destroy pathogens directly and can activate or collaborate with other components of the innate and adaptive immune response. The factors produced during the activation of the complement system are one of the body's most powerful defenses, especially against bacterial infections.

Activation of the complement system can be achieved in three different pathways, all of which converge on the third component pathway (C3): (1). Classical pathway: activated by adaptive immune system proteins (antibodies) that bind to their specific targets (antigens). (2). Lectin pathway: activated by bacterial carbohydrates containing mannose. 3. Alternative pathway: activated by gram-negative bacteria and fungal cell wall polysaccharides. Activation classic line begins with the activation of complement protein C1 and is preceded by the formation of complexes between antigen and antibody to form antigen-antibody complexes (immune complexes). Antigens may be unique chemical components of the surface of bacteria or other microorganisms. Most pathogens express multiple antigens; therefore, several antibodies are usually bound in complexes. The first component of the classical complement cascade, C1, has six sites that can bind to antibodies, and efficient activation of the complement cascade usually requires concomitant binding of C1 to at least two antibody molecules. The complex formed by the C1 antigen-antibody complement bond is a macromolecular complex

consisting of C1q and two molecules of C1r and C1s, respectively. The conformational change at C1 results in an enzymatically active molecule whose substrates are C4 and C2. The complex resulting from the interaction of C1, C4, and C2 uses C3 as a substrate, resulting in the production of C3a and C3b. Complexes that have C3 as a substrate are generally referred to as C3 convertases. The addition of C3b to the complex changes the substrate specificity to C5, resulting in the conversion of C5 to C5a and C5b. Complexes that have C5 as a substrate are generally called C5

convertases. Thus C1 activation initiates sequential enzymatic activation of all other components of the classical pathway, ultimately resulting in C5 activation. The classical pathway can also be activated to a lesser extent by biological molecules other than antibodies, including heparin (a charged molecule that prevents clotting), deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), and C-reactive protein, which is increased in the blood during inflammation.^{8,9}

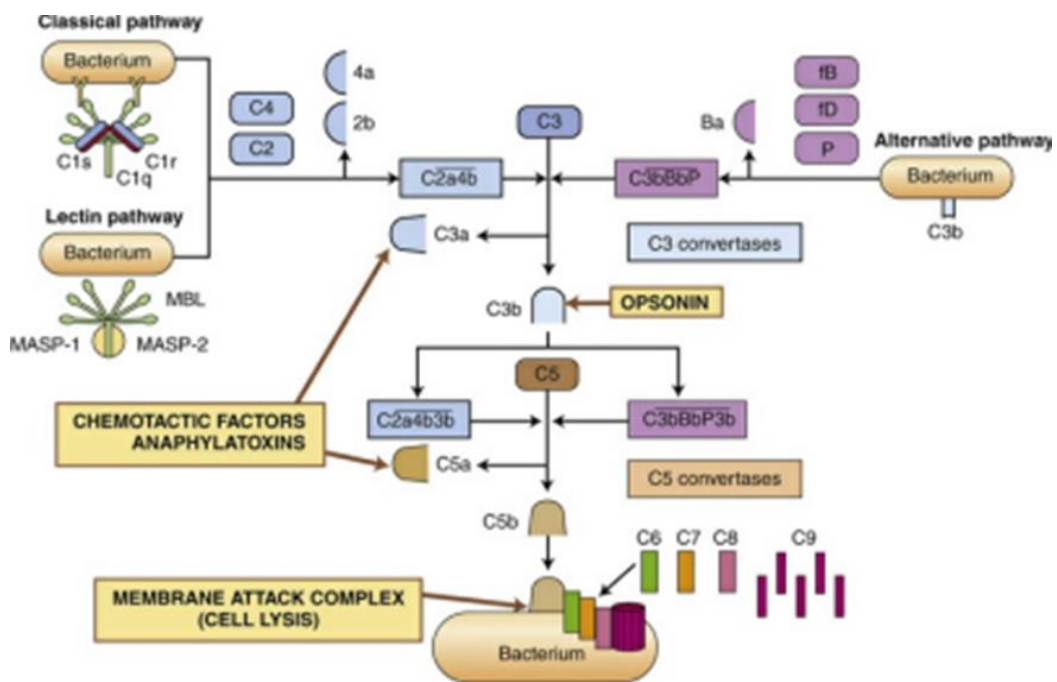


Figure 1. Complementary cascade activation pathway. The complement system is activated by three pathways: the classical pathway, the lectin pathway, and the alternative pathway. During activation, many complement components are broken down into fragments (2b, 4a, Ba, C3a, and C5a). The smaller fragments often have strong biological activity and can function as chemotactic factors and activated anaphylatoxins in the larger ones. The fragments are usually converted into active enzymes (indicated by the bar above the name) and form complexes with additional components in a cascade. The classical pathway is usually activated by antigen-antibody complexes via the C1 component, which is composed of C1q and two C1r molecules, and C1s. As shown, C1q must simultaneously bind two antibody molecules (indicated by the Y-shaped structure). The lectin pathway is activated by the mannose-binding lectin (MBL), which binds to two mannose-rich pathogen-associated molecular patterns on the bacterial surface. MBL contains two related enzymes, MASP-1 and MASP-2, and functions in a similar way to C1. C1 and MBL activate complement components C4 and C2, respectively. Alternative pathways are activated by many agents, such as bacterial polysaccharides, which bind and stabilize C3b, which is produced by the normal breakdown of C3 in the blood. C3b forms the binding site for factor B (fB), which is activated by factor D (fD) into Bb and small fragments of Ba. Properdin (P) helps stabilize the complex. Each pathway produces convertases C3 and C5, which are the active complexes of enzymes that activate C3 and C5, respectively. C3b produced by C3 convertase can function as an opsonin. C5b initiates the assembly of the membrane attack complex (MAC), which generates several C9 molecules that form pores in the bacterial membrane.

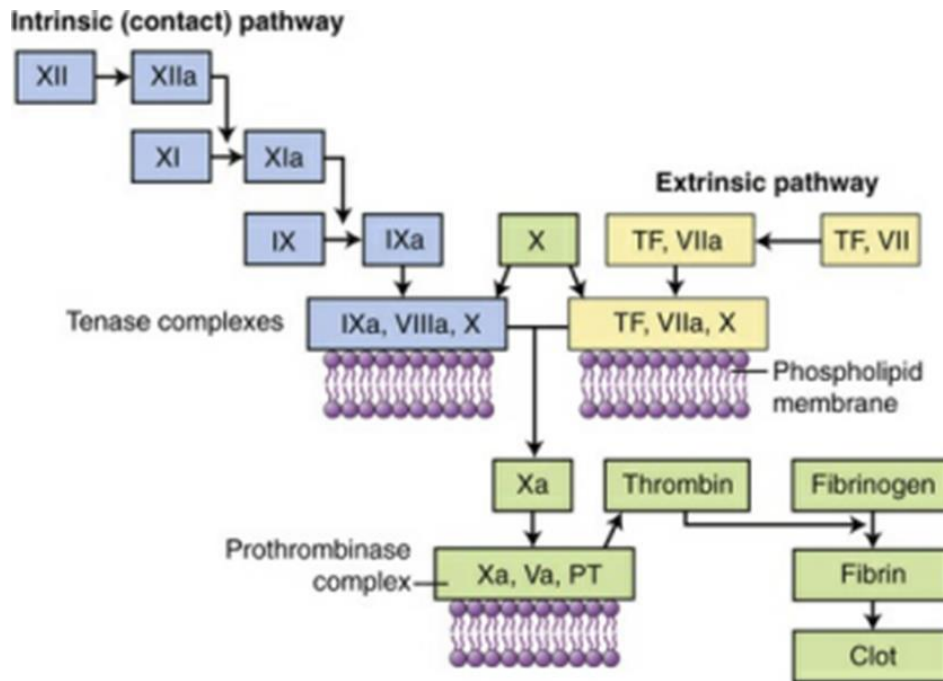


Figure 2. Coagulation cascade. Freezing is activated via two pathways: the intrinsic (contact) pathway and the extrinsic pathway. The intrinsic pathway is initiated by Hageman factor activation (XII) into XIIa (the activated factor is an enzyme and is shown in lowercase letters a). Sequential activation of other components of the intrinsic pathway results in the formation of complexes IXa, VIIIa, and X. The extrinsic pathway is activated by exposure to tissue factors (TF) during tissue breakdown. TF complex with factor VII, which is activated (VIIa), and forms a complex with factor X (TF, VIIa, X). Both the intrinsic and extrinsic pathway complexes are calcium-dependent, form on phosphatidylserine-rich phospholipid membranes, and have "tenase" activity (can activate factor X to Xa). Factor X starts the common pathway where Xa complexes with Va and prothrombin (PT), with calcium and membrane phospholipids, to form active prothrombinase (activates prothrombin to thrombin). Thrombin is an enzyme that cleaves high molecular weight fibrinogen into fibrin molecules. Fibrin polymerizes to form a lump.

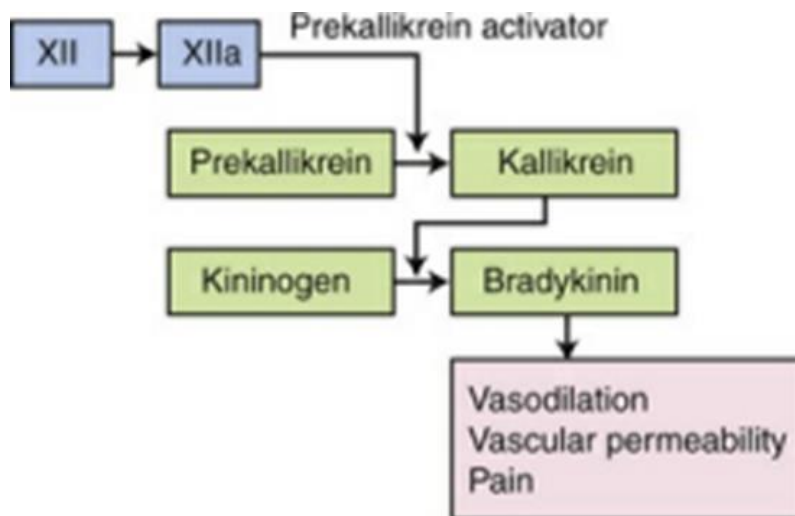


Figure 3. Kinin plasma cascade. The kinin pathway is activated by factor XIIa of the clotting system, which functions as an enzyme (prekallikrein activator) to convert prekallikrein to kallikrein. Kallikrein, which is enzymatically active, converts kininogen to bradykinin.

Even under normal conditions, the small amount of circulating C3 is spontaneously broken down into C3b and C3a by a number of natural enzymes in the blood. The rate of spontaneous activation of C3 is generally very low, and C3b is readily inactivated by complement regulatory proteins in the blood (e.g., factor H and factor I). However, substances produced by some infectious microorganisms (e.g., lipopolysaccharide [endotoxin] on bacterial surfaces, yeast cell wall carbohydrates [zymosans]) can bind naturally produced C3b and protect it from inactivation. This will initiate the activation of the alternative complement pathway. C3b bound to bacterial products can react with another normally occurring component, factor B. The complex of C3b and factor B is recognized by an enzyme, factor D, which activates factor B, producing factor Bb. The resulting C3b/Bb complex is very unstable unless it binds to properdin (P). The C3b/Bb/P complex is a C3 convertase which further produces C3b, yielding a C3b/Bb/P/C3b complex which is a C5 convertase, which activates C5.

The lectin pathway is similar to the classical pathway but is independent of antibodies. It is activated by a plasma protein called a mannose-binding lectin (MBL). MBL is similar to C1q and binds to the bacterial polysaccharide containing carbohydrate mannose and activates complement via two MBL-associated serine proteases (MASP-1 and MASP-2) that displace C1r and C1s and activate C4 and C2 to make C3 convertase. Thus, infectious agents that do not activate alternative pathways may be susceptible to complement via the lectin pathway. After C5 activation, the cascade continues through the terminal components C6, C7, C8, and C9. Components C5b through C9 assemble to form a complex (membrane attack, or MAC) which is able to create pores in the cell membrane and allow the entry of water and ions and can ultimately result in cell lysis.¹⁰

The most important outcome of complement activation is the production of fragments during C4, C2, C3, and C5 activation. Fragments C4a, C2b, C3a,

and C5a are low-weight, soluble molecules that contribute in other ways to the inflammatory response. C2b affects smooth muscle, causing vasodilation and increased vascular permeability. C3a and C5a, and to some extent C4a, are anaphylatoxins, namely, those that induce rapid mast cell degranulation (release of granular contents) and histamine release, causing vasodilation and increased capillary permeability. C5a is the main chemotactic factor for neutrophils. C3a is approximately 100 times more potent in chemotactic and anaphylactic activity. Chemotactic factors are biochemical substances that attract leukocytes to the site of inflammation.¹¹

The dual function of a chemotactic factor and anaphylatoxin is not required simultaneously or to the same degree. Anaphylatoxic activity is required early in inflammation and occurs near inflammatory sites to induce local mast cell degranulation and to increase the number of soluble mediators available to increase vascular permeability and vasodilation. Chemotactic activity, on the other hand, is required for a longer period and occurs distal to the site of inflammation to draw leukocytes from the circulation. It is, therefore, beneficial for an effective inflammatory response to limit the range of anaphylactic activity while allowing for a broad range of chemotactic activity. A plasma enzyme, a carboxypeptidase, removes the terminal arginine at the C3a and C5a peptides, thereby producing "C3a desArg" and "C5a desArg," respectively, which are inactive as anaphylatoxins but retain chemotactic activity. Thus the chemotactic activity is maintained while not inducing the distal mast cell degranulation that would result in the magnification of a large enough inflammatory response to the detriment of surrounding healthy tissue.

C3b attaches to the surface of pathogenic microorganisms and functions as an efficient opsonin. Opsonins are molecules that "mark" microorganisms for destruction by cells of the inflammatory system (mainly neutrophils and macrophages). C3b on the cell surface can also be broken down by several enzymes in the blood into inactive fragments (eg, iC3b), which

maintain opsonic activity. In summary, the complement cascade can be activated in at least three different ways, and its products serve four functions: (1) anaphylactic activity resulting in mast cell degranulation (C3a, C3b), (2) leukocyte chemotaxis (C5a), (3) opsonization (C3b), and (4) cell lysis (C5b-C9, MAC).¹²

The clotting system

The clotting (coagulation) system is a group of plasma proteins that, when activated sequentially, form a blood clot in an injured or inflamed area. A blood clot is a tangle of protein strands (fibrin) that contains platelets (the main cellular initiator of clotting) and traps other cells, such as erythrocytes, phagocytes, and microorganisms. This (1) prevents the spread of infection to adjacent tissues, (2) traps microorganisms and foreign matter in place inflammation for removal by infiltrating cells (e.g., neutrophils and macrophages), (3) forms a clot that stops bleeding, and (4) provides a framework for future repair and healing. The main substance in the protein chain is so-called insoluble fibrin. This is the one. It is the end product of the coagulation cascade.

The clotting system can be activated by many substances released during tissue injury and infection, including collagen, proteinases, calicrein, and plasmin, as well as bacterial products such as endotoxins. Like the complement cascade, the coagulation cascade can be activated via different convergent pathways. The tissue factor (extrinsic) pathway activated by tissue factor (TF) (also called tissue thromboplastin) is released by damaged endothelial cells in blood vessels and reacts with activated factor VII (VIIa). The intrinsic (contact) pathway is activated when the vessel wall is damaged, and Hageman's factor (factor XII) in plasma is in contact with negatively charged subendothelial substances. The pathway converges on factor X. Activation of factor X initiates a common pathway leading to the activation of fibrin, which polymerizes to form a fibrin clot.

Like the complement system, activation of the clotting system produces protein fragments that increase the inflammatory response. Two low molecular weight fibrinopeptide's, A and B, are released from fibrinogen when fibrin is produced. Both fibrinopeptides (especially fibrinopeptide B) are chemotactic for neutrophils and increase the vascular permeability of endothelial cells by enhancing the effects of bradykinin (formed from the kinin system).^{13,14}

The kinin system

The third plasma protein system, the kinin system, increases internal inflammation in several ways. The main product of the kinin system is bradykinin, which causes dilation of blood vessels, works with prostaglandins to stimulate nerve endings and induce pain, causes contraction of smooth muscle cells, increases vascular permeability, and can enhance leukocyte chemotaxis. Bradykinin induces smooth muscle contraction more slowly than histamine and, together with series E prostaglandins, may be responsible for endothelial cell retraction and increased vascular permeability in later phases of inflammation.

The kinin system is activated by stimulation of the plasma kinin cascade. Conversion of plasma prekallikrein to calicrein is induced by activator prekallikrein, which is identical to factor XIIa (a product resulting from the activation of Hageman's factor —factor XII) of the coagulation cascade. Kallikrein then converts kininogen to bradykinin. Although the plasma kinin cascade is one pathway leading to bradykinin production, tissue kallikrein in saliva, sweat, tears, urine, and feces provides another source for these inflammatory mediators. This tissue kallikrein converts serum kininogen to callidin, also known as Lys-bradykinin, which can be converted to bradykinin by plasma aminopeptidases. To limit the extent of inflammation, kinins are rapidly degraded by kinase enzymes present in plasma and tissues.¹⁵⁻¹⁷

Control and interaction of plasma protein systems

The three plasma protein systems are highly interactive, so the activation of one system results in the production of large quantities of highly potent biologically active substances, which in turn activate other systems. Tight control of this process is essential for two reasons: (1). The inflammatory process is essential for individual survival; thus, efficient activation must be guaranteed regardless of the cause of tissue injury. (2). The biochemical mediators produced during this process are very potent and potentially harmful to individuals, and their action must be strictly limited to injured or infected tissues.¹⁸

Various mechanisms are available to enable or disable (set) the plasma protein system. For example, plasma that enters tissues during inflammation (edema) contains enzymes that destroy inflammatory mediators. Carboxypeptidase inactivates the anaphylactic activity of C3a and C5a, and kininase degrades kinin. Histaminase degrades histamine and kallikrein and reduces the inflammatory response. Blood clot formation also activates the fibrinolytic system, which is designed to limit clot size and expel the clot after the bleeding has stopped. Thrombin activates plasminogen in the blood to form the enzyme plasmin. The main activity of plasmin is to degrade fibrin polymers in the clot. However, plasmin can also activate the complement cascade via components C1, C3, and C5 and the kinin cascade by activating factor XII and producing a prekallikrein activator. Hageman factor activation has four effects that affect all three plasma protein systems: (1). Activation of the clotting cascade via factor XI, (2). Control of clotting through the conversion of the plasminogen pro activator to plasminogen activator, resulting in the generation of plasmin (3). Activation of the kinin system by activating the Hageman factor (prekallikrein activator), (4). Activation of C1 in the complement cascade.

The activity of plasmin itself is also regulated because it is synthesized as a proenzyme, plasminogen. Plasminogen is converted to plasmin by several factors, including plasminogen activator

produced by the kallikrein system, thrombin produced by the clotting system, streptokinase-like bacterial factors produced by hemolytic streptococci, plasminogen activator produced by endothelial cells, and several cellular enzymes released during the breakdown network. Another example of a general regulator is the C1-esterase inhibitor (C1-inh). C1-inh inhibits complement activation through reactivity with C1 (classical pathway), MASP-2 (lectin pathway), and C3b (alternative pathway). It is also a major inhibitor of coagulation pathway components and kinins (eg, kallikrein, XIIa). A genetic defect in C1-inh (C1-inh deficiency) causes hereditary angioedema, which is self-limiting edema of the skin and mucosal layers resulting from relatively minor or imperceptible stress, disease or trauma. This disease is characterized by hyperactivation of all three plasma protein systems, although overproduction of bradykinin appears to be the main cause of increased vascular permeability.¹⁹

Inflammatory cellular mediators

Inflammation is a process in the vascular tissue; thus, cellular components are found in blood and tissues around blood vessels. Blood vessels are lined with endothelial cells, which under normal conditions, actively maintain normal blood flow. During inflammation, the vascular endothelium is the main coordinator of blood clotting and the passage of cells and fluids into tissues. Tissues close to blood vessels contain mast cells, which are perhaps the most important activators of inflammation, and dendritic cells, which link innate and adaptive immune responses. Blood contains a complex mixture of cells. Blood cells are divided into erythrocytes (red blood cells), platelets, and leukocytes (white blood cells). Erythrocytes carry oxygen to tissues, and platelets are small cell fragments involved in blood clotting. Leukocytes are further divided into granulocytes (contain many cytoplasmic granules containing enzymes), monocytes, and lymphocytes. Granulocytes are the most common leukocytes and are classified according to the type of stain required to visualize their granules (basophils, eosinophils, and neutrophils).

Monocytes in the blood are the precursors of macrophages which are found in tissues. Different forms of lymphocytes participate in innate (e.g., natural killer [NK] cells) and adaptive (B and T cells) immune responses.

Cells of the innate and acquired immune systems are recruited and activated by biochemical mediators produced at sites of cell damage. These molecules originate from destroyed or damaged cells, contaminating microbes, activation of plasma protein systems, or secretion by other cells of the innate or acquired immune system. Activation may result in the cell acquiring a function essential for the inflammatory response or inducing the release of additional cellular products that promote inflammation, or both.²⁰

2. Conclusion

Inflammatory cells and various protein systems (complement, kinin, and clotting), together with the substances they produce, act at the site of tissue injury to limit the extent of damage, kill microorganisms, and remove debris in preparation for healing: tissue regeneration or repair.

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Inflammatory Response Plays a Role in Innate Immunity: A Narrative Literature Review

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A B S T R A C T

The inflammatory response is the rapid initiation and interplay of humoral (dissolved in the blood) and cellular systems designed to limit the degree of tissue damage, destroy infectious microorganisms, initiate an adaptive immune response, and initiate the healing process. This review aimed to comprehensively describe the role of the inflammatory response in innate immunity. Three key plasma protein systems are essential for an effective inflammatory response. These are the complement system, clotting system, and kinin system. Although each system has a unique role in inflammation, they also share many similarities. Each system consists of several proteins in the blood. To prevent activation in unnecessary situations, each protein is normally in an inactive form. Some proteins are enzymes that circulate in an inactive form as proenzymes. Each system contains several proteins that can be activated at the start of inflammation. Cells of the innate and acquired immune systems are recruited and activated by biochemical mediators produced at sites of cell damage. These molecules originate from destroyed or damaged cells, contaminating microbes, activation of plasma protein systems, or secretion by other cells of the innate or acquired immune system. Activation may result in the cell acquiring a function essential for the inflammatory response or inducing the release of additional cellular products that promote inflammation, or both. In conclusion, inflammatory cells and various protein systems (complement, kinin, and clotting), together with the substances they produce, act at the site of tissue injury to limit the extent of damage, kill microorganisms, and remove debris in preparation for healing: tissue regeneration or repair.

1. Introduction

The body's defense system is a series of mechanisms the body to eliminate various aspects of threats from the external environment, whether in the form of threats from microorganisms or various environmental stimuli, both physical and chemical. The body has two main defense systems, namely innate immunity and adaptive immunity. Innate immunity is an immune response that is always ready to provide protection against various external threats, whereas Adaptive immunity provides protection after the activation process is first carried out, and adaptive immunity activation takes time.¹

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Vascular response

Almost any injury to the vascularized tissue will activate inflammation. Injury can occur from a variety of causes, including infection or necrosis (eg, trauma, oxygen deprivation [ischemia], nutritional deficiencies, genetic or immune defects, chemical injury, foreign bodies, temperature extremes, and ionizing radiation). The classic symptoms of acute inflammation include redness (erythema), heat, swelling (edema), and pain. This tetrad represented the cardinal sign of inflammation and was identified in the first century by the Roman writer Celsus. A fifth sign was added later: loss of function. Microscopically, inflammatory changes can be seen at the vascular level. Three characteristic changes in the microcirculation (arterioles, capillaries, and venules) near the site of injury are as follows: (1). Vasodilation (increased size of blood vessels) causes slower blood velocity and increases blood flow to the injured site. (2). Increased permeability of blood vessels (blood vessels become porous due to contraction of endothelial cells) and leakage of fluid out of blood vessels (exudation) causes swelling (edema) at the site of injury; as the plasma moves outward, the blood in the microcirculation becomes more viscous and flows more slowly, and the increased blood flow and increased concentration of red blood cells in the inflammation causes increased redness (erythema) and local warmth. (3). White blood cells attach to the inner walls of blood vessels, and they migrate through the enlarged junctions between

the endothelial cells lining the blood vessels to the surrounding tissues (diapedesis).³

Inflammatory effects are visible within seconds. First, the arterioles near the site of infection or injury narrow briefly. Vasodilation then causes slower blood velocity and increases local blood flow to the injury site. The increased capillary flow and permeability result in leakage of plasma from the vessels, causing edema of the surrounding tissues. As the plasma moves out, the blood remaining in the microcirculation flows more slowly and becomes more viscous. Increased blood flow and increased concentration of red blood cells in place of inflammation cause a local increase in warmth and redness. Leukocytes stick to the walls of blood vessels. At the same time, biochemical mediators (e.g., histamine, bradykinin, leukotrienes, prostaglandins) stimulate the endothelial cells lining the capillaries and venules to retract, creating spaces at the junctions between cells, allowing leukocytes and plasma to enter the surrounding tissues (intercellular junctions).⁴

Each of the characteristic changes associated with inflammation is a direct result of the activity and interactions of a number of chemical substances and cellular components found in blood and tissues. Vascular changes deliver leukocytes (mainly neutrophils), plasma proteins, and other biochemical mediators to the site of injury, where they work together.

The benefits of inflammation include (1). Prevention of infection and further damage by contaminating microorganisms through ingress of fluids to dilute toxins produced by bacteria and released from dying cells, entry and activation of plasma protein systems that help destroy and contain bacteria (e.g., the complement, coagulation systems), and the influx of cells (e.g., neutrophils, macrophages) that phagocytize and destroy cellular debris and infectious agents. (2). Limitation and control of the inflammatory process through the inclusion of plasma protein systems (e.g., clotting systems), plasma enzymes, and cells (e.g., eosinophils) that prevent the inflammatory response from spreading to areas of healthy tissue. (3).

Interaction with components of the adaptive immune system to obtain a more specific response to contaminating pathogens through the influx of macrophages and lymphocytes. (4). Preparation of the injured area for healing through the removal of bacterial products, dead cells, and other inflammatory products (for example, through a passage through the epithelium or drainage by lymphatic vessels) and initiation of healing and repair mechanisms.⁵

Extravascular fluid and debris that has accumulated in the inflamed area are removed by lymphatic vessels. This process also facilitates the development of adaptive immunity because microbial antigens in the lymphatic fluid pass through the lymph nodes, where they activate B and T lymphocytes. Lymphatic vessels may undergo secondary inflammation. Lymphangitis of the lymph vessels and lymphadenitis of the lymph nodes, which become hyperplastic, enlarged, and often painful.

Inflammation and repair can be divided into several phases. The characteristics of the initial (i.e., acute) inflammatory response differ from those of later (i.e., chronic) responses, and each phase involves different biochemical mediators and cells that function together. The acute inflammatory response is brief; that is, it continues only until the immediate threat to the host is eliminated. This process usually takes 8 to 10 days from onset to healing.⁶

Plasma protein system

Three key plasma protein systems are essential for an effective inflammatory response. These are the complement system, coagulation system, and kinin system. Although each system has a unique role in inflammation, they also share many similarities. Each system consists of several proteins in the blood. To prevent activation in unnecessary situations, each protein is normally in an inactive form. Some proteins are enzymes that circulate in an inactive form as proenzymes. Each system contains several proteins that can be activated at the start of inflammation. Activation of the first component of a system results in the sequential activation of other components, leading

to biological functions that help protect the individual. This sequential activation is referred to as a cascade. Thus, we refer to the complement cascade, the coagulation cascade, or the kinin cascade. In some cases, protein activation may require that it be enzymatically cleaved into two parts or fragments of different sizes. Usually, the larger fragments continue the cascade by activating the next component, and the smaller fragments often have a strong biologic activity to promote inflammation.⁷

Complement system

The complement system is composed of several plasma proteins (sometimes called complement components), which together constitute about 10% of the total circulating serum protein. Activation of the complement system produces several factors that can destroy pathogens directly and can activate or collaborate with other components of the innate and adaptive immune response. The factors produced during the activation of the complement system are one of the body's most powerful defenses, especially against bacterial infections.

Activation of the complement system can be achieved in three different pathways, all of which converge on the third component pathway (C3): (1). Classical pathway: activated by adaptive immune system proteins (antibodies) that bind to their specific targets (antigens). (2). Lectin pathway: activated by bacterial carbohydrates containing mannose. 3. Alternative pathway: activated by gram-negative bacteria and fungal cell wall polysaccharides. Activation classic line begins with the activation of complement protein C1 and is preceded by the formation of complexes between antigen and antibody to form antigen-antibody complexes (immune complexes). Antigens may be unique chemical components of the surface of bacteria or other microorganisms. Most pathogens express multiple antigens; therefore, several antibodies are usually bound in complexes. The first component of the classical complement cascade, C1, has six sites that can bind to antibodies, and efficient activation of the

complement cascade usually requires concomitant binding of C1 to at least two antibody molecules. The complex formed by the C1 antigen-antibody complement bond is a macromolecular complex consisting of C1q and two molecules of C1r and C1s, respectively. The conformational change at C1 results in an enzymatically active molecule whose substrates are C4 and C2. The complex resulting from the interaction of C1, C4, and C2 uses C3 as a substrate, resulting in the production of C3a and C3b. Complexes that have C3 as a substrate are generally referred to as C3 convertases. The addition of C3b to the complex changes the substrate specificity to C5, resulting in

the conversion of C5 to C5a and C5b. Complexes that have C5 as a substrate are generally called C5 convertases. Thus C1 activation initiates sequential enzymatic activation of all other components of the classical pathway, ultimately resulting in C5 activation. The classical pathway can also be activated to a lesser extent by biological molecules other than antibodies, including heparin (a charged molecule that prevents clotting), deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), and C-reactive protein, which is increased in the blood during inflammation.^{8,9}

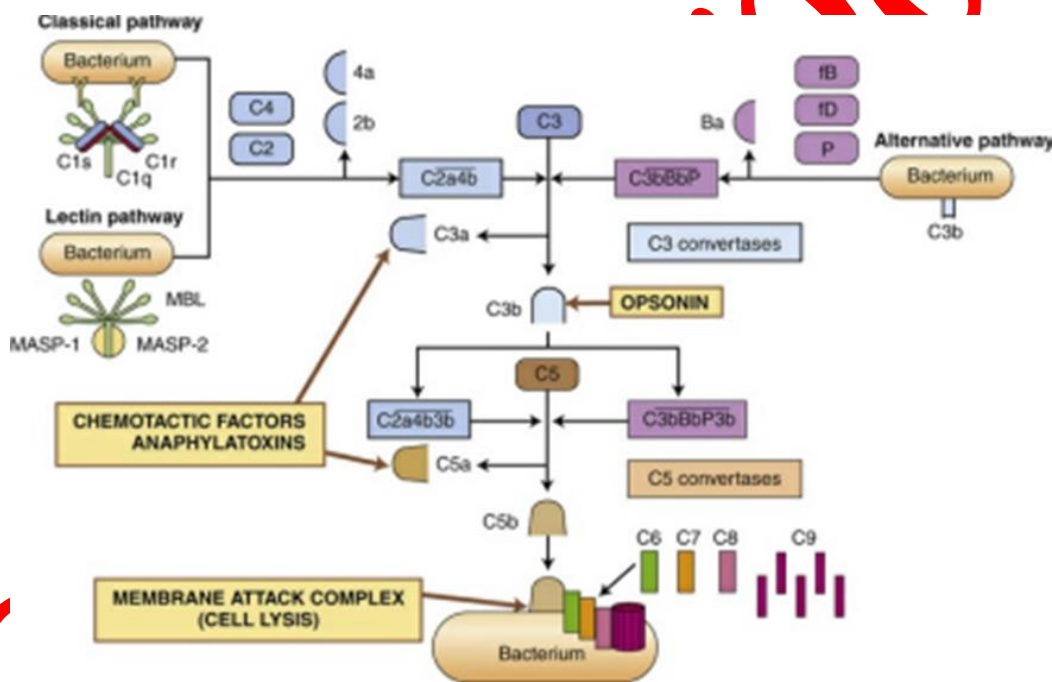


Figure 1. Complementary cascade activation pathway. The complement system is activated by three pathways: the classical pathway, the lectin pathway, and the alternative pathway. During activation, many complement components are broken down into fragments (2b, 4a, Ba, C3a, and C5a). The smaller fragments often have strong biological activity and can function as chemotactic factors and activated anaphylatoxins in the larger ones. The fragments are usually converted into active enzymes (indicated by the bar above the name) and form complexes with additional components in a cascade. The classical pathway is usually activated by antigen-antibody complexes via the C1 component, which is composed of C1q and two C1r molecules, and C1s. As shown, C1q must simultaneously bind two antibody molecules (indicated by the Y-shaped structure). The lectin pathway is activated by the mannose-binding lectin (MBL), which binds to two mannose-rich pathogen-associated molecular patterns on the bacterial surface. MBL contains two related enzymes, MASP-1 and MASP-2, and functions in a similar way to C1. C1 and MBL activate complement components C4 and C2, respectively. Alternative pathways are activated by many agents, such as bacterial polysaccharides, which bind and stabilize C3b, which is produced by the normal breakdown of C3 in the blood. C3b forms the binding site for factor B (fB), which is activated by factor D (fD) into Bb and small fragments of Ba. Properdin (P) helps stabilize the complex. Each pathway produces convertases C3 and C5, which are the active

complexes of enzymes that activate C3 and C5, respectively. C3b produced by C3 convertase can function as an opsonin. C5b initiates the assembly of the membrane attack complex (MAC), which generates several C9 molecules that form pores in the bacterial membrane.

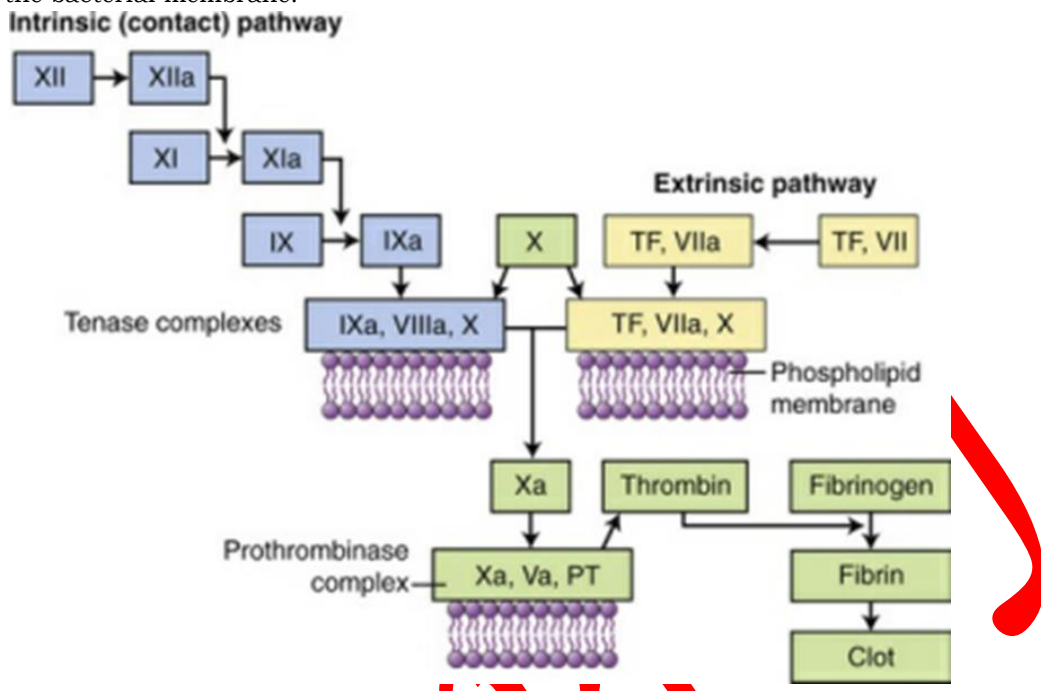


Figure 2. Coagulation cascade. Freezing is activated via two pathways: the intrinsic (contact) pathway and the extrinsic pathway. The intrinsic pathway is initiated by Hageman factor activation (XII) into XIIa (the activated factor is an enzyme and is shown in lowercase letters a). Sequential activation of other components of the intrinsic pathway results in the formation of complexes IXa, VIIIa, and X. The extrinsic pathway is activated by exposure to tissue factors (TF) during tissue breakdown. TF complex with factor VII, which is activated (VIIa), and forms a complex with factor X (TF, VIIa, X). Both the intrinsic and extrinsic pathway complexes are calcium-dependent, form on phosphatidylserine-rich phospholipid membranes, and have "tenase" activity (can activate factor X to Xa). Factor X starts the common pathway where Xa complexes with Va and prothrombin (PT), with calcium and membrane phospholipids, to form active prothrombinase (activates prothrombin to thrombin). Thrombin is an enzyme that cleaves high molecular weight fibrinogen into fibrin molecules. Fibrin polymerizes to form a lump.

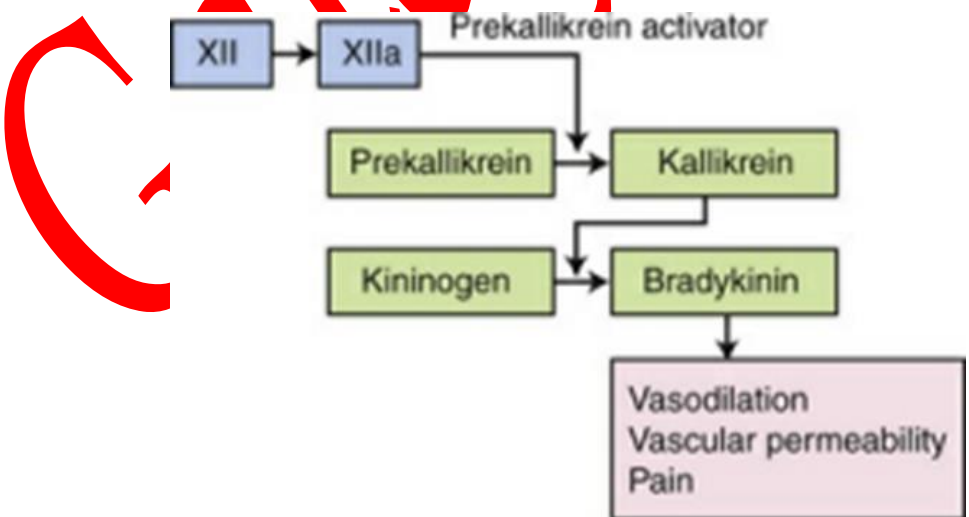


Figure 3. Kinin plasma cascade. The kinin pathway is activated by factor XIIIa of the clotting system, which functions as an enzyme (prekallikrein activator) to convert prekallikrein to kallikrein. Kallikrein, which is enzymatically active, converts kininogen to bradykinin.

Even under normal conditions, the small amount of circulating C3 is spontaneously broken down into C3b and C3a by a number of natural enzymes in the blood. The rate of spontaneous activation of C3 is generally very low, and C3b is readily inactivated by complement regulatory proteins in the blood (e.g., factor H and factor I). However, substances produced by some infectious microorganisms (e.g., lipopolysaccharide [endotoxin] on bacterial surfaces, yeast cell wall carbohydrates [zymosans]) can bind naturally produced C3b and protect it from inactivation. This will initiate the activation of the alternative complement pathway. C3b bound to bacterial products can react with another normally occurring component, factor B. The complex of C3b and factor B is recognized by an enzyme, factor D, which activates factor B, producing factor Bb. The resulting C3b/Bb complex is very unstable unless it binds to properdin (P). The C3b/Bb/P complex is a C3 convertase which further produces C3b, yielding a C3b/Bb/P/C3b complex which is a C5 convertase, which activates C5.

The lectin pathway is similar to the classical pathway but is independent of antibodies. It is activated by a plasma protein called a mannose-binding lectin (MBL). MBL is similar to C1q and binds to the bacterial polysaccharide containing carbohydrate mannose and activates complement via two MBL-associated serine proteases (MASP-1 and MASP-2) that displace C1r and C1s and activate C4 and C2 to make C3 convertase. Thus, infectious agents that do not activate alternative pathways may be susceptible to complement via the lectin pathway. After C5 activation, the cascade continues through the terminal components C6, C7, C8, and C9. Components C5b through C9 assemble to form a complex (membrane attack, or MAC) which is able to create pores in the cell membrane and allow the entry

of water and ions and can ultimately result in cell lysis.¹⁰

The most important outcome of complement activation is the production of fragments during C4, C2, C3, and C5 activation. Fragments C4a, C2b, C3a, and C5a are low-weight, soluble molecules that contribute in other ways to the inflammatory response. C2b affects smooth muscle, causing vasodilation and increased vascular permeability. C3a and C5a, and to some extent C4a, are anaphylatoxins, namely, those that induce rapid mast cell degranulation (release of granular contents) and histamine release, causing vasodilation and increased capillary permeability. C5a is the main chemotactic factor for neutrophils. C3a is approximately 100 times more potent in chemotactic and anaphylactic activity. Chemotactic factors are biochemical substances that attract leukocytes to the site of inflammation.¹¹

The dual function of a chemotactic factor and anaphylatoxin is not required simultaneously or to the same degree. Anaphylatoxic activity is required early in inflammation and occurs near inflammatory sites to induce local mast cell degranulation and to increase the number of soluble mediators available to increase vascular permeability and vasodilation. Chemotactic activity, on the other hand, is required for a longer period and occurs distal to the site of inflammation to draw leukocytes from the circulation. It is, therefore, beneficial for an effective inflammatory response to limit the range of anaphylactic activity while allowing for a broad range of chemotactic activity. A plasma enzyme, a carboxypeptidase, removes the terminal arginine at the C3a and C5a peptides, thereby producing "C3a desArg" and "C5a desArg," respectively, which are inactive as anaphylatoxins but retain chemotactic activity. Thus the chemotactic activity is maintained while not inducing the distal mast cell degranulation that would result in the magnification of a large enough inflammatory

response to the detriment of surrounding healthy tissue.

C3b attaches to the surface of pathogenic microorganisms and functions as an efficient opsonin. Opsonins are molecules that "mark" microorganisms for destruction by cells of the inflammatory system (mainly neutrophils and macrophages). C3b on the cell surface can also be broken down by several enzymes in the blood into inactive fragments (eg, iC3b), which maintain opsonic activity. In summary, the complement cascade can be activated in at least three different ways, and its products serve four functions: (1) anaphylactic activity resulting in mast cell degranulation (C3a, C3b), (2) leukocyte chemotaxis (C5a), (3) opsonization (C3b), and (4) cell lysis (C5b-C9, MAC).¹²

The clotting system

The clotting (coagulation) system is a group of plasma proteins that, when activated sequentially, form a blood clot in an injured or inflamed area. A blood clot is a tangle of protein strands (fibrin) that contains platelets (the main cellular initiator of clotting) and traps other cells, such as erythrocytes, phagocytes, and microorganisms. This (1) prevents the spread of infection to adjacent tissues, (2) traps microorganisms and foreign matter in place inflammation for removal by infiltrating cells (e.g., neutrophils and macrophages), (3) forms a clot that stops bleeding, and (4) provides a framework for future repair and healing. The main substance in the protein chain is so-called insoluble fibrin. This is the one. It is the end product of the coagulation cascade.

The clotting system can be activated by many substances released during tissue injury and infection, including collagen, proteinases, calicrein, and plasmin, as well as bacterial products such as endotoxins. Like the complement cascade, the coagulation cascade can be activated via different convergent pathways. The tissue factor (extrinsic) pathway activated by tissue factor (TF) (also called tissue thromboplastin) is released by damaged endothelial cells in blood vessels and reacts with

activated factor VII (VIIa). The intrinsic (contact) pathway is activated when the vessel wall is damaged, and Hageman's factor (factor XII) in plasma is in contact with negatively charged subendothelial substances. The pathway converges on factor X. Activation of factor X initiates a common pathway leading to the activation of fibrin, which polymerizes to form a fibrin clot.

Like the complement system, activation of the clotting system produces protein fragments that increase the inflammatory response. Two low molecular weight fibrinopeptides, A and B, are released from fibrinogen when fibrin is produced. Both fibrinopeptides (especially fibrinopeptide B) are chemotactic for neutrophils and increase the vascular permeability of endothelial cells by enhancing the effects of bradykinin (formed from the kinin system).^{13,14}

The kinin system

The third plasma protein system, the kinin system, increases internal inflammation in several ways. The main product of the kinin system is bradykinin, which causes dilation of blood vessels, works with prostaglandins to stimulate nerve endings and induce pain, causes contraction of smooth muscle cells, increases vascular permeability, and can enhance leukocyte chemotaxis. Bradykinin induces smooth muscle contraction more slowly than histamine and, together with series E prostaglandins, may be responsible for endothelial cell retraction and increased vascular permeability in later phases of inflammation.

The kinin system is activated by stimulation of the plasma kinin cascade. Conversion of plasma prekallikrein to calicrein is induced by activator prekallikrein, which is identical to factor XIIa (a product resulting from the activation of Hageman's factor —factor XII) of the coagulation cascade. Kallikrein then converts kininogen to bradykinin. Although the plasma kinin cascade is one pathway leading to bradykinin production, tissue kallikrein in saliva, sweat, tears, urine, and feces provides another

source for these inflammatory mediators. This tissue kallikrein converts serum kininogen to callidin, also known as Lys-bradykinin, which can be converted to bradykinin by plasma aminopeptidases. To limit the extent of inflammation, kinins are rapidly degraded by kinase enzymes present in plasma and tissues.¹⁵⁻¹⁷

Control and interaction of plasma protein systems

The three plasma protein systems are highly interactive, so the activation of one system results in the production of large quantities of highly potent biologically active substances, which in turn activate other systems. Tight control of this process is essential for two reasons: (1). The inflammatory process is essential for individual survival; thus, efficient activation must be guaranteed regardless of the cause of tissue injury. (2). The biochemical mediators produced during this process are very potent and potentially harmful to individuals, and their action must be strictly limited to injured or infected tissues.¹⁸

Various mechanisms are available to enable or disable (set) the plasma protein system. For example, plasma that enters tissues during inflammation (edema) contains enzymes that destroy inflammatory mediators. Carboxypeptidase inactivates the anaphylactic activity of C3a and C5a, and kininase degrades kinin. Histaminase degrades histamine and kallikrein and reduces the inflammatory response. Blood clot formation also activates the fibrinolytic system, which is designed to limit clot size and expel the clot after the bleeding has stopped. Thrombin activates plasminogen in the blood to form the enzyme plasmin. The main activity of plasmin is to degrade fibrin polymers in the clot. However, plasmin can also activate the complement cascade via components C1, C3, and C5 and the kinin cascade by activating factor XII and producing a prekallikrein activator. Hageman factor activation has four effects that affect all three plasma protein systems: (1). Activation of the clotting cascade via factor XI, (2). Control of clotting through the conversion of the plasminogen pro activator to

plasminogen activator, resulting in the generation of plasmin (3). Activation of the kinin system by activating the Hageman factor (prekallikrein activator), (4). Activation of C1 in the complement cascade.

The activity of plasmin itself is also regulated because it is synthesized as a proenzyme, plasminogen. Plasminogen is converted to plasmin by several factors, including plasminogen activator produced by the kallikrein system, thrombin produced by the clotting system, streptokinase-like bacterial factors produced by hemolytic streptococci, plasminogen activator produced by endothelial cells, and several cellular enzymes released during the breakdown network. Another example of a general regulator is the C1-esterase inhibitor (C1-inh). C1-inh inhibits complement activation through reactivity with C1 (classical pathway), MASP-2 (lectin pathway), and C3b (alternative pathway). It is also a major inhibitor of coagulation pathway components and kinins (eg, kallikrein, XIIa). A genetic defect in C1-inh (C1-inh deficiency) causes hereditary angioedema, which is self-limiting edema of the skin and mucosal layers resulting from relatively minor or imperceptible stress, disease or trauma. This disease is characterized by hyperactivation of all three plasma protein systems, although overproduction of bradykinin appears to be the main cause of increased vascular permeability.¹⁹

Inflammatory cellular mediators

Inflammation is a process in the vascular tissue; thus, cellular components are found in blood and tissues around blood vessels. Blood vessels are lined with endothelial cells, which under normal conditions, actively maintain normal blood flow. During inflammation, the vascular endothelium is the main coordinator of blood clotting and the passage of cells and fluids into tissues. Tissues close to blood vessels contain mast cells, which are perhaps the most important activators of inflammation, and dendritic cells, which link innate and adaptive immune responses. Blood contains a complex mixture of cells. Blood cells are divided into erythrocytes (red blood cells), platelets, and leukocytes (white blood cells).

Erythrocytes carry oxygen to tissues, and platelets are small cell fragments involved in blood clotting. Leukocytes are further divided into granulocytes (contain many cytoplasmic granules containing enzymes), monocytes, and lymphocytes. Granulocytes are the most common leukocytes and are classified according to the type of stain required to visualize their granules (basophils, eosinophils, and neutrophils). Monocytes in the blood are the precursors of macrophages which are found in tissues. Different forms of lymphocytes participate in innate (e.g., natural killer [NK] cells) and adaptive (B and T cells) immune responses.

Cells of the innate and acquired immune systems are recruited and activated by biochemical mediators produced at sites of cell damage. These molecules originate from destroyed or damaged cells, contaminating microbes, activation of plasma protein systems, or secretion by other cells of the innate or acquired immune system. Activation may result in the cell acquiring a function essential for the inflammatory response or inducing the release of additional cellular products that promote inflammation, or both.²⁰

2. Conclusion

Inflammatory cells and various protein systems (complement, kinin, and clotting), together with the substances they produce, act at the site of tissue injury to limit the extent of damage, kill microorganisms, and remove debris in preparation for healing: tissue regeneration or repair.

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