Hemostasis Movers & Shakers: Platelets, Proteases, & Friends

By Margaret Ragni, MD

This year ASH is initiating an exciting new Special Session on the Basic Science of Hemostasis and Thombosis. Slated for tomorrow afternoon, the program will be chaired by Dr. Bruce Furie and co-chaired by Drs. Mortimer Poncz and Barbara C. Furie, who championed the concept. Featuring six invited speakers, the session will also showcase 40 abstracts chosen as poster presentations by ASH in the category "Hemostasis, Thrombosis, and Vascular Wall Biology" for oral presentation. The overriding goal of this new endeavor is to increase student, fellow, and postdoc participation, and to increase the content on hemostasis and thrombosis issues at the annual meeting.

The first speaker, David Ginsburg, MD, PhD, University of Michigan, will lead off with a presentation of his studies in ADAMTS13-deficient mice and with the molecular structure of ADAMTS13. Mutations in ADAMTS13, the VWF-cleaving protein deficient in thrombotic thrombocytopenic purpura (TTP), led to protein misfolding or disrupted protease function. These mutations apparently account for all familial cases of TTP thus far, and all result in reduced secretion of ADAMTS13. Following shigatoxin challenge, a TTP-like illness occurs in ADAMTS13-deficient mice with a genetic background CASA/Rk (mouse with elevated VWF). These findings and the absence of correlation between TTP severity and VWF level in these mice suggest that other genetic susceptibility factors are required to cause TTP.

Jim Huntington, PhD, University of Cambridge, U.K., will next make the case that antithrombin III (ATIII) is the most important inhibitor of coagulation proteases. ATIII maintains a fine balance between procoagulant and anticoagulant properties of the coagulation system through conformational changes induced by its interaction with heparins. The conformational changes occur in the reactive center loop of ATIII. The ATIII conformational changes determine allosteric interactions which provide the molecular basis for protease recognition and differential anticoagulant properties of low-molecular-weight heparin and heparin.

Sriam Krishnaswamy, PhD, Children's Hospital of Philadelphia and University of Pennsylvania, will explain his studies with reconstituted coagulation reaction systems that provide new insights and understanding of the regulation of the extrinsic (VIIa/TF) and intrinsic coagulation (IXa/VIIIa) pathways. By altering concentrations and conditions, this system provides the opportunity to determine the contributions of the extrinsic and intrinsic pathways to clot formation following vessel injury.

Andrew Weyrich, PhD, University of Utah, will discuss the thrombogenicity of platelets and the modulating role of pre-mRNA splicing. Studies in his lab have shown that platelets contain functional spliceosome, rRNA processing units consisting of over 100 of proteins and specialized nuclear RNAs. Pre-RNA splicing provides platelets with a signal to produce proteins that regulate thrombosis and inflammation. For example, when platelets are activated, spliceosomes promote production of cytokines that increase the adhesiveness of endothelial cells for WBCs. The spliceosomes also increase expression of tissue factor expression in platelets and enhanced TF procoagulant activity. Many of these functions become dysregulated in patients with sepsis.

Mingdong Huang, PhD, Beth Israel Deaconess Hospital, Harvard, will report on the crystal structure of the urokinase-urokinase receptor complex he and his colleagues have solved. The UK receptor structure, characterized by three finger-fold domains, permits the UK receptor to bind with many ligands. These ligands include vitronectin, uPAR-associated protein, integrins, and G-protein-coupled receptors. This explains the structural basis for the diverse cellular functions and role in tissue remodeling and atherosclerosis.

Lawrence Brass, MD, PhD, University of Pennsylvania, concludes the session with a discussion of his work on the emerging role of connections and gaps between platelets following vascular injury and their role in promoting thrombus activity and stability. Following platelet activation by collagen or thrombin, signaling, platelet adhesion, and aggregation, the gaps between platelets provide a site for activated platelets to bind ligands, including integrins, ephrins, sema4D of the semaphorin family proteins, and cell adhesion molecules PECAM and ESAM. The amount of shed or secreted ligands accumulating in the gaps between platelets determine platelet thrombus stability and activity.