THROMBOSIS AS AN INTRAVASCULAR EFFECTOR OF INNATE IMMUNITY: A REVIEW

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ABSTRACT

Background: Thrombosis is the pathological creation of blood clots in the circulatory system; it is a significant worldwide health burden that increases morbidity and mortality, especially in cardiovascular illnesses such as myocardial infarction, stroke, and venous thromboembolism. The discovery of immunothrombosis, a condition in which the innate immune system participates in the development of clots as a defense mechanism against infections, better our understanding of thrombosis.

Aim: This review aimed to present a thorough analysis of the molecular mechanisms underpinning immunothrombosis, with a particular emphasis on thrombosis as an intravascular effector of innate immunity.

Methodology: In this review 36 primary studies from various electronic databases such as Google scholar, Semantic scholar, Research Gate and PubMed were obtained on the basis that they were focused on Platelets and immune responses during thromboinflammation, innate immunity signaling and immunothrombosis, as the molecular processes of immunothrombosis, with emphasis on the release of Neutrophil Extracellular Traps (NETs), which act as clot formation scaffolds, by immune cells like neutrophils. This was made possible by the use of Boolean function.

Result: Coagulation process is promoted by platelets, endothelial cells, and inflammatory cytokines such as Tumor necrotic factor alpha (TNF-α) and Interleukin 6 (IL-6). Immunothrombosis is necessary for ensnaring and neutralizing pathogens, but when it is dysregulated, it can lead to pathological states like pulmonary embolism, disseminated intravascular coagulation (DIC), and deep vein thrombosis (DVT). This is especially true in systemic inflammatory conditions like autoimmune disorders and sepsis. The interaction of the complement system and the coagulation cascade, which further connects immune activation and thrombosis, was also covered in this review. Treatments for thromboinflammatory disorders may benefit from novel therapeutic approaches that modify immunothrombosis. Examples of these approaches include focusing on NET formation, inflammatory cytokines, and platelet-immune interactions.

Conclusion: However, to avoid excessive clotting and preserve the body's defense mechanisms, these strategies need to be carefully balanced. Comprehending the dual character of immunothrombosis provides essential knowledge for formulating tactics to alleviate thrombotic consequences while maintaining immunological integrity.

Keywords: Coagulation cascade, Immunothrombosis, Innate immunity, Neutrophil Extracellular Traps (NETs), Thrombosis.

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It underpins the pathogenesis of critical cardiovascular conditions, including venous thromboembolism, myocardial infarction, and stroke. Physiologically, thrombus formation is an essential mechanism to mitigate blood loss following vascular injury. This process is initiated by a tightly regulated cascade that culminates in the conversion of fibrinogen to fibrin, which provides structural stability to clots, alongside platelet aggregation to form a barrier at the injury site, thereby promoting haemostasis and tissue repair (Stiel *et al*., 2018).

Pathological thrombosis arises when the coagulation system becomes dysregulated, resulting in excessive or inappropriate clot formation. These pathological clots can obstruct blood flow, leading to tissue ischemia, organ damage, and necrosis. For instance, thrombosis in coronary arteries precipitates myocardial infarction, while clots in cerebral vessels result in ischemic strokes. Furthermore, venous thromboembolism can lead to potentially fatal complications such as pulmonary embolism (Engelmann & Massberg, 2013). These outcomes underscore the significant clinical and economic burden of thrombosis and highlight the need for improved strategies in prevention, detection, and management.

The innate immune system, the body's first line of defense against pathogens and tissue injury, plays a crucial role in the pathophysiology of thrombosis. Unlike the adaptive immune system, which provides a highly specific and memory-driven response, innate immunity acts rapidly and broadly against diverse threats. Key components include physical barriers (e.g., skin, mucosal membranes), cellular mediators (e.g., neutrophils, macrophages, dendritic cells), and soluble factors (e.g., complement proteins, cytokines) (Ryan & O'Neill, 2022). Immune cells detect pathogen-associated molecular patterns (PAMPs) via pattern recognition receptors (PRRs), such as Toll-like receptors, which activate inflammatory responses to eliminate threats and promote tissue repair (Laera *et al*., 2023).

Emerging evidence indicates a strong interplay between the innate immune system and coagulation pathways, a phenomenon termed "immunothrombosis." Immunothrombosis is an evolutionary adaptation wherein coagulation mechanisms are co-opted to trap and neutralize pathogens within the bloodstream. This process primarily occurs in the microvasculature, where immune cells such as neutrophils release neutrophil extracellular traps (NETs). These structures, composed of decondensed chromatin and antimicrobial proteins, ensnare pathogens and enhance their clearance (Wang *et al*., 2024). Additionally, platelets and endothelial cells actively participate in immunothrombosis, interacting through pro-inflammatory mediators, tissue factors, and chemokines (Libby, 2021).

While immunothrombosis is crucial for host defense, its dysregulation can lead to pathological outcomes. For instance, widespread activation of clotting cascades during sepsis can result in disseminated intravascular coagulation (DIC), characterized by simultaneous thrombotic and hemorrhagic complications (Libby, 2021). Similarly, excessive immunothrombosis contributes to thromboembolic disorders, including deep vein thrombosis and arterial thrombosis, posing significant risks to patients (Libby, 2021).

This review aimed to elucidate the molecular mechanisms underlying immunothrombosis, emphasizing its dual role as a physiological effector of innate immunity and a pathological contributor to thrombotic diseases. By exploring this intersection of immunological and coagulation pathways, the study seeks to advance understanding and inform therapeutic strategies in this critical area.

This study reviewed theoretical paper that synthesized findings from 36 primary studies obtained from systematic searches across four major electronic databases: Google Scholar, Semantic Scholar, ResearchGate, and PubMed. Boolean search operators were applied to narrow down search results, focusing on peer-reviewed studies relevant to thrombosis and innate immunity. Specific keywords such as "thrombosis," "innate immunity," "immunothrombosis," "NETs," and "thromboinflammatory diseases" were combined using AND, OR, and NOT functions to refine the scope of the retrieved literature (Stiel *et al*., 2018).

The review focused on the evolutionary significance of immunothrombosis, its dual role in host defense and pathology, and its clinical implications in conditions like sepsis, cardiovascular diseases, and thromboinflammatory disorders. Key molecular and cellular mechanisms were explored, with particular emphasis on neutrophil extracellular traps (NETs), tissue factor, and immune cell-platelet interactions (Gollomp *et al*., 2021). Additionally, emerging therapeutic strategies to modulate immunothrombosis for treating thromboinflammatory diseases were critically analyzed, highlighting areas for future investigation (Stiel et al., 2018; Gollomp *et al*., 2021).

Inclusion Criteria

This revie included articles published between 2013 and 2023 to ensure the review reflects recent advancements, Peer-reviewed studies focusing on the molecular mechanisms, clinical roles, and therapeutic implications of immunothrombosis, and also studies discussing the interaction between innate immunity and coagulation pathways.

Exclusion Criteria

This study excluded non-English articles and unpublished works, and studies unrelated to the intersection of innate immunity and thrombosis.

Innate Immunity and Thrombosis: Key Connections

Definition and Components of Innate Immunity

Innate immunity represents the body's first line of defense against infections, offering rapid and generalized responses to pathogens. Unlike the adaptive immune system, which has a delayed but highly specific response, innate immunity provides immediate protection upon exposure to harmful stimuli. Its primary functions include pathogen recognition, initiation of inflammation, and recruitment of adaptive immune cells to establish long-term immunity (Medzhitov, 2018).

Key components of the innate immune system include: physical barriers (skin and mucosal membranes) serve as the first line of defense, immune cells (neutrophils, macrophages, and dendritic cells) play pivotal roles in pathogen recognition and clearance, chemical mediators (cytokines and chemokines) drive signaling cascades that recruit and activate immune cells.

The system's pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), recognize conserved molecular structures known as pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). Once activated, these receptors trigger signaling cascades, resulting in cytokine production and immune cell activation (Ryan *et al*., 2022). These responses are critical for infection control, tissue repair, and maintaining homeostasis.

Haemostasis and Thrombosis: Similarities and Difference

Haemostasis is a physiological process that prevents excessive bleeding by forming clots at sites of vascular injury. It involves sequential steps: vasoconstriction, formation of a platelet plug, activation of the coagulation cascade, and stabilization of the clot with fibrin (Engelmann & Massberg, 2013).

Following vascular repair, fibrinolysis dissolves the clot to restore normal blood flow. Thrombosis, by contrast, is the pathological formation of clots within intact vasculature. It often results from aberrant signals such as endothelial dysfunction, inflammation, or stasis of blood flow. Conditions like myocardial infarction, pulmonary embolism, and deep vein thrombosis are direct consequences of thrombosis (Greinacher *et al*., 2021). Though distinct, both processes share mechanisms such as platelet activation and the coagulation cascade, underscoring their interconnected nature.

How the Innate Immune System Influences Thrombus Formation

The interplay between innate immunity and thrombosis, termed immunothrombosis, is a central concept in thromboinflammatory diseases. It highlights the dual role of immune and coagulation systems in health and disease. Several key mechanisms include:

Inflammatory Cytokines and Coagulation Activation

Cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 (IL-1) act as bridges between inflammation and coagulation. These inflammatory mediators activate endothelial cells, promoting the expression of tissue factor (TF), a critical initiator of the coagulation cascade. TF binds to circulating clotting factors, activating the extrinsic pathway, leading to thrombin generation and fibrin clot formation (Engelmann & Massberg, 2013).

Neutrophil Extracellular Traps (NETs)

Neutrophils contribute to thrombosis through the release of neutrophil extracellular traps (NETs), web-like DNA structures containing histones and antimicrobial proteins. NETs trap pathogens and facilitate clot formation by enhancing platelet aggregation and fibrin deposition. Overproduction of NETs is implicated in conditions like sepsis, where it exacerbates disseminated intravascular coagulation (DIC) (Gollomp *et al*., 2018).

Platelet-Leukocyte Interactions

Platelets not only mediate haemostasis but also play a vital role in immune responses. They interact with leukocytes, such as monocytes and neutrophils, through pathways like CD40L-CD40 signaling. This interaction amplifies tissue factor expression on monocytes, thereby accelerating thrombin generation. Additionally, activated platelets release pro-inflammatory mediators like thromboxane A2, further driving thrombosis and inflammation (Ryan *et al*., 2022).

The Complement System

The complement cascade, a critical component of innate immunity, also contributes to thrombus formation. Complement fragments such as C3a and C5a act as chemoattractants, recruiting immune cells to sites of injury. Moreover, the terminal complement complex (C5b-9) damages endothelial cells, exposing tissue factor and promoting coagulation (Gollomp *et al*., 2018).

Endothelial Dysfunction and Thrombosis

Endothelial cells play a vital role in maintaining vascular homeostasis, controlling blood flow, and preventing thrombus formation. Under normal conditions, these cells release anticoagulant factors like prostacyclin and nitric oxide (NO), which inhibit platelet aggregation and promote vasodilation. However, in response to inflammatory stimuli, endothelial cells switch to a prothrombotic state, releasing molecules such as von Willebrand factor (vWF) and tissue factor (TF), both of which promote thrombus formation (Libby, 2021). Additionally, cytokines like TNF-α induce endothelial activation, further enhancing the prothrombotic environment (Liao *et al*., 2022).

Mechanisms of Thrombosis

Thrombosis involves a complex interaction between platelets, the coagulation cascade, and the vascular endothelium. While thrombosis is essential for haemostasis after vascular injury, its dysregulation can lead to pathological conditions such as myocardial infarction, stroke, and deep vein thrombosis (DVT). The key stages of thrombosis include platelet activation and aggregation, the interaction of the coagulation and complement systems, and endothelial dysfunction, all of which contribute to thrombus formation.

Platelet Activation and Aggregation

Platelet activation is the first response in thrombosis. Following vascular injury, platelets interact with the extracellular matrix, including collagen, via receptors such as glycoprotein VI (GPVI) and integrin α2β1. The von Willebrand factor (vWF) binds to platelet receptor glycoprotein Ib (GPIb), facilitating platelet adhesion (Jackson *et al*., 2019). Activated platelets undergo a shape change and release pro-thrombotic substances like ADP and thromboxane A2, which recruit additional platelets to the injury site, forming a platelet plug. Thrombin, a pivotal enzyme in the coagulation cascade, activates platelets by binding to protease-activated receptors (PARs), particularly PAR-1, facilitating intracellular signaling pathways that enhance platelet aggregation and thrombus formation (Heuberger & Schuepbach, 2019).

Coagulation Cascade

The coagulation cascade involves the activation of clotting factors leading to thrombin production, which converts fibrinogen into fibrin, thereby forming the clot. The cascade is initiated by the intrinsic and extrinsic pathways, which converge at the common pathway.

The Intrinsic Pathway is activated by factor XII (FXII) upon contact with subendothelial collagen, FXIIa activates factor XI (FXI), which in turn activates factor IX (FIX). FIXa, in combination with factor VIIIa (FVIIIa), activates factor X (FX) (Versteeg *et al*., 2021). Consequently, the extrinsic pathway is initiated by the release of tissue factor (TF) from endothelial cells, which binds to factor VII (FVII) and activates FX (Grover and Mackman, 2020).

The Common Pathway, activated FXa in complex with FVa, converts prothrombin into thrombin. Thrombin cleaves fibrinogen into fibrin, which forms the clot structure (Furie & Furie, 2022).

Role of Vascular Endothelial cells

Endothelial cells balance prothrombotic and antithrombotic activities. In a normal state, they produce prostacyclin, nitric oxide (NO), and tissue plasminogen activator (tPA), which prevent platelet aggregation and promote fibrinolysis (Sandoo *et al*., 2020). Upon endothelial activation due to vascular injury or inflammation, endothelial cells switch to a prothrombotic phenotype, expressing adhesion molecules like P-selectin and E-selectin, which recruit platelets and leukocytes. Endothelial cells also release tissue factor (TF), which triggers the extrinsic coagulation pathway (Buttari *et al.*, 2019).

Endothelial dysfunction, which is a hallmark of cardiovascular diseases, contributes to a prothrombotic state by reducing the production of anticoagulant factors like thrombomodulin and protein C (Libby, 2021). Furthermore, endothelial cells can increase the expression of plasminogen activator inhibitor-1 (PAI-1), which inhibits fibrinolysis and enhances thrombus stability (Gresele *et al*., 2021). This shift in endothelial function can lead to excessive thrombus formation, particularly in conditions like atherosclerosis, where plaque rupture exposes tissue factor-rich lipid cores to circulating blood, initiating rapid thrombus formation (Gisterå & Hansson, 2019).

Interaction between the Coagulation and Complement Systems

Recent studies have highlighted the interplay between the complement and coagulation systems, particularly in thromboinflammation, a condition where both systems contribute to pathological thrombosis while also defending the body against infection (Engelmann & Massberg, 2022). The complement system is activated through classical, lectin, and alternative pathways, leading to the production of anaphylatoxins like C3a and C5a, which promote inflammation and pathogen clearance (Markiewski & Lambris, 2020). This cross-talk contributes to thromboinflammatory conditions like systemic lupus erythematosus (SLE) and severe COVID-19, where excessive complement activation exacerbates vascular damage and thrombosis (Magro *et al*., 2020).

Thrombosis as a Defense Mechanism

Thrombosis, often considered harmful due to its association with diseases such as stroke, myocardial infarction, and venous thromboembolism, is also an important part of the body's innate immune system. This process, termed immunothrombosis, involves the formation of blood clots within the vasculature that function as a defense mechanism by trapping pathogens and preventing their spread. Coagulation factors, which are involved in blood clotting, also possess antimicrobial properties that help the host defend against infections (Renne & Stavrou, 2021).

Pathogen Entrapment by Thrombi (Bacteria, Viruses)

One of the key roles of immunothrombosis is the physical trapping of pathogens within thrombi, which prevents their dissemination through the bloodstream. This is particularly effective in combating bacteria and viruses. During an infection, platelets, immune cells, and endothelial cells collaborate to initiate thrombus formation, creating a fibrin network that ensnares bacteria, thereby limiting their ability to spread and aiding in localized infection control (Engelmann & Massberg, 2020). For example, thrombi can restrict the growth of pathogens like *Staphylococcus aureus* and *Escherichia coli* by immobilizing them within the clot, which plays a critical role in preventing sepsis (Renne & Stavrou, 2021).

In viral infections, such as COVID-19, thrombi can also trap viral particles, reducing their ability to spread. However, excessive immunothrombosis in such cases can lead to pathological thrombosis, contributing to complications such as venous and arterial thrombosis (Thachil, 2020).

A significant component of pathogen entrapment involves neutrophil extracellular traps (NETs), which are DNA structures expelled by neutrophils during infection. These NETs provide a scaffold for thrombus formation and enhance the capture of pathogens, as observed in conditions such as deep vein thrombosis (DVT) (Brill *et al*., 2020).

Antimicrobial Activity of Coagulation Factors

Several coagulation factors have direct antibacterial properties that support the body's immune response. Thrombin, a key enzyme in the coagulation cascade, has been shown to exhibit antimicrobial activity, particularly against Gram-positive bacteria. Thrombin can disrupt bacterial membranes, leading to bacterial lysis (Markiewski *et al*., 2020). Similarly, fibrinogen also has antimicrobial properties. Fibrinogen-derived peptides can prevent bacterial adhesion and biofilm formation, which are crucial for bacterial colonization and immune evasion (van der Poll *et al*., 2019).

Additionally, tissue factor (TF), expressed by immune cells like endothelial cells and monocytes during infection, and triggers the coagulation cascade, promoting the deposition of fibrin at infection sites.

This process not only helps trap pathogens but also recruits immune cells such as neutrophils, enhancing the local immune response (Schmidt & Mertens, 2021).

The Concept of Immunothrombosis in Controlling Infections

Immunothrombosis is a mechanism by which the immune system and thrombus formation collaborate to control infections. Unlike haemostasis, which is designed to prevent blood loss, immunothrombosis uses the coagulation cascade to selectively target infections and aid in their removal. Tissue factor (TF) is expressed by immune cells during infection, initiating the coagulation cascade and promoting pathogen containment (Koupenova *et al*., 2020). Neutrophils contribute to immunothrombosis by releasing NETs, which trap pathogens and provide a fibrin scaffold that prevents their spread (Middleton *et al*., 2020).

Although immunothrombosis is essential for infection control, dysregulation can result in excessive clot formation, systemic inflammation, and organ damage, as observed in conditions such as sepsis and COVID-19 infection (Levi & van der Poll, 2021). The activation of pathogen-associated molecular patterns (PAMPs) on immune cells via Toll-like receptors (TLRs) leads to the release of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which promote the expression of prothrombotic factors like TF, facilitating thrombus formation (Jackson *et al*., 2019).

Complement activation also plays a vital role in immunothrombosis. The complement system, especially the C5a protein, interacts with endothelial cells and platelets to enhance clot formation, further improving pathogen containment (Merle and van der Poll, 2021).

Molecular Pathways Linking Immune Signaling and Thrombosis

The connection between immune signaling and thrombosis is mediated through several molecular pathways. Central to these processes are the activation of pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) and NOD-like receptors (NLRs). These receptors, which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), trigger immune responses that activate coagulation cascades. TLR activation, particularly on immune cells, induces the production of pro-inflammatory cytokines such as TNF-α and IL-1β. These cytokines in turn, up regulate the expression of tissue factor (TF) on monocytes and endothelial cells, fostering thrombin production and fibrin deposition, which are essential for thrombus formation (Ryan *et al*., 2022).

The complement system, a key part of innate immunity, further bridges the gap between coagulation and immune response. Activation of the complement cascade not only enhances clot formation but also promotes inflammation by assisting in immune complex deposition (Greinacher *et al*., 2021).

Immune Cells in Thrombus Formation

Immunothrombosis is characterized by the involvement of immune cells such as platelets, neutrophils, and macrophages. Neutrophils are the first responders to infection and injury, releasing neutrophil extracellular traps (NETs), which play a critical role in thrombus formation. These NETs, composed of decondensed chromatin and antimicrobial proteins, trap pathogens and serve as scaffolds for platelet aggregation, thereby activating coagulation (Engelmann & Massberg, 2013). Tissue macrophages produce tissue factor (TF), which activates the coagulation cascade through binding to Factor VIIa, ultimately leading to thrombin production. Additionally, macrophages produce pro-inflammatory cytokines that further promote thrombus formation (Engelmann & Massberg, 2013).

Platelets, traditionally known for their role in haemostasis, also play a critical part in immunothrombosis. Activated platelets express P-selectin, which recruits neutrophils and monocytes to sites of infection or injury. They also release pro-coagulant substance such as fibrinogen and thromboxane A2, promoting clot formation (Ryan *et al.*, 2022).

Activation of Inflammasomes, STING Pathway, and Coagulation

Inflammasomes, particularly the NLRP3 inflammasome, are multiprotein complexes that detect intracellular pathogens and stress signals. Activation of inflammasomes results in the release of pro-inflammatory cytokines like IL-1β, which enhances platelet activation and TF expression, thus linking inflammation and coagulation (Ryan *et al*., 2022).

The STING (stimulator of interferon genes) pathway, activated by cytosolic DNA from pathogens or damaged cells, leads to the synthesis of type I interferons and other inflammatory mediators. Recent studies have shown that STING activation can promote coagulation and thrombus formation by enhancing endothelial activation and the release of NETs (Ryan *et al*., 2022).

Neutrophil Extracellular Traps (NETs) and Thrombosis

NETs, released by neutrophils in response to infection or injury, not only capture and neutralize pathogens but also play a significant role in thrombosis. NETs provide a scaffold for platelet aggregation and the activation of coagulation factors, particularly Factor XII, which triggers the intrinsic pathway of coagulation. This leads to thrombin generation and fibrin synthesis, contributing to thrombus stabilization (Ryan *et al*., 2022). Histones, a key component of NETs, can damage endothelial cells, exposing subendothelial tissue and promoting platelet adhesion and aggregation (Engelmann & Massberg, 2013). Histones are cytotoxic and exacerbate thrombosis. NETs engage platelets via receptors like TLR4, further enhancing platelet activation and aggregation. This creates a vicious cycle, with platelets promoting additional NET formation and amplifying thrombus development (Ryan *et al*., 2022). Excessive NET production is linked to pathological thrombo-inflammatory disorders such as sepsis and venous thromboembolism (VTE) (Ryan *et al*., 2022).

Evolutionary Significance of Immunothrombosis

Immunothrombosis has evolved as a defense mechanism in vertebrates, where it plays a critical role in containing pathogens within thrombi, preventing their spread, and enhancing immune responses. This evolutionary mechanism reflects the integration of coagulation and immune responses, allowing for rapid containment of infection (Ryan *et al*., 2022).

However, while immunothrombosis is essential in pathogen defense, its dysregulation can lead to pathological thrombotic events such as stroke or deep vein thrombosis (DVT). Early vertebrates' development of a closed circulatory system likely prompted the evolution of this defense mechanism, which balances immune detection and clotting to prevent infection spread (Greinacher *et al*., 2021).

Clinical Implications of Immunothrombosis

Immunothrombosis has both protective and pathological roles. Dysregulation can lead to thrombotic events in conditions such as DVT, sepsis, and autoimmune diseases. In Deep Vein Thrombosis, immunothrombosis is triggered by the activation of immune cells such as neutrophils and monocytes, which express TF. NETs, by providing a framework for clot stabilization, contribute to thrombus formation. Excessive clot formation can impair blood flow, leading to complications like pulmonary embolism (Ryan *et al*., 2022).

Sepsis can lead to disseminated intravascular coagulation (DIC), where systemic inflammation activates coagulation cascades, resulting in widespread thrombus formation. In sepsis, immunothrombosis often leads to excessive clotting, overwhelming the body's anticoagulant mechanisms and increasing the risk of lethal bleeding (Engelmann & Massberg, 2013). In Autoimmune disorders like antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) involve hypercoagulability, where autoantibodies target phospholipids and coagulation proteins, leading to thrombus formation. In these disorders, immune complexes and activated platelets predominantly contribute to thrombus development (Greinacher *et al*., 2021).

Therapeutic Approaches and Challenges in Treating Immunothrombosis

Anticoagulation Therapy, traditional anticoagulants, such as heparin and direct oral anticoagulants (DOACs), effectively prevent clot formation by targeting key enzymes in the coagulation cascade. However, these therapies do not address the underlying immune component of immunothrombosis (Ryan *et al*., 2022). Anti-inflammatory therapies target inflammation, especially cytokine inhibitors, has shown promise in reducing thrombotic risks. For example, IL-1 inhibitors have been effective in lowering thrombosis in autoimmune conditions like APS and SLE (Engelmann & Massberg, 2013). However, managing inflammation without compromising immune function remains a challenge. Inhibiting NET formation using agents like DNase, which degrade NETs, has been explored as a strategy to reduce thrombus formation. Early studies suggest that targeting NETs could mitigate thrombotic risk in conditions like DVT and sepsis (Ryan *et al*., 2022). Platelet Inhibition, antiplatelet medications, including aspirin and P2Y12 inhibitors, help reduce platelet aggregation and thrombus formation. However, these therapies can increase bleeding risk, especially in autoimmune diseases like APS (Greinacher *et al*., 2021).

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