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Fibrinogen as a contributor and therapeutic target in neuroinflammatory disease

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The blood protein fibrinogen as a ligand for integrin receptors functions as the molecular nexus of coagulation, inflammation and immunity. Fibrinogen extravasates in the nervous system after injury or disease associated with vascular damage or blood-brain barrier (BBB) disruption. In multiple sclerosis (MS), perivascular demyelination is accompanied by increased vascular permeability resulting to extensive deposition of fibrin. Our studies in animal models for MS have demonstrated that fibrinogen is not merely a marker of BBB disruption, but a mediator of neuroinflammation. Fibrinogen mediates pro-inflammatory functions in the nervous system by activating the Mac-1 integrin receptor (also known as CD11b/CD18 and complement receptor 3) in microglial cells. In vivo imaging in the mouse spinal cord using two-photon microscopy shows that microglia perform constant surveillance of blood vessel walls in myelinated areas. Pharmacologic or genetic disruption of the fibrinogen/Mac-1 interaction suppresses neurologic symptoms, inflammation and demyelination in Experimental Autoimmune Excephalomyelitis (EAE), a model of MS. Because blocking fibrinogen/Mac-1 interaction affects the proinflammatory but not the procoagulant properties of fibrinogen, strategies to target fibrinogen receptors within the tissue microenvironment could reveal selective and disease-specific agents for therapeutic intervention in neuroinflammatory diseases.

Biography

Katerina Akassoglou, Ph.D. performed her graduate studies at the University of Athens in Greece and the University of Vienna in Austria, where she developed a novel transgenic animal model for multiple sclerosis. As a recipient of the Human Frontier Science Program (HFSP) fellowship Katerina performed her postdoctoral studies at SUNY at Stony Brook and the Rockefeller University. Following research associate positions at Rockefeller University and New York University, she became assistant professor of pharmacology at the University of California, San Diego in 2003. Since 2008, she is an associate professor of neurology at the University of California, San Francisco and an associate investigator at the Gladstone Institute of Neurologic Disease. Her lab studies molecular mechanisms triggered by vascular damage to induce inflammation and inhibit tissue repair. Her research on interactions of the blood protein fibrinogen with the nervous system identified fibrinogen as a potential therapeutic target in multiple sclerosis. For her work on fibrin and fibrinogen and their role in various neuropathological states, she was recognized by the White House as a recipient of the 2006 Presidential Early Career Award for Scientists and Engineers (PECASE), the highest honor bestowed by the United States government on outstanding scientists and engineers beginning their independent careers, and the 2008 John J. Abel Award, given by ASPET and Eli Lilly & Co to a single young investigator for original, outstanding research contributions in the field of pharmacology. Her research program is funded by the National Institutes of Health, Fast Forward and the National Multiple Sclerosis Society.

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