Preface

Contact Activation: Where Thrombosis and Hemostasis Meet on a Foreign Surface, Plus a Mini-editorial Compilation ("Part XVI")

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Semin Thromb Hemost

Welcome to the latest issue of *Seminars in Thrombosis and Hemostasis* (STH); this issue primarily devoted to highlighting the contact activation pathway of coagulation. Developed to provide an overview of the current body of knowledge around the roles, applications, and new knowledge of the contact pathway, this compilation serves as an appetizer for the modern thrombosis and inflammation enthusiast.

This issue begins with a contribution from Dr. Shamanaev and colleagues, who start at the top of the coagulation cascade and examine the structure and function of coagulation factor XII (FXII), a serine protease, as it relates to disease.[1] The zymogen FXII can convert prekallikrein and factor XI to the proteases kallikrein and activated FXI (FXIa); this process is instrumental in certain disease states to facilitate abnormal incidents like angioedema and thrombotic events. Drawing on its homolog—pro-hepatocyte growth factor activator—a combination of isolated domains was selected for replacement and then assessed for resulting FXII activation and FXIIa activity. This review acts to establish the circulating closed and bound open conformations of FXII that are resistant to and expedite activation, respectively. Such information may prove integral as we proceed to unravel the complexities of key pathological processes in the quest to ultimately develop treatments for thromboinflammatory disorders.

The second manuscript in this issue, by Kearney and colleagues, refocuses the spotlight on plasma kallikrein (PKa) and its additional role within the coagulation cascade in directly activating coagulation factor IX (FIX).[2] Three independent studies corroborate a classic canonical intrinsic pathway (FXII–FXI–FIX) and a noncanonical pathway (PKa–FIX). With the existence of PKa as a coagulation clotting factor established, the next step is the investigation of the products of its cleavage as it relates to the functioning of the body. This manuscript will eventually inform on novel anticoagulant compounds to be researched, tested, and developed for future use.

In the third manuscript, Dr. Lira and colleagues shift our attention to coagulation factor XI (FXI)—a zymogen of plasma protease FXIa, which is key in facilitating normal physiological functions and driving some abnormal pathological processes.[3] On top of sharing a convergence history, mirroring PKa, FXI has also been demonstrated to play additional roles, in this case, promoting the generation of thrombin, lending to its versatility in function. Furthermore, FXI activity ventures beyond the intrinsic pathway of coagulation into the world of platelets, endothelial cells, and inflammation. This work summarizes FXI's many responsibilities and informs potential future research directions targeting FXI as a focus for therapeutic intervention.

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The fourth manuscript, by Vappala and colleagues, highlights fundamental triggers of the contact pathway of coagulation: polyphosphates, DNA, and RNA.[4] More specifically, extracellular DNA in the form of neutrophil extracellular traps (NETs) have been identified as advancing the occurrence and severity of thrombotic events. From that standpoint, this article explores the understood functions of extracellular polyphosphate and nucleic acids in thrombosis, and it ponders the notion of engineering innovative agents designed to target the prothrombotic activities linked to polyphosphate and NETs.

Dr. Petersen and colleagues follow with discussion of the C1-inhibitor, which is a vital regulator of the intrinsic coagulation pathway, fibrinolytic system, and complement cascade.[5] The critical loss in level and function of the C1-inhibitor, resulting from a mutation in the *SERPING1* gene, gives rise to the rare, genetic disorder known as hereditary angioedema, a condition severely debilitating to patients. Furthermore, C1-inhibitor deficiency is associated with activation of the contact activation cascade and kallikrein–kinin pathway, resulting in undesired vascular leakage. The authors tell the story of hereditary angioedema from the clinical presentation to biological processes, concluding in management options to improve the quality of life for impacted individuals.

The final manuscript under the theme of contact activation, by Goel and colleagues, considers a prominent complication of anticoagulant therapy linked to the severity of subsequent bleeding incidents.[6] As such, it is imperative to strike that delicate balance between hemostasis and hemorrhage and especially so for the subset of patients utilizing medical devices, such as extracorporeal devices and central venous catheters. Viable targets for future investigation include FXI, FXII, and prekallikrein, for selective inhibition of these steps within the contact pathway does not overtly affect normal hemostasis. This review consolidates the latest in vivo and clinical data that involve the inhibition of these select contact pathway members and is optimistic that in doing so, effective and safer anticoagulation options for the population seeking utilization of medical devices will be achieved.

In summary, within the realms of thrombosis, inflammation, and innate immunity, the contact pathway has surfaced as a potential focus for safer and effective intervention, as it does not compromise physiological hemostasis. We are proud to share this compilation in the current issue of STH, comprising valuable contributions from our leading experts. We hope the journal's readers discover significant value in these works.

Given this compilation around the contact activation pathway of coagulation reflects a "short issue" for STH, the issue has been supplemented with a selection of noncontact themed contributions that would normally be published in our Editorial Compilation series, for which we are up to Part XVI. Accordingly, in this issue "addendum," we have included four contributions that we have ascribed to "Editorial Compilation Part XVI."

In the first contribution for this mini compilation, Noone and colleagues take us through a journey discussing the role of myeloid cells in thromboinflammatory disease.[7] Indeed, this contribution represents that of a prior Young Investigator Award winner, Aisling M. Rehill.[8] As readers of this journal may know, inflammation contributes to the development of thrombosis, but the mechanistic basis for this association remains poorly understood. Innate immune responses and coagulation pathways are activated in parallel following infection or injury and represent an important host defense mechanism to limit pathogen spread in the bloodstream. However, dysregulated proinflammatory activity is implicated in the progression of venous thromboembolism and arterial thrombosis. In this review, the authors focus on the role of myeloid cells in propagating thromboinflammation in acute inflammatory conditions, such as sepsis and coronavirus disease 2019 (COVID-19), and chronic inflammatory conditions, such as obesity, atherosclerosis, and inflammatory bowel disease. Myeloid cells are considered key drivers of thromboinflammation via upregulated tissue factor activity, formation of NETs, contact pathway activation, and aberrant coagulation factor-mediated protease-activated receptor signaling. The authors discuss how strategies to target the intersection between myeloid cell-mediated inflammation and activation of blood coagulation represent an exciting new approach to combat immunothrombosis. Specifically, repurposed anti-inflammatory drugs, immunometabolic regulators and NETosis inhibitors present opportunities that have the potential to dampen immunothrombotic activity without interfering with hemostasis. Such therapies could have far-reaching benefits for patient care across many thromboinflammatory conditions.

In the next contribution, a Commentary from Iba and colleagues, the authors propose that heparins may not provide the optimal anticoagulant for sepsis and sepsis-associated disseminated intravascular coagulation (DIC).[9] Historically, heparin has had the longest historical use as an anticoagulant and continues this day to be the primary therapeutic option for preventing thrombosis and thromboembolism in critically ill hospitalized patients. Heparin is also used to treat sepsis and sepsis-associated DIC in various countries. However, the efficacy and safety of heparin for this indication remains controversial, as adequately powered randomized clinical studies have not demonstrated as yet a survival benefit in sepsis and sepsis-associated DIC, despite meta-analyses and propensity analyses reporting improved outcomes without increasing bleeding risk. Further, activated protein C and recombinant thrombomodulin showed greater improvements in outcomes compared with heparin, although these effects were inconclusive. In summary, the authors propose that further research is warranted, despite the ongoing clinical use of heparin for sepsis and sepsis-associated DIC. Based on Japanese guidelines, antithrombin or recombinant thrombomodulin may be a preferable choice if they are accessible.

Next is another Commentary, this time from Lippi and colleagues, who discuss the pros and cons of prone versus

supine position in critically ill patients with COVID-19.[10] First, ventilation in prone position may significantly improve lung function in critically ill patients with acute respiratory distress syndrome (ARDS) due to the more uniform distribution of tidal volume and improved recruitment, which contribute to ameliorate the ventilation–perfusion ratio. Nevertheless, the overall clinical benefit of long periods of pronation over the supine position during mechanical ventilation remains controversial, even in patients with COVID-19-related ARDS. The authors evaluate recent studies in this area and conclude that these preliminary results suggest that prone positioning may contribute to increase an already elevated risk of developing venous thrombosis in COVID-19 patients with respiratory failure, likely due to position-related reduction in venous blood flow, up to stasis. Thus, although short-term benefit is seen in prone position in regard to increased ventilation in these patients, prolongation of maintenance in prone position appears to increase the risk venous thrombosis, so that as lung injury advances, the benefit of maintaining a prone positioning to improve gas exchange diminishes, with patients instead placed at increased risk of thrombosis.

The final contribution attributable to Editorial Compilation XVI in this issue of the journal is a Letter to the Editor, from Arachchillage and coworkers,[11] who compare the incidence, diagnosis, and pathology of heparin-induced thrombocytopenia (HIT) with thrombosis (HITT) and COVID-19 versus vaccine-induced immune thrombocytopenia and thrombosis (VITT) in the United Kingdom. In brief, HITT and VITT are both rare but very serious complications characterized by thrombocytopenia and positive anti-platelet factor 4 (PF4) antibodies. Although mortality is similar, VITT is rarer than COVID-19-associated HIT. The authors propose that further work to identify the antigen(s) and immune complex(es) involved in these pathologies will shed light on thrombosis in these conditions, especially cerebral venous sinus thrombosis, and facilitate improved vaccine design in the future.

Finally, given that this issue is publishing in 2024, we have also included a few items of historical interest. As previously noted,[12–18] STH is celebrating 50 years of publishing this year. Each issue of 2024 will therefore include a paper republished from the "archives," as well as an accompanying Commentary. In this issue, we are republishing a paper on next-generation sequencing and emerging technologies from the authorship team of Kumar, Cowley, and Davis.[19,20] This manuscript is the top-downloaded manuscript from STH[21] and regularly appears in the journal's top 10 online list.[22] We also include in this issue of STH an accompanying Commentary from the same authors,[23] who discuss the advances in this field since their popular review was published in 2019.

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Conflict of Interest
None declared.

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