



Progress in Neuroscience Seminar Series (PINS)

Seminar Series of the
Brain & Mind Research Institute
Weill Cornell Medical College (WCMC)

&

The Graduate Program in Neuroscience of
WCMC and Sloan Kettering Institute

Thursday, 5/11/17, 4 PM, coffee at 3:45 PM

Weill Auditorium



"Neurovascular Interactions: Mechanisms, Imaging, Therapeutics"

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Abstract



Protection of the CNS from leakage of plasma proteins by the blood-brain barrier (BBB) is lifted in a wide range of neuroimmune and neurodegenerative diseases, as well as after traumatic injury. However, whether plasma proteins contribute to neuroinflammation and nervous system repair remains poorly understood. Our laboratory has discovered pleiotropic functions for the plasma protein fibrinogen in the activation of innate immunity in the CNS, induction of gliotic scar formation, and inhibition of remyelination. Such diverse functions have mechanistic underpinnings on the unique structure of fibrinogen, which contains multiple binding sites for cellular receptors and proteins expressed in the nervous system. Fibrinogen is a potent pro-inflammatory mediator in the nervous system by activating the CD11b/CD18 integrin receptor (also known as Mac-1 and complement receptor 3) in microglial cells. Fibrinogen stimulates a unique transcriptional signature on CD11b⁺ antigen presenting cells inducing the recruitment, differentiation, and local CNS activation of myelin-specific Th1 cells. Using in vivo imaging in the mouse spinal cord using two-photon microscopy, we showed that in Experimental Autoimmune Encephalomyelitis (EAE), a model of multiple sclerosis (MS), microglia rapidly perform constant surveillance of blood vessel walls and specifically cluster around blood vessels with fibrin deposition. Pharmacologic or genetic disruption of the fibrinogen/CD11b interaction suppresses microglial cluster formation, neurologic symptoms, inflammation, demyelination, and axonal damage in EAE. These studies identified fibrinogen as a novel molecular link between BBB disruption and activation of CNS innate immunity. Our recent findings implicate fibrin in CNS repair processes, such as remyelination, via both its effects on innate immunity and direct effects on cells required for the production of new myelin in the CNS. The role of fibrin in CNS innate immune activation and inhibition of repair will be discussed.

Recent Relevant Publications:

1. Ryu JK, Petersen MA, Murray SG, Baeten KM, Meyer-Franke A, Chan JP, Vagena E, Bedard C, Machado MR, Rios PE, Prod'homme T, Charo IF, Lassmann H, Degen JL, Zamvil SS, Akassoglou K. Blood coagulation factor fibrinogen promotes autoimmunity and demyelination via chemokine release and antigen presentation. *Nat Commun* 2015, 6:8164.
2. Schachtrun P. C, Ryu JK, Mammadzada K, Khan AS, Carlton PM, Perez A, Christian F, Le Moan N, Perez A, Vagena E, Baeza-Raja B, Rafalski V, Chan PJ, Nitschke R, Houslay MD, Ellisman MH, Wyss-Coray T, Palo JJ, Akassoglou K. Nuclear core α -tubulin remodeling by the cleaved p75 neurotrophin receptor controls TGF- β signaling and astrocyte functions. *Nat Neurosci* 2015, 18(8):1077-80.



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