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Inflammatory and Hemostatic Responses: An Overview of the Bidirectional Relationship

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ABSTRACT: Inflammation and hemostasis are interrelated physiological processes that considerably affect eachother. Inflammation is the immune response of the body towards injury, pathogens or any other harmful stimuli. Hemostasis, on the other hand,is a process of immediate stopping of bleeding and maintaining the blood in the fluid form within blood vessels. Recent research highlightsthat inflammation and hemostasis influence each other through overlapping pathways and regulatory mechanisms.During inflammation, several inflammatory cytokines are released. This includes tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) and many more. These factors can alter the hemostatic balance by promoting procoagulant state. During this process the upregulation of the tissue factor and downregulation of the natural coagulants leads to thrombin generation and platelet activation, thus promotes coagulation.Alternately, components of the hemostatic system also effect the inflammatory responses. Platelet, one of the important components of the system, release a variety of proinflammatory mediators and propagates inflammation. Furthermore, fibrinogen interact with leucocytes and endothelial cells and promotes inflammatory responses.Understanding the relationship between inflammation and hemostasis is very important for developing therapies for conditions like autoimmune diseases, sepsis, and atherosclerosis where these physiologicalprocesses are imbalanced. The upcoming researches should focus on understanding the molecular mechanism of these interactions and exploring therapeutic strategies that can simultaneously address both inflammatory and hemostatic abnormalities to improve the treatment outcomes.

***Keywords**: Inflammation, hemostasis,cytokines, inflammatory mediators, thrombin, platelets.

I. INTRODUCTION

Inflammation is a complex biological response triggered bytissue injury, infection, or pathogens.The immune system recognises and respond to these stimuli through immune cells and inflammatory mediators. Inflammation can be acute or chronic. Acute inflammation is rapid, short term inflammation which lasts for few days, while a chronic inflammation is slow, prolonged inflammation which may last for months to years and may even lead to death. The extent and effect of inflammation depends on the cause of injury and ability of body to respond to the inflammation[1].

Concurrently, hemostasis is the physiological process that maintains vascular integrity by preventing and stopping bleeding. The natural hemostatic system of the body can manage the mild to moderate bleedings. Hemostatic agents act through clotting factor activation, vasoconstriction and platelet aggregation [2].

Inflammation and hemostasis are two closely linked physiological processes that affects each other. In this mutual relationship, inflammation triggers activation of the hemostatic system, which in turn also impacts inflammatory activity[3].

These molecules can alter the function of endothelial cells lining blood vessels, leading to increased expression of adhesion molecules and tissue factor. This promotes platelet activation and aggregation, which can initiate thrombus formation. Additionally, inflammation can disrupt the balance between pro-coagulant and anti-coagulant factors in the blood. It can lead to decreased levels of natural anticoagulants such as protein C and antithrombin III, while increasing levels of pro-coagulant factors like fibrinogen. This imbalance favours clot formation and can contribute to a hypercoagulable state[4]. Moreover,

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inflammatory processes can affect fibrinolysis, the process of breaking down clots[5].

The activated hemostatic system also significantly influences inflammatory activity. Specific elements of the activated hemostatic system, such as activated coagulation factors like thrombin, FXa, and the TF-FVIIa complex, have the ability to directly stimulate cells engaged in the inflammatory response-such as platelets, leukocytes, and endothelial cells (ECs). This stimulation leads to an enhanced production of pro-inflammatory mediators by these cells[6].

Local activation of the hemostatic system is essential for the body's defense in both infectious and non-infectious inflammatory conditions. However, excessive and poorly controlled hemostatic activity induced by inflammation can significantly amplify the severity of diseases.Once the hemostatic system becomes activated during inflammatory conditions, it can lead to an increase in clotting issues, potentially causing thrombosis and damage to organs. Conversely, uncontrolled activation of the hemostatic system can worsen the initial inflammatory response, leading to further organ injury[7]. Hence the body creates a cycle where inflammation and hemostasis reinforce each other, operating in a loop where each activated process mutually amplifies each other,thereby forming a positive feedback loop[8].

In conclusion, inflammation and hemostasis are integral components of the body's immune system, with complex interactions that influence disease pathogenesis and progression. In recent years significant efforts have been made in investigating and clarifying the molecular mechanisms involved in this mutual relationship. This review provides an overview of the current understanding of the intricate interactions within this bidirectional relationship of inflammation and hemostasis

MECHANISMS THROUGH WHICH INFLAMMATION CAUSES DISRUPTIONS IN THE HEMOSTATIC SYSTEM

During an inflammatory response, inflammatory mediators, particularly pro-inflammatory cytokines, play a central role in influencing the hemostatic system. The primary mediators responsible for activating the hemostatic system during inflammation include pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6)[9]. These inflammatory mediators disrupt the hemostatic system through various mechanisms, including endothelial cell dysfunction, heightened platelet activation, initiation of the plasma coagulation cascade by tissue factor (TF), impairment of natural anticoagulant pathways, and inhibition of fibrinolytic activity[10].

DISFUNCTION OF VASCULAR ENDOTHELIAL CELLS

In inflammation, endothelial cell dysfunction is characterized by activation and altered behaviour of vascular endothelial cells.

During exposure to inflammatory stimuli like cytokines and chemokines, endothelial cells upregulate adhesion molecules like ICAM-1(intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1), thus facilitate leukocyte adhesion and migration into tissues. This results in increased vascular permeabilityand leads to tissue edema and inflammation.At the same time, inflammatory signalling pathways including NF-kB and MAP kinases are activated inside endothelial cell and promotes the production of pro-inflammatory cytokines, chemokines, and reactive oxygen species.These molecules further enhancesendothelial dysfunction by increasing the expression of adhesion molecules, promoting a pro-coagulant environment through upregulation of tissue factor, and impairing nitric oxide mediated vasodilation[11].Chronic inflammation may also cause endothelial cell apoptosis, compromising vascular integrity[12].Altogether these mechanisms contribute to the pathogenesis of vascular dysfunction in various inflammatory diseases.

PLATELET ACTIVATION TRIGGERED BY INFLAMMATION

Platelets plays a critical role in hemostasis. It also serves as important mediators in inflammation by contributing to both vascular and immune responses. Under physiological conditions, platelets are shielded from activation by inhibitory molecules like nitric oxide (NO) and prostacyclin (PGI2) released by intact endothelial cells (ECs). During inflammation, endothelial dysfunctioncauses an imbalance to this state. EC dysfunction leads to increased platelet reactivity due to elevated production of thromboxane A2 (TXA2) and von Willebrand factor (vWF) and decreased production of PGI2[13]. Following vessel injury, platelets adhere to the exposed subendothelial matrix via cellular receptors and adhesive proteins andfacilitates interactions with the vessel wall, thus initiates thrombus formation.Inflammatory stimuli further activate platelets. Pro-inflammatory cytokines, such as

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interleukins and tumor necrosis factor-alpha, and molecules like platelet-activating factor (PAF) directly induce platelet activation in both non-infectious and infectious inflammatory conditions[14].

Upon activation, platelets undergo a change in shape from a disc-like to a spherical form and release various pro-inflammatory and pro-coagulant substances into their local environment. These include adhesion molecules, growth factors, cytokines, chemokines, certain coagulation factors, and the fibrinolytic inhibitor PAI-1. Additionally, activated platelets can generate microparticles (MPs), which are small cell fragments derived from activated or apoptotic cells. MPs contain negatively charged phospholipids crucial for coagulation and express tissue factor (TF) on their surface, contributing to the pro-thrombotic state[15].

Upon activation, platelets release mediators that influence the function of other platelets, leukocytes, and endothelial cells (ECs). For instance, activated platelets secrete IL-1β, which stimulates ECs to produce IL-6, monocyte chemotactic protein 1 (MCP-1), and express adhesion molecules like E-selectin, VCAM-1, and ICAM-1. This interaction facilitates the recruitment of neutrophils into inflammatory tissues, enhancing host defense mechanisms. Platelet interactions with leukocytes and ECs are primarily mediated through P-selectin, an adhesion receptor found in platelet alpha-granules. Upon activation, P-selectin translocates to the platelet surface and binds to its ligand, P-selectin glycoprotein ligand (PSGL-1), on neutrophils, monocytes, and ECs. This interaction amplifies the production of pro-inflammatory cytokines and chemokines in neutrophils and mononuclear cells, increases the expression of adhesion molecules and tissue factor (TF) on both leukocytes and ECs, and activates nuclear factor kappa B (NF-κB) signalling pathways[14,15].

INITIATION OF PLASMA COAGULATION CASCADE DURING INFLAMMATION

The molecular mechanism underlying the initiation of the plasma coagulation cascade during inflammation involves several key steps.The primary mechanism of activating the plasma coagulation cascade in inflammation involves tissue factor (TF). TF also known as thromboplastin, is a transmembrane protein expressed constitutively by various cell types, including circulating blood cells and endothelial cells (ECs). Normally, TF is not exposed to blood, as it is typically present in blood-tissue barriers such as the adventitial layer of vessel walls. When tissues are inflamed, there is an increased release of pro-inflammatory cytokines and tissue factors. TF is exposed or released from damaged endothelial cells, leukocytes, or other cells at the site of inflammation. TF binds with factor VIIa to form a TF-VIIa complex. This complex then activates factor X to Xa, which in turn converts prothrombin (factor II) into thrombin (factor IIa)[16].

Thrombin plays a central role in the coagulation cascade by converting fibrinogen into fibrin strands, which polymerize to form a stable blood clot. Thrombin also activates factor XIII, which cross-links fibrin strands to strengthen the clot. Furthermore, thrombin amplifies the coagulation process by activating factors V and VIII, which enhances the conversion of more prothrombin to thrombin, leading to a positive feedback loop.

Inflammatory mediators such as cytokines can also directly influence the coagulation cascade by modulating the expression of pro-coagulant and anti-coagulant proteins on endothelial cells and leukocytes. For example, cytokines like TNF-alpha and IL-1β can increase tissue factor expression on endothelial cells and monocytes, promoting thrombin generation and clot formation.Overall, the initiation of the plasma coagulation cascade during inflammation is a tightly regulated process involving the interaction of tissue factor, coagulation factors, and inflammatory mediators, aimed at preventing excessive bleeding and maintaining vascular homeostasis in response to tissue injury or infection[17].

ANTICOAGULANTS AND INFLAMMATION

The anticoagulants play crucial roles in maintaining vascular integrity and preventing excessive clot formation during inflammatory responses.Three primary mechanisms involved in regulating coagulation activation are antithrombin (AT), the protein C (PC) system, and tissue factor pathway inhibitor (TFPI)[18].

ANTITHROMBIN (AT):

Mechanism: AT inhibits thrombin (factor IIa) and factor Xa through direct binding, thereby blocking their pro-coagulant activities.

Impairment in Inflammation: Inflammation can impair antithrombin (AT) function through increased consumption by activated coagulation processes, reduced synthesis due to a negative acute phase response, and enhanced degradation by enzymes like elastase from neutrophils. Additionally, proinflammatory cytokines may decrease the synthesis of glycosaminoglycans

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(GAGs), such as heparan sulfate on endothelial surfaces, which normally enhance AT's anticoagulant activity as natural cofactors resembling heparin.

Additional Role: AT exhibits anti-inflammatory effects by binding to leukocyte receptors, inhibiting leukocyte-endothelial cell interactions, and promoting prostacyclin (PGI2) release from endothelial cells, which inhibits platelet aggregation and reduces cytokine production[19].

PROTEIN C (PC) SYSTEM:

Mechanism: The protein C (PC) system plays a crucial role in regulating inflammatory responses but is significantly affected by inflammation itself. Normally, thrombin bound to endothelial cell membrane protein thrombomodulin (TM) activates protein C (PC), which, along with protein S (PS), inactivates factors Va and VIIIa. Apart from its role in preventing blood clotting, the PC system demonstrates anti-inflammatory and profibrinolytic activities. Activated protein C (APC) suppresses cytokine production by monocytes/macrophages, reduces leukocyte adhesion to endothelial cells, and inhibits NF-κB transcription by interacting with the endothelial protein C receptor (EPCR). Additionally, APC neutralizes plasminogen activator inhibitor-1 (PAI-1), promoting fibrinolysis[18].

Anti-inflammatory Properties: Thrombomodulin activates the PC system and suppresses inflammation by dampening thrombin's pro-inflammatory effects and activating thrombin-activatable fibrinolysis inhibitor (TAFI). Inflammation can impair the PC system by reducing thrombomodulin (TM) and endothelial protein C receptor (EPCR) expression on endothelial cells, influenced by proinflammatory cytokines and neutrophil elastase. Additionally, acute phase reactants like C4b-binding protein (C4B-BP) can lead to a relative protein S (PS) deficiency, promoting a procoagulant state. Impairment of the PC system is linked to the development of sepsis and organ dysfunction[20].

TISSUE FACTOR PATHWAY INHIBITOR (TFPI):

Mechanism: TFPI inhibits the initiation of the coagulation cascade by binding to and inhibiting the TF-FVIIa complex, thus preventing factor X activation and thrombin formation[21].

Regulation in Inflammation: TFPI expression may be influenced by inflammatory cytokines, contributing to the regulation of coagulation during inflammatory responses.

These mechanisms highlight how AT, the PC system, and TFPI act synergistically to maintain a delicate balance between hemostasis and inflammation, crucial for preventing pathological clotting while responding to tissue damage and infection.

FIBRINOLYTIC SYSTEM

The fibrinolytic system plays a crucial role in maintaining hemostasis by regulating the breakdown of fibrin clots. Plasmin, generated from plasminogen by activators like tPA and urokinase plasminogen activator (uPA), is key to this process. However, its activity is tightly controlled by PAI-1, the main inhibitor of these activators, which suppresses fibrinolytic activity by binding and inactivating them[22].

During inflammatory states, there is an initial increase in fibrinolytic activity due to the release of tPA from endothelial cells (ECs). This is followed by a sustained increase in PAI-1 production induced by proinflammatory cytokines like TNF-α and IL-1β. Elevated PAI-1 levels significantly suppress fibrinolytic activity, leading to inadequate fibrin removal and contributing to hemostatic disorders in inflammation.

Platelet alpha granules also release PAI-1 upon activation, further enhancing its levels and fibrinolytic suppression. Dysfunction of endothelial cells under inflammatory conditions can additionally reduce tPA production, exacerbating fibrinolytic inhibition[23].

IMPACTOF THE ACTIVATED HEMOSTATIC SYSTEM ON INFLAMMATORYRESPONSES

The bidirectional communication between inflammation and hemostasis involves the activated hemostatic system significantly influencing inflammatory activity. Coagulation factors like thrombin, FXa, and the TF-FVIIa complex directly stimulate platelets, leukocytes, and endothelial cells, leading to increased production of proinflammatory mediators.This activation occurs through proteolytic cleavage of PAR receptors (PAR-1 to PAR-4), which triggers transmembrane signalling and amplifies inflammatory responses[21]. Activated platelets and fibrinogen/fibrin from the coagulation cascade further contribute to cellular activation in inflammation by binding to specific receptors such as toll-like receptors (TLR) on inflammatory cells, promoting the expression of cytokines and chemokines.Factor XIII (FXIII) also

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plays multifaceted roles in inflammation, encompassing both plasmatic (pFXIII) and cellular (cFXIII) forms[23].

ROLES OF PLASMATIC AND CELLULAR FXIII IN INFLAMMATION

Both plasmatic and cellular forms of factor XIII (FXIII) play diverse and crucial roles in inflammation, impacting a range of physiological processes. Plasmatic FXIII (pFXIII), traditionally associated with hemostasis, esxtends its influence to inflammation-related pathways. It contributes significantly to wound healing and tissue repair by stabilizing fibrin clots through cross-linking fibrin molecules, thereby bolstering thrombus stability and preventing excessive bleeding. Additionally, pFXIII regulates inflammatory cell migration and adhesion, pivotal for immune cell recruitment to sites of tissue damage or infection. Its role in modulating the extracellular matrix composition further influences tissue remodeling processes associated with inflammation[24].

In contrast, cellular FXIII (cFXIII) is found in various cell types, prominently in monocytes and macrophages, where it exerts distinct regulatory functions. Within these cells, cFXIII modulates gene expression patterns, particularly in alternatively activated macrophages (M2 phenotype), crucial for tissue repair and anti-inflammatory responses. Moreover, cFXIII enhances the phagocytic capacity of macrophages, facilitating the clearance of apoptotic cells and debris during inflammatory responses. While its involvement in intracellular signaling pathways is less understood, cFXIII's impact on cellular functions underscores its importance beyond hemostasis[23].

The multifaceted roles of FXIII in inflammation highlight its pivotal contributions to physiological processes beyond blood coagulation. Understanding these roles not only enhances our comprehension of FXIII's biological functions but also suggests potential therapeutic avenues for managing inflammatory conditions and diseases characterized by dysregulated immune responses. Further research is needed to elucidate the precise mechanisms through which FXIII influences inflammation and to explore its therapeutic potential in clinical settings.

EFFECT OF Fxa IN INFLAMMATORY DISEASES

Factor Xa (FXa) exerts pleiotropic effects in inflammatory diseases through various molecular mechanisms, contributing to the pathogenesis and progression of conditions such as atherosclerosis, rheumatoid arthritis, and inflammatory bowel disease.

Firstly, FXa activates protease-activated receptors (PARs) on endothelial cells, leukocytes, and platelets, triggering the release of pro-inflammatory cytokines and chemokines that recruit immune cells to sites of inflammation. This leads to chronic inflammation and tissue damage typical of conditions like atherosclerosis and rheumatoid arthritis[25].

Secondly, FXa activates the NF-κB pathway, a pivotal regulator of inflammatory gene expression. This results in increased production of adhesion molecules and cytokines, promoting leukocyte adhesion, migration, and tissue infiltration, thereby perpetuating inflammation in diseases such as atherosclerosis and inflammatory bowel disease.

Thirdly, FXa's involvement in the coagulation cascade links thrombin generation to inflammatory responses. Thrombin, generated downstream of FXa activity, enhances vascular permeability, promotes platelet aggregation, and activates endothelial cells, exacerbating tissue inflammation and contributing to vascular dysfunction seen in inflammatory diseases.

Moreover, FXa directly interacts with endothelial cells, disrupting barrier function and increasing vascular permeability. This facilitates immune cell infiltration into tissues, perpetuating chronic inflammation and tissue injury observed in conditions like rheumatoid arthritis.Additionally, FXa influences immune cell function by altering cytokine secretion profiles and enhancing monocyte and macrophage activation, which exacerbates local inflammation within affected tissues.In summary, FXa's pleiotropic effects in inflammatory diseases underscore its significant role in disease pathogenesis and progression[26].

ROLE OF THROMBIN IN INFLAMMATION

Thrombin, an essential enzyme in blood clotting, also plays a significant role in inflammation. It activates immune cells such as platelets and leukocytes via protease-activated receptors (PARs), leading to the release of inflammatory cytokines and chemokines. Thrombin enhances vascular permeability by inducing contraction of endothelial cells, which aids in the recruitment of leukocytes to inflamed areas. Furthermore, it facilitates the formation of fibrin clots that help manage and resolve inflammation. Thrombin also interacts with the complement system, further affecting the inflammatory

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response. These varied effects underscore thrombin's critical role in both initiating and modulating inflammation[27].

II. CONCLUSION

In conclusion, exploring the intricate relationship between inflammation and hemostasis reveals a dynamic interplay critical to both health and disease. While traditionally viewed as distinct processes, recent research underscores their profound interconnectedness at molecular, cellular, and systemic levels. Inflammatory mediators intricately regulate hemostatic pathways, influencing thrombosis and fibrinolysis, while coagulation factors reciprocally modulate immune responses. Understanding these interactions not only enhances our comprehension of disease pathogenesis but also holds promise for developing targeted therapeutic strategies that could potentially mitigate thrombotic complications in inflammatory disorders. Moving forward, further elucidating these mechanisms promises to unveil novel insights into disease mechanisms and therapeutic avenues, potentially revolutionizing clinical management in diverse pathological contexts.

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