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Vascular Endothelial Cell-Secreted Protein Functions as Early Sensor and Propagator of Neuroinflammation

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Acute pathogenic infections, if not effectively kept in check, often transforms into systemic inflammation, leading to breakdown of the blood-brain barrier (BBB), intensive inflammatory response in the brain parenchyma and impairment of brain function. In previous work, we showed that i.p. lipopolysaccharide (LPS) injection significantly elevated expression of chemokine CCL2 in pericytes, and that CCL2, in turn, elevated excitatory synaptic transmission in glutamatergic neurons of multiple brain regions (Duan et al., 2018). While *Ccl2* loss-of-function attenuated LPS-induced behavioral immobility, it did not inhibit microglial activation. We thus further explored other mechanisms signaling downstream of LPS. We found that conditional knockout of the LPS receptor *Tlr4*, specifically in vascular endothelial cells (VEC), effectively attenuated neuroinflammation in the entire brain. Through single-cell RNA sequencing of VEC-specific cKO of *Tlr4*, and proteomic assays, we found the serine protease PAI to be the most promising candidate. PAI expression increased rapidly and dramatically after proinflammatory mediator challenge. Using loss- and gain-of-function manipulations, we found that PAI secreted by brain VEC is a key signaling molecule bridging peripheral inflammation and neuroinflammation. The strategic location of PAI-1-expressing cells makes it a promising new molecular drug target that enables early intervention at the source of neuroinflammation, without the need to cross the BBB.

Reference:

[1] L. Duan, X.-D. Zhang, W.-Y. Miao, et al., Neuron 100, 183-200.e188 (2018).