Inflammation and hemostatic system: a selection of involved clinical disorders

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ABSTRACT

The role of the hemostatic system in host defense underscores the significant connection among coagulation, platelets, and inflammation. Both the hemostatic and the immune systems share a common ancestral origin. During infections, blood coagulation and platelet activation work in tandem with the immune system to combat bacterial and viral threats. Together, they help limit the spread of these pathogens by forming a fibrin clot network that not only kills pathogens but also promotes tissue repair. However, an excessive response is dangerous, as it can lead to both thrombosis and bleeding. The aim of this narrative review is to present the link between inflammation and the hemostatic system across different pathological conditions, such as infectious diseases (sepsis, plague, COVID-19 infection, Ebola, and Dengue virus infection, and malaria) and autoimmune diseases (antiphospholipid syndrome, systemic sclerosis, and rheumatoid arthritis). Although infectious diseases are characterized by a direct attack on the innate immune system, which in turn activates blood coagulation and platelets, Autoimmune diseases, through antibody production, can induce a coagulative reaction that can generate both thrombosis and fibrosis.

Key words: tissue factor, thrombin, fibrosis, infectious and autoimmune diseases, fibrinolysis, thrombosis.

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Introduction

The hemostatic system plays a crucial role in host defense, highlighting the interplay among coagulation, platelets, and inflammation. Both the hemostatic and immune systems share a common ancestral origin. During infections, blood coagulation and platelet activation work together with the immune system to fight against bacterial and viral threats. This collaboration helps limit the spread of pathogens by forming a fibrin clot network that not only kills these invading microbes but also promotes tissue repair.[1] However, an excessive response is dangerous, as it can lead to both thrombosis and bleeding in various organs, as seen with COVID-19 infection: the so-called immunothrombosis.[2] The aim of this narrative review is to present the link between inflammation and the hemostatic system across different pathological conditions.[3-5] Although infectious diseases are characterized by a direct attack on the innate immune system, which in turn activates blood coagulation and platelets,[6] autoimmune diseases, through antibody production, can induce a coagulative reaction that can generate both thrombosis and fibrosis.[7] In this review, we aimed to present the complex pathophysiology of these conditions in the simplest terms to benefit non-specialist readers. This review includes illustrations to enhance understanding of the lecture. It is dedicated to our dear friend Armando D'Angelo, a prominent international researcher who had a keen interest in the pathophysiology of hemostatic and thrombotic disorders. We chose this complex topic in honor of his dedication to the field.

Literature search methods

We identified and chose the following keywords and search strategy: "virus" OR "bacteria" OR "parasites" AND "thrombosis "OR "hemorrhage" OR "fibrinolysis" AND "outcome", AND

"autoimmune diseases" AND "thrombosis", AND "thrombin" AND "fibrosis". Articles were defined as eligible if they i) were related to the review topic, ii) had a clear aim, relevant results, and discussion, iii) were published in peer-reviewed journals, and iv) were in English. A first-level screening of articles extracted from PubMed was done by reading titles and abstracts.

Infectious diseases: inflammation and a thrombotic phenotype

Sepsis

In sepsis, disseminated intravascular coagulation (DIC), a severe complication, may develop, thereby provoking a life-threatening condition.[8] Both Gram-positive and Gram-negative bacterial fragments, *i.e.,* lipopolysaccharide (LPS), activate monocytes, which release cytokines [Interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor, etc.] that, in turn, induce endothelial damage. Tissue factor (TF) is exposed on the cell membrane of monocytes after contact with LPS.[9] Pathogen-Associated Molecular Patterns (PAMPs) and LPS activate both the contact pathway of blood coagulation and the formation of inflammasomes. This triggers the caspase cascade, leading to monocyte pyroptosis and the release of TF and several cytokines.[10] Blood coagulation is therefore activated, and thrombin is generated (Figure 1). This pathway is normally dedicated to trapping bacteria, viruses, parasites, and fungi, but if an excessive reaction occurs, diffuse microvascular thrombosis develops. Platelet activation by thrombin via protease-activated receptor (PAR) is another crucial step in the development of a thrombotic process.[11] The final outcome is DIC, which leads to multiorgan damage.[12] During sepsis, the von Willebrand factor-cleaving protease ADAMTS13 is expressed at significantly lower levels on endothelial cells, allowing platelets to function more effectively.[13] Thrombin generation can also result from endothelial damage caused by cytokines, which can trigger TF production. Additionally, another factor in the interaction between hemostasis and the innate immune system is the involvement of neutrophil extracellular traps (NETs). These NETs comprise DNA, histones, elastase, cathepsin G, myeloperoxidase, and antimicrobial proteins, which are typically designed to combat bacteria and viruses.[14] An excess of NETs can activate both the intrinsic and extrinsic pathways of blood coagulation, thereby inducing fibrin deposition in the microvasculature (Figure 2).[15] NETs can initiate thrombus formation in both veins and arteries. This occurs when NETs interact with platelets, which catch neutrophil-derived microparticles containing TF. This interaction results in additional TF accumulation, ultimately increasing fibrin deposition in the blood vessels.[16] Fibrinolysis behavior is another aspect of this complex pathway: plasminogen activator inhibitor-1 (PAI-1) levels rise, leading to a fibrinolytic shutdown. This phenomenon is consistent with the primary defensive purpose of entrapping bacteria in a net of more resistant fibrin. The final result is a DIC characterized by a thrombotic phenotype.[17]

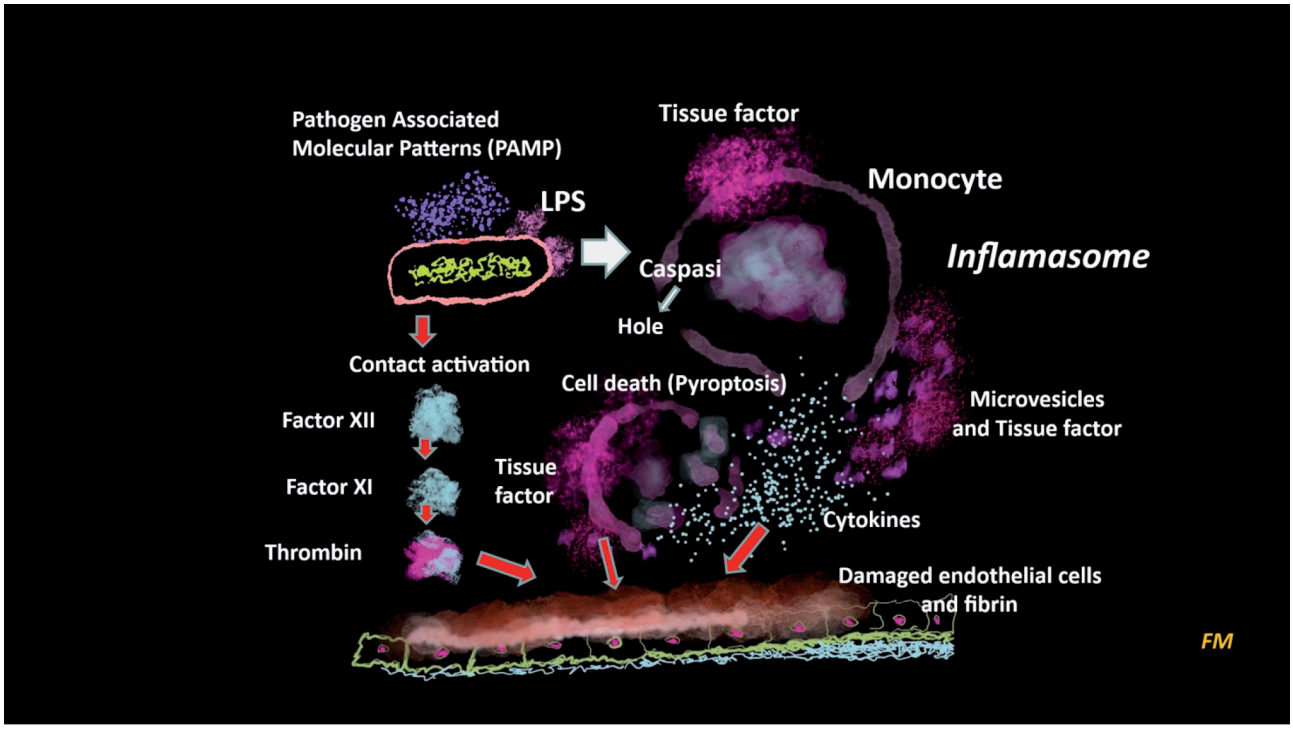

Figure 1. Relationship between bacterial lipopolysaccharide (LPS), pathogen-associated molecular patterns (PAMPs), and monocytes. PAMPs and LPS activate both the contact pathway of blood coagulation and inflammasome formation, thus triggering the caspase cascade, leading to monocyte pyroptosis and the release of tissue factor and several cytokines. Blood coagulation is therefore activated, and thrombin is generated.

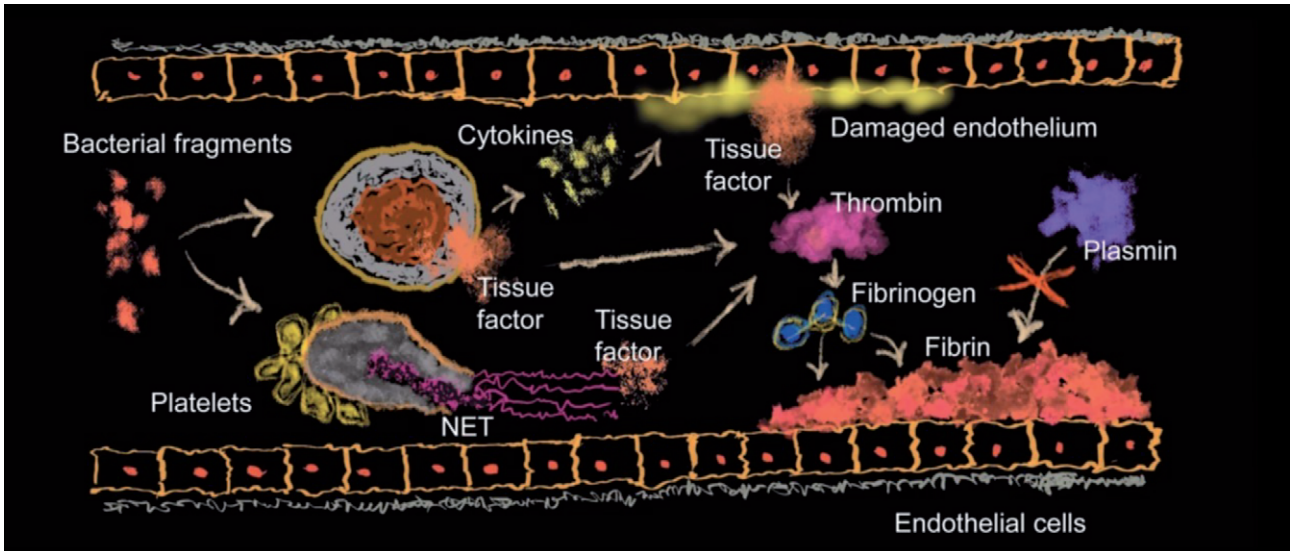

Figure 2. Main pathophysiological aspects of disseminated intravascular coagulation (see text for details).

Malaria

Plasmodium falciparum infections are more prevalent in children aged 5 to 15 years compared to adults.[18] While thrombosis is quite common, bleeding rarely occurs unless in exceedingly severe disease. Fibrin thrombi have been found in skin biopsies and in post-mortem investigations of the microcirculation.[19] These findings have been interpreted as a result of a DIC, which has been reported in children with cerebral malaria.[20] Similar to bacterial sepsis, *Plasmodium falciparum* infection is marked by impaired fibrinolysis. Patients with this infection exhibit higher plasma levels of PAI-1 compared to control subjects. Additionally, there is a significant increase in monocyte procoagulant activity, indicating hypercoagulability.[21] Parasitized red blood cells (RBCs) adhere to endothelial cells, causing damage that exposes TF on these cells. Moreover, phosphatidylserine is exposed on parasitized RBCs, facilitating the adsorption of clotting factors, thus rendering them coagulable. Damaged endothelial cells release von Willebrand factor, which, in turn, activates platelets and significantly contributes to thrombus development.[22] Either ischemic or hemorrhagic stroke, as well as cerebral vein thrombosis, is a common complication of this infection. Challenges are encountered in the correct diagnosis because of the concomitant symptoms due to cerebral malaria. Stroke is generally due to mechanical obstruction of cerebral vessels and hypercoagulability.[23] Finally, blood viscosity in Malaria is another prothrombotic factor due to RBCs, which aggregate and exhibit reduced red cell deformability. Anemia is a compensatory response to this phenomenon.[24]

COVID-19 infection

The novel coronavirus (SARS-CoV-2) is an RNA virus characterized by its envelope and surface proteins, including glycoproteins and spike proteins. It enters lung cells by binding to the angiotensin converting enzyme (ACE)2 receptor, which triggers endocytosis and subsequent infection.[25] This process directly damages pneumocytes, leading to the release of cytokines, activation of monocytes, and a cascade of inflammatory and coagulation responses.[26] Clinical studies have reported findings of DIC.[27] However, we considered the possibility of localized pulmonary thrombosis rather than full DIC,[28] as confirmed by autopsy findings.[29] Since ACE2 is also expressed in endothelial cells, vascular injury is common and can explain why deep vein thrombosis and pulmonary embolism may occur.[30] Even ischemic stroke, especially in younger patients, may complicate the course of the disease.[31] Elevated von Willebrand factor levels in severe cases indicate significant endothelial damage. In patients with severe COVID-19 infection, von Willebrand factor propeptide is significantly elevated and correlates well with disease severity, as reflected in sequential organ failure assessment and sepsis-induced coagulopathy (SIC) scores.[32] Additionally, fibrinolysis exhibits a dual role: in some areas, it leads to local bleeding, while in others, it promotes microthrombosis and pulmonary fibrosis.[33,34] Overall, these effects are linked to ACE2's central role in infection and coagulation imbalance (Figure 3).

Inflammation and a hemorrhagic phenotype: the viral attack

Viral hemorrhagic fever (VHF) represents different diseases caused by several viruses from 6 virus families: *Filoviridae, Nairoviridae, Phenuiviridae, Hantaviridae, Arenaviridae*, and *Flaviviridae*. The number of VHF cases worldwide is rising. As the name indicates, VHF is associated with bleeding. Among all, the Ebola and Dengue viruses are the most frequent infections, primarily found in Africa, although they can also be found in other geographic areas, such as Latin America and Eastern countries.[35] Viral infections trigger TF expression in monocytes, thereby activating the coagulation cascade, leading to a consumption coagulopathy. If the liver is involved, the levels of the clotting factors further decrease. Platelet activation also occurs,

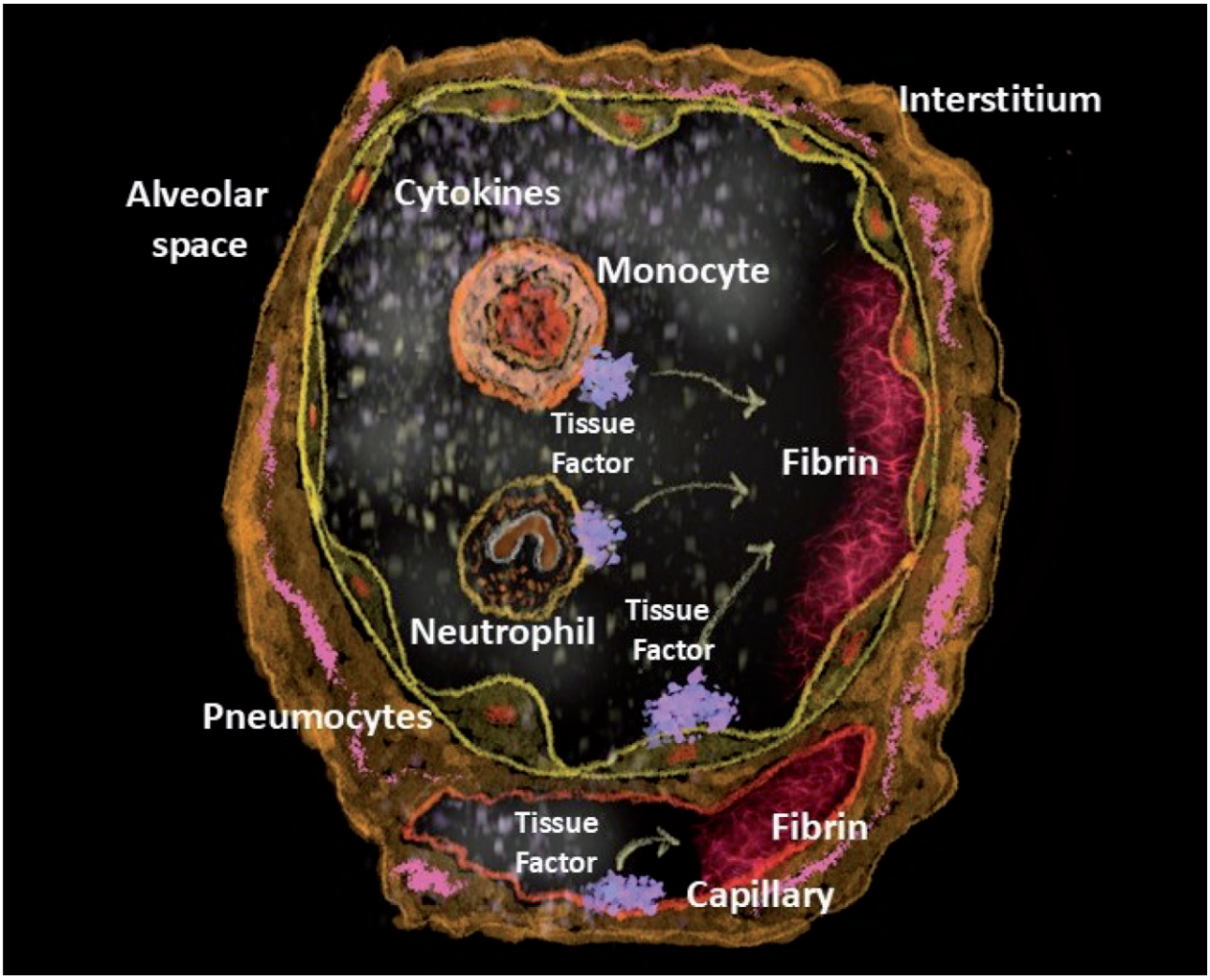

Figure 3. COVID-19 infection activates monocytes, which release cytokines that can provoke interstitial inflammation and endothelial capillary damage. Tissue factor, which can be exposed by monocytes and damaged endothelial cells, triggers coagulation activation, leading to fibrin deposition in both the alveolar space and the capillaries.

determining the appearance of thrombocytopenia. Additionally, viral infections target endothelial cells (ECs), increasing vascular permeability while reducing the anti-coagulant activity of protein C. Most importantly, activated ECs also release tissue plasminogen activator (tPA), thereby increasing plasmin levels and greatly enhancing fibrinolysis, which explains why these viral infections are characterized by severe bleeding. Huang *et al.* found thrombocytopenia, activated partial thromboplastin time prolongation, and increased tPA in patients with dengue infection in the acute phase of the disease, indicating a strong fibrinolysis activation.[36] In a study conducted during the Ebola outbreak in Uganda in 2000, 123 patients with positive results were included.[37] In a fatal case occurring five days after the onset of symptoms, D-Dimer levels were significantly elevated, reaching approximately 520,000 ng/mL. Other patients also exhibited high D-Dimer levels, ranging from about 240,000 to 390,000 ng/mL. Notably, D-Dimer levels were four times higher in patients with fatal outcomes compared to those who survived, with levels of 180,000 ng/mL for fatalities versus 44,000 ng/mL for survivors during the acute phase of the infection.

When bacteria exploit fibrinolysis and platelets: the case of *Yersinia pestis*

Yersinia pestis (YP) is a Gram-negative bacterium responsible for plague, a life-threatening disease that has not completely disappeared worldwide. Plague is transmitted by a flea bite, but infection can also be acquired through inhalation of contaminated aerosols and ingestion of infected food, as recently reported.[38] YP contains a transmembrane protein called plasminogen activator, which converts plasminogen into plasmin. This significantly aids in the spread of the bacteria once it enters the skin through a fleabite that carries the bacteria from infected rats and marmots.[39] In addition to this malicious weapon, YP can inhibit platelet aggregation through the type III secretion system

(T3SS), a nano-syringe protein that directly injects effector proteins into eukaryotic cells.[40] That system impairs cytoskeletal rearrangements in platelets via YopE and YopH, two other effector proteins. The final results indicate destabilization of platelet function and a reduction in protective platelet-neutrophil interactions, allowing bacterial escape from neutrophil killing by inhibiting neutrophil phagocytosis and NET formation, as brilliantly shown by Palace *et al.*[41] In the accompanying editorial, Alice Assinger pointed out that even other bacterial species may utilize such armamentaria to fight the host's defenses: *Chlamydia, Pseudomonas, Salmonella, Shigella,* and *Vibrio*.[42] They share the same T3SS, and identifying its specific functions is crucial for targeting foreign invaders.

Autoimmune diseases: inflammation, thrombosis, and fibrosis

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a rare, acquired thrombophilia first described in 1983 by Graham Hughes,[43] even though the association of lupus anticoagulant and thrombosis had been recognized several years earlier by Bowie *et al*.[44] We distinguish primary APS from that associated with other autoimmune diseases, such as Systemic Lupus Erythematosus.[45] In the absence of definitive diagnostic criteria, for making a diagnosis of APS two criteria are needed: the first is a positive history of venous and/or arterial thrombosis and obstetric complications (miscarriage and fetal loss) while the second requires confirmed presence for more than 12 weeks of antiphospholipid antibodies (aPL): lupus anticoagulant, anticardiolipin antibodies, and anti-β2-Glycoprotein I antibodies (aβGPI) IgG and IgM.[46] New classification criteria were published in 2023 (ACR/EULAR).[47] However, relevant discrepancies have been highlighted in comparison with those of the START2 Italian Antiphospholipid Registry.[48] APS is due to the production of autoantibodies directed against anionic phospholipids, *i.e.*, cardiolipin, or against associated proteins, such as β2GP1 or prothrombin. β2GPI circulates in a coil form composed of 5 domains. If anionic phospholipids are exposed on cell membranes, the protein changes its conformation, becoming an open molecule that exposes Domain I, which becomes the target of aPL.[49] The binding of aPLs' Fab domains to β2GPI enhances its affinity for membranous anionic phospholipids. aPL influences various cellular and systemic functions:[50] a) the endothelium reduces nitric oxide production but increases tissue factor synthesis. Moreover, leukocyte-endothelial interactions via adhesive molecules are products of the inflammatory response. Microvesicles derived from endothelial cells have been found in APS patients as an indirect sign of endothelial activation.[51] b) Monocytes expose TF on their membrane, so activating blood coagulation, along with inflammatory cytokines such as tumor necrosis factor-α and IL-1β.[52] As endothelial cells, monocytes deliver microparticles carrying TF into the circulation, further enhancing a prothrombotic state.[53] c) aPL can activate platelets *per se* along with the formation of platelet-neutrophil aggregates, indicating a subclinical consumption.[54] Thrombin itself can promote platelet activation,[55] which is also due to endothelial cell damage.[56] d) The complement system is also involved in the response to the aPL attack.[57] Once activated by aPL, complement induces chemotaxis and cell activation (monocytes, endothelial cells, and platelets), leading to thrombosis and tissue damage through the anaphylatoxins C3a and C5a.[58] A close link between complement and coagulation exists because both systems are mutually linked in the defensive response to every inflammatory attack. The two systems work together.[59] Complement activation has also been demonstrated in the pathophysiology of the Catastrophic Anti-Phospholipid Syndrome (CAPS).[60] The useful role of eculizumab, a humanized monoclonal antibody that inhibits the cleavage of human complement component C5 into its pro-inflammatory components,[61] has been anecdotally described in the treatment of CAPS, further supporting the role of the complement system in APS.[62,63] e) The release of NET in the course of APS was first discovered in 2015 by Yalavarthi *et al.*[64] NETs release decondensed chromatin, along with histones and proteases that degrade antithrombotic molecules such as tissue factor pathway inhibitor (TFPI) and antithrombin. This process activates blood coagulation by involving TF, factor XI, and factor XII. While NETs play a natural defensive role in counteracting bacterial and viral infections, they disproportionately influence the hypercoagulable state in APS.[65] f) If blood coagulation shows activation due to the prothrombotic effects of several cells, as mentioned earlier, on top of that, other key prothrombotic mechanisms contribute to a prothrombotic tendency. These include the inhibition of the natural anti-thrombotic properties of β2 GP1, which helps mitigate platelet aggregation via von Willebrand factor,[66] and the inhibition of Annexin 5 function, which normally neutralizes procoagulant phospholipids, such as phosphatidylserine, on cell surfaces.[67] g). Fibrinolysis is also impaired in APS. aPL inhibits the capacity of β2GPI to induce the release of tPA, thereby impairing fibrinolysis.[68] Moreover, aPL antagonize various profibrinolytic factors such as anti-annexin-A2, tPA, and anti-plasmin. On the other hand, PAI-1 is elevated in APS, thereby significantly contributing to the formation and stabilization of blood clots.[69] A recent study of our group considered 25 patients with primary APS who underwent brain single-photon emission computed tomography (SPECT) imaging and statistical parametric mapping analysis.[70] Compared to age- and sex-matched controls, APS patients demonstrated significant cerebral hypoperfusion affecting the bilateral frontoparietal cortices. Notably, the patients showed no clinical neurological manifestations, and these observations were independent of magnetic resonance imaging results. Interestingly, SPECT abnormalities were more pronounced in patients who had experienced a venous thromboembolism compared to those who had suffered an arterial thrombotic event. These abnormalities suggest functional microvascular impairment potentially mediated by chronic endothelial dysfunction, complement activation, and aPL-induced neuroinflammatory cascades. These findings support the hypothesis that cerebral involvement in APS goes beyond thrombotic injury, also encompassing immune-mediated microvascular and neuroglial dysregulation (Figure 4).

Systemic sclerosis

Systemic sclerosis (SSc) is a connective tissue disease characterized by endothelial autoimmune activation, which leads to tissue and vascular fibrosis, vasculopathy, and reduced angiogenesis.[71] The damage and apoptosis of ECs activate immune

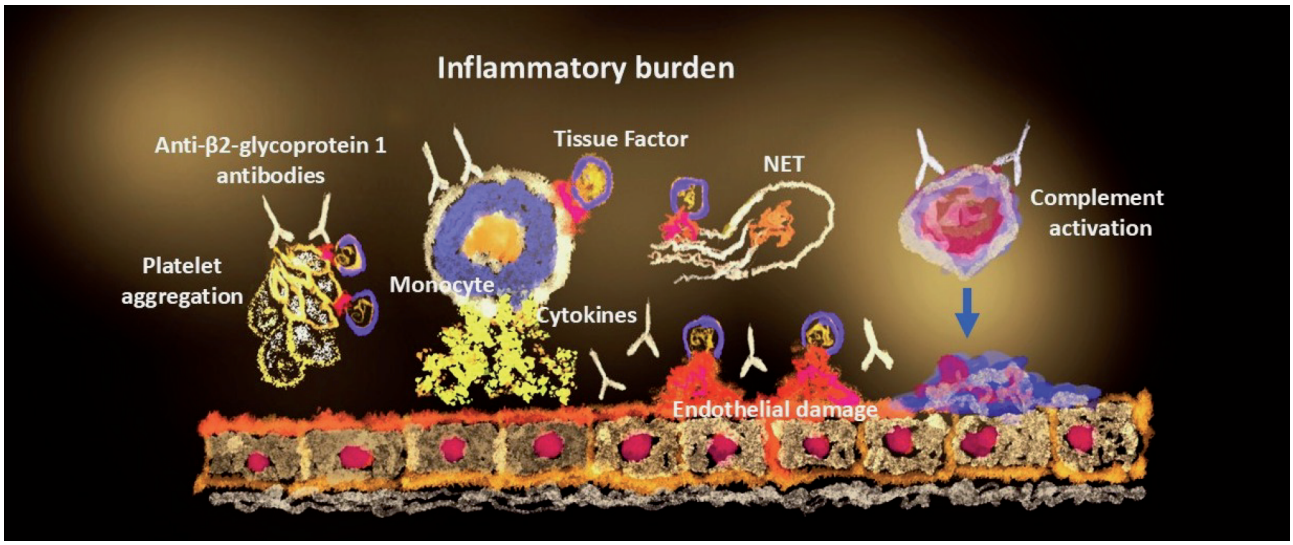

Figure 4. Anti-phospholipid antibodies activate platelets, monocytes, neutrophil extracellular traps, endothelial cells, and complement, creating an inflammatory burden that leads to fibrin deposition and thrombosis.

cells, which release chemokines, provoking an inflammatory perivascular infiltrate and tissue hypoxia, leading to multiple organ damage.[72] The first attack on the endothelium is probably due to still-unknown autoimmune agents that reduce nitric oxide release and increase vasoconstrictive molecules (*e.g.*, endothelin-1). The anti-thrombotic barrier of endothelial cells becomes increasingly compromised, leading to gap formation. These gaps allow for vascular leakage into the surrounding tissues. This process may also cause cell detachment, which is indicated by an increase in circulating endothelial cells (CECs). The presence of CECs can be used to assess disease severity.[73] The detachment of ECs results in platelet adhesion to collagen in the exposed subendothelial layer, a process mediated by glycoprotein VI. Once the platelets adhere, they aggregate through the activity of von Willebrand factor. Following their activation, platelets expose phosphatidylserine on their membranes, which enhances the binding of clotting factors and amplifies the coagulation cascade. TF plays a critical role in this process, serving as the trigger for blood coagulation. TF is typically located in subendothelial collagen and is also produced by fibroblasts. This forms a hemostatic film that activates coagulation in response to endothelial injury. Thrombin, the final product of blood coagulation activation, then converts fibrinogen into fibrin and further activates platelets. Thrombin also induces fibrogenesis by acting on fibroblasts and smooth muscle cells. It also promotes the differentiation of lung fibroblasts into myofibroblasts, contributing to tissue fibrosis in multiple organs.[74] Recently, we demonstrated that a hypercoagulable state is present in SSc. Elevated prothrombin time and activated partial thromboplastin time levels, as well as increased thrombin generation, have been observed in this context. Additionally, a higher density of clots detected through electron microscopy supports the conclusion that blood coagulation plays a primary role in the anatomical complications associated with the disease.[75] This hypercoagulable state may activate thrombin in the interstitium, leading to fibrosis.[76] The formation of thrombin within the interstitial space, secondary to inflammation, is probably due, once again, to an excess of thrombin generation.[77] Taken together, these data prompted us to offer anticoagulants to patients with SSc to limit excess thrombin activity (Figure 5).[78]

Rheumatoid arthritis

Rheumatoid arthritis (RA) is linked to a significantly higher risk of both venous and arterial thrombotic events, regardless of traditional cardiovascular risk factors. Epidemiological studies indicate a 1.5 to 3-fold increase in the incidence of venous thromboembolism, along with a notable rise in major adverse cardiovascular events. This supports the concept that RA contributes to a systemic prothrombotic state. RA begins as a chronic inflammatory condition affecting the synovial membrane. It is characterized by leukocyte infiltration, fibrin deposition, new blood vessel formation (angiogenesis), and local activation of coagulation pathways. The expression of tissue factor in the inflamed synovium leads to the generation of thrombin, while impaired fibrinolysis allows for the persistence of fibrin. Consequently, coagulation activation in RA is closely linked to inflammation rather than being a secondary phenomenon.[80] Elevated fibrinogen, increased factor VIII activity, enhanced thrombin generation, and elevated D-Dimer levels reflect sustained systemic hypercoagulability.[81] Platelet hyperreactivity, endothelial cell activation, and NET formation significantly enhance thrombin generation, establishing a self-perpetuating thrombo-inflammatory loop. In addition to fibrin formation, thrombin activates PAR-1/4, which promote fibroblast activation and matrix remodeling.[82] The profibrotic effects seen in RA extend beyond the joints. In patients with RA-related interstitial lung disease, chronic endothelial cell injury and localized activation of the coagulation cascade can lead to fibroblast activation and extracellular matrix deposition. Specifically, thrombin signaling through the PAR-1 enhances TGF-β activation, which drives myofibroblast differentiation and collagen synthesis.

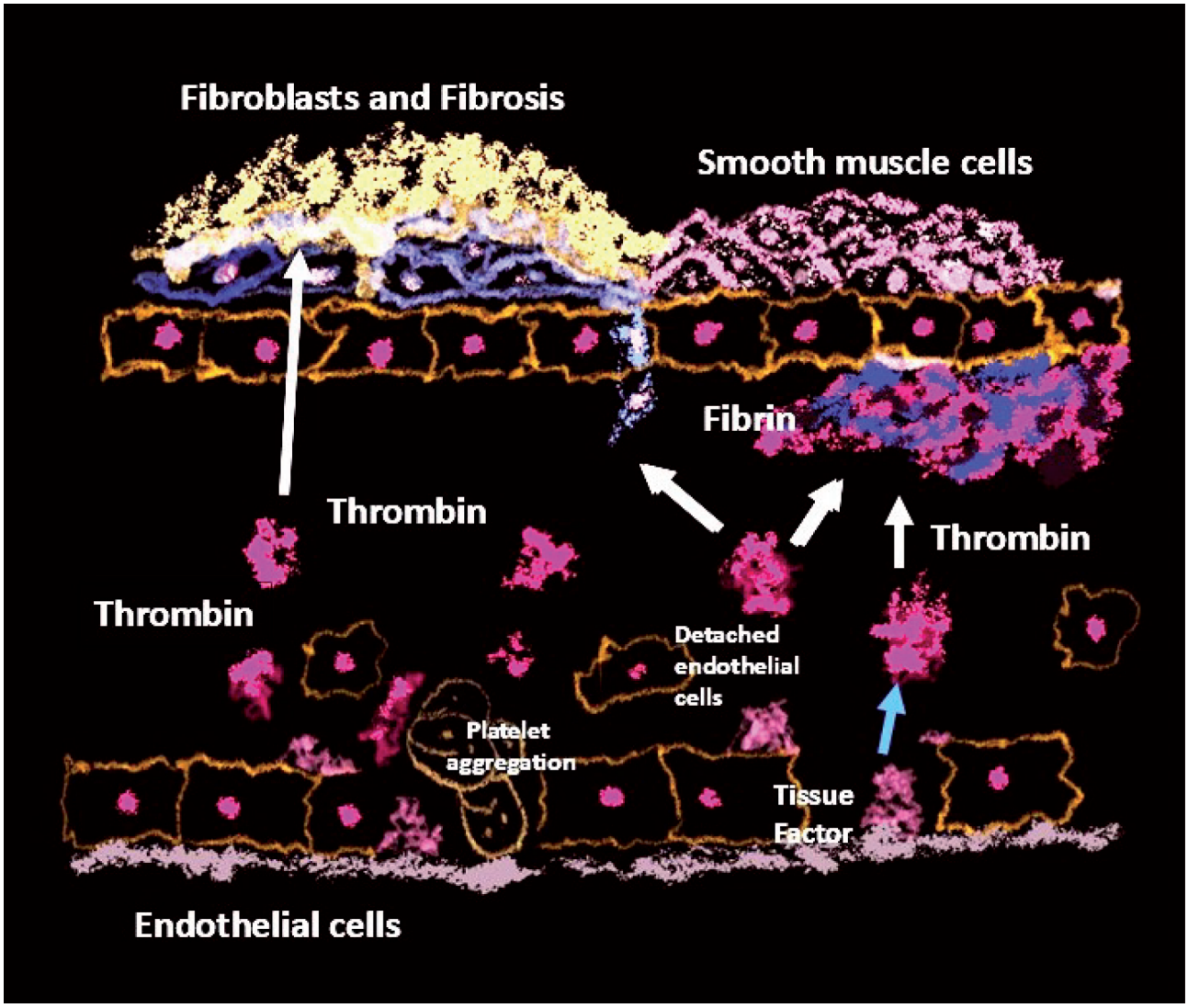

Figure 5. In systemic sclerosis, antibodies induce endothelial cell damage, which in turn leads to cell detachment. The detachment of endothelial cells results in platelet adhesion to collagen in the exposed subendothelial layer and aggregation. Tissue factor plays a critical role in this process, serving as the trigger for blood coagulation. It is commonly found in subendothelial collagen and is also expressed by fibroblasts, forming a hemostatic film that activates coagulation as a reaction in response to endothelial injury. Thrombin, the final product of blood coagulation activation, then converts fibrinogen into fibrin and further activates platelets. Thrombin also induces fibrogenesis by acting on fibroblasts and smooth muscle cells. It also promotes the differentiation of lung fibroblasts into myofibroblasts, contributing to tissue fibrosis in multiple organs.

These processes are key mechanisms underlying the progression of pulmonary fibrosis. Therefore, persistent thrombin generation may link chronic synovitis to lung involvement outside the joints.[83] As we described above, the possible fibrogenic action of thrombin in the interstitium can contribute to the pathogenesis of lung fibrosis in RA.[84]

Future directions

The hemostatic system has been the target of both antiplatelet agents and anticoagulants for many years. It may now be time to consider alternative approaches to reduce the inflammatory burden, which activates both the thrombotic and hemorrhagic phenotypes associated with various diseases, as discussed in this review. Potential targets include tumor necrosis factor, IL-6, and IL-1, particularly in conditions such as APS, sepsis, and viral attacks, given that specific antibodies already widely used in the treatment of inflammatory diseases are available. The rationale is that these cytokines damage endothelial cells, induce NET formation, and promote blood coagulation, as reported here. Additionally, targeting macrophage metabolism could be another therapeutic pathway to explore in disorders such as sepsis.[85]

Conclusions

This review, despite its limitations stemming from the topic's wide and complex nature and the need to select content, highlights the various and sometimes similar ways in which the hemostatic system is involved in both infectious and autoimmune diseases. Our aim was to describe the close connections between two defensive systems (inflammation and coagulation) along with the roles of platelets and fibrinolysis, especially when infectious agents and autoimmune antibodies attack the body. It is important to recognize how bacterial and viral infections, as well as autoimmune diseases, exploit the hemostatic system to gain an advantage over host defenses. In fact, an exaggerated response from these systems, especially that linked to inflammation, can lead to life-threatening conditions, particularly in severe underlying diseases. We also discussed the crucial role of thrombin, which can promote fibrosis in various organs over time. This process may significantly impact the progression of certain diseases, such as scleroderma and rheumatoid arthritis.

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