

Preface

Inflammation, Endothelial Dysfunction, and Thromboembolism

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Inflammatory mechanisms are intimately tied up with direct defense against infection, immunity, and healing. In order for processes to proceed at affected sites within tissues, capillary walls have to be able to modify their permeability to soluble mediators, particles, and cells. These systems are in a delicate balance, which can be easily disrupted, giving rise to exacerbating diseases or dysfunctions. The situation is further complicated by the equally sensitive homeostatic mechanisms controlling thrombosis and fibrinolysis, which are also involved in defense against environmental damage and tissue repair and they are most active in the circulation and at the blood/tissue interface. This issue of *Seminars in Thrombosis & Hemostasis* embraces a wide range of pathologies that exhibit dysfunctionality in this web of fluid interactions.

All tissues of any size (perhaps the most well-documented example is the >2 mm³ minimum normally quoted in cancer biology), normal or abnormal, need nutritional and hormonal support from blood, through microvasculature. Inflammation requires cellular traffic between endothelial cells and through capillary walls. Maintaining fluidity in plasma without compromising its ability to coagulate at times and places of need is a fundamental homeostatic mechanism in all warm-blooded and at least in some poikilothermic animals. It is unsurprising that aberrations in this system are commonly causes or sequelae of diseases. This general proposition is expanded in the article by Dr. Kazmi and associates.¹

A time-honored view might be that coagulation is a localized extracellular process mediated by soluble factors activated by an altered surface. Seeking a more specific theme in this issue, it might be characterized as the activities of extracellular structures, typically completely independent microparticles, neutrophil extracellular traps (NETs) as

described by Drs. Matevosyan and Sarode,² which are composed of fibrillar DNA and protein in strands up to 50 nm wide (like the eukaryotic equivalent of a bacterial biofilm), or the chunky extracellular domains of integrins, anchored to their parent cell membranes. The latter are discussed by Drs. Allen and Moran³ as attractive therapeutic targets in a range of diseases, their theoretical utility hampered by redundancy on one hand and their wide importance in key physiological systems on the other hand.

Arguably, platelets represent the earliest described “microparticle,” albeit at 2 to 3 μM toward the upper end of a scale generally considered to go down to 0.1 μM. Platelets are the main focus of the contributions from Dr. Thachil,⁴ where research findings are related to present and future therapies, the latter extending from manipulation of numbers to influencing their interactions with leukocytes or endothelial cells as in the article by Dr. Senchenkova and coworkers,⁵ where an inflammatory cytokine-induced increase in production of platelets is implicated in the pathogenesis of inflammatory bowel disease. Aggregation and interaction between platelets are also observed in that condition.

Microparticles, as conventionally defined are vesicles in the 0.1 to 1 μM diameter range, budded off from cells are discussed in the context of atherosclerosis and inflammation in cardiovascular disease by Dr. Suades and colleagues.⁶ Novel functions ascribed to microparticles, besides their utility as biomarkers, include mechanisms to alter the vascular cell milieu, disseminating proinflammatory mediators ultimately causing vascular wall inflammation, aggravating the atherothrombosis. It is the role of plasma protein β₂-glycoprotein I in the clearance of microparticles that prompts Drs. de Groot and Urbanus⁷ to argue in favor of an inflammatory

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component in antiphospholipid syndrome where overt inflammation is not a characteristic feature. Platelet activation, microparticles, and NETs all figure as a consequence of the inflammatory “cytokine storm” arising after surgery as discussed by Dr. Albayati and associates.⁸ Indeed, microparticles are a common means of intercellular communication, liberated by normal and neoplastic epithelial cells.⁹

Moving to abnormal endothelial cell properties and function, Dr. Butta and coworkers¹⁰ describe how an increased oxidative condition contributes to endothelial cell damage and induces platelet, leukocyte, and endothelial cell activation and the hypercoagulable state seen in Behçet disease. Endothelial dysfunction interacting with inflammation is also a feature of the hepatic veno-occlusive disease that can complicate bone marrow transplantation. This situation is addressed by Dr. Vion and associates.¹¹

Dr. Epaulard and coworkers¹² highlight medical treatments and procedures as risking coagulopathy. Iatrogenic factors are among the comorbidities precipitating in vascular thromboembolism including surgery, catheterization, and several anticancer treatments. Certain chronic infections are also proposed as initiating patient characteristics; how this impinges on management is discussed. They highlight venous thromboembolic disease as a consequence of chronic infective diseases, among which they include fungal and parasitic infestations as well as bacterial pathogens, pointing out gaps in current knowledge consequent on most works being conducted in developed countries and on those conditions prevalent locally. Acute infections are no less associated with coagulopathy, ranging from subclinical hypercoagulability to disseminated intravascular coagulation, with depletion of platelets and soluble factors eventually causing bleeding. Semeraro and colleagues¹³ are hopeful that insights into the pathogenesis of sepsis-associated coagulopathy may result in new diagnostic and therapeutic tools. Murugesan and colleagues¹⁴ describe in diabetic retinopathy another condition that exhibits bleeding consequent on thrombotic processes that contribute toward the neovascularization, macular edema, and vision loss.

To conclude, by returning to the title of this themed issue and emphasizing the close interrelationship between inflammation and thrombosis, a further process bridging between them is complement activation; Dr. Boyce and associates¹⁵ explore this relationship in conditions characterized by complement hyperactivity. Overall, the driving argument throughout this series of articles is exemplified and encapsu-

lated in the final sentence of Dr. Murugesan’s contribution,¹⁴ which states that further understanding of the role for specific coagulation factors in all of the diseases and dysfunctions considered here may provide new therapeutic opportunities.

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