THE INTERDISCIPLINARY CENTER FOR THE STUDY OF BIOCOMPLEXITY

Blood Clot Structure and Mechanics from Nanometers to Centimeters

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TUES, APR 14
4:00 PM
127 Hayes-Healy
Tea in 154 Hurley Hall at 3:30 pm

A new field of biomedical research, biomechanics of hemostasis and thrombosis, has been quickly developing over the past few years. The mechanical properties of fibrin are essential in vivo for the ability of clots to stop bleeding in flowing blood but also determine the likelihood of obstructive thrombi that cause heart attacks and strokes. Despite such critical importance, the molecular structural basis of clot mechanics is not well understood. This seminar will focus on recent biophysical research on both platelet aggregation/adhesion and blood clots. An optical trap system has been developed to study protein-protein binding/unbinding at the single molecule level, and used to characterize fibrinogen-integrin interactions that are responsible for platelet aggregation. The results of this research are relevant to the behavior of platelets in flowing blood. Through studies of the structure and mechanical behavior of fibrin clots at the macroscopic, network, fiber and molecular levels, we show that they can only be understood by integration of their materials properties at all these levels and propose a molecular basis for their remarkable extensibility and compressibility. Studies of the forced elongation of fibrin provide important qualitative and quantitative characteristics of the molecular mechanisms underlying fibrin mechanical properties at the microscopic and macroscopic scales. The long-term goal is to relate these basic science discoveries to thrombotic disorders, bleeding, and embolization in coronary artery disease, stroke and cancer, as well as angioplasty and methods of clot ablation and removal, and application of fibrin sealants.

John Weisel received his B.S. in Engineering at Swarthmore College and his Ph.D. in Biophysics from Brandeis University. His graduate research was on muscle structure and assembly with Andrew G. Szent-Gyorgyi, and he was a post-doctoral fellow with Carolyn Cohen at the Rosenstiel Basic Sciences Research Center, Brandeis University, where he started structural biology studies on fibrinogen. At the University of Pennsylvania, he carries out basic research on a variety of aspects of molecular and cellular mechanisms of blood clotting, hemostasis, and thrombosis. Major projects in his laboratory now include: blood clot formation and the structural origins of clot and thrombus mechanical properties; multiscale modeling of blood clot growth; platelet aggregation, including the regulation and interactions of platelet and endothelial cell integrins; specific interactions of pathogenic antibodies in heparin induced thrombocytopenia; clot properties in hemophilia; effects of defensins in clotting. The research utilizes purified proteins, platelet-poor and platelet-rich plasma, whole blood, and human and mouse hemostasis/thrombosis models. The molecular and cellular mechanisms are analyzed through the use of various biophysical and structural techniques, including visualization of molecules and supramolecular aggregates by transmission and scanning electron microscopy, confocal and deconvolution light microscopy, total internal reflection fluorescence microscopy, atomic force microscopy and measurements of mechanical properties of cellular and extracellular structures. We have developed an optical trapping technique that has been to study protein-protein binding/unbinding at the single molecule level, including kinetics and thermodynamics. The results of these studies have implications for basic mechanisms of protein-protein and protein-cell interactions as well as for clinical aspects of hemostasis and thrombosis.