underlying mechanisms of brain development in health and disease.

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Inflaming the Brain

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https://doi.org/10.1016/j.neuron.2019.03.007

Exactly how cerebrovascular alterations contribute to Alzheimer's disease (AD) is still unknown. Merlini et al. (2019) show that blood-derived fibrinogen leads to dendritic spine elimination and cognitive deficit via microglial CD11b/CD18. Fibrinogen may be a significant contributor to AD pathogenesis.

The mighty neuron has dominated discussion of brain function for decades. After all, neurons perform the critical business of transmitting signals throughout the body. Certainly a nod was given to astrocytes and oligodendrocytes, given their roles in supporting and myelinating axons, thereby preserving and enhancing signal propagation. But other prominent cells in the brain—the microglia—were given scant attention. In fact, in the 2013 edition of a leading neuroscience textbook, there are only two paragraphs dedicated to microglia out of 1,617 pages of text.

In the past few years, there has been an explosion of interest in microglia. These cells are recognized as providing a critical role in innate immunity in the brain. It has been proposed that a specialized subset of brain microglia, disease-associated microglia, can sense damage in the central nervous system (CNS) and work to clean up the mess (Deczkowska et al., 2018). But like a lot of protective mechanisms, chronic stimulation of the beneficial pathway can lead to its own pathology.

The advent of genetic analysis tools, such as genome-wide association studies and whole-genome sequencing, has revealed genetic risk factors implicated in Alzheimer's disease (AD). Among these AD risk genes, many of them are directly associated with microglial function, including complement receptor 1 (CR1), triggering receptor expressed on myeloid cells 2 (TREM2), and ATP-binding cassette transporter A7 (ABCA7) (Efthymiou and Goate, 2017). Thus, molecular pathways controlling microglial function are highly associated with AD pathologies. However, molecular mechanisms underlying microglial involvement in cognitive impairment in AD are still elusive.

Since fibrin is highly proinflammatory and can interact with receptors on macrophages and microglia, fibrin deposits in the AD brain can lead to chronic inflammation as shown by Merlini et al. (2019) in this issue of Neuron. Moreover, fibrinogen interacts with beta-amyloid (Aβ), leading to structurally altered fibrin clots that are resistant to degradation and therefore elicit
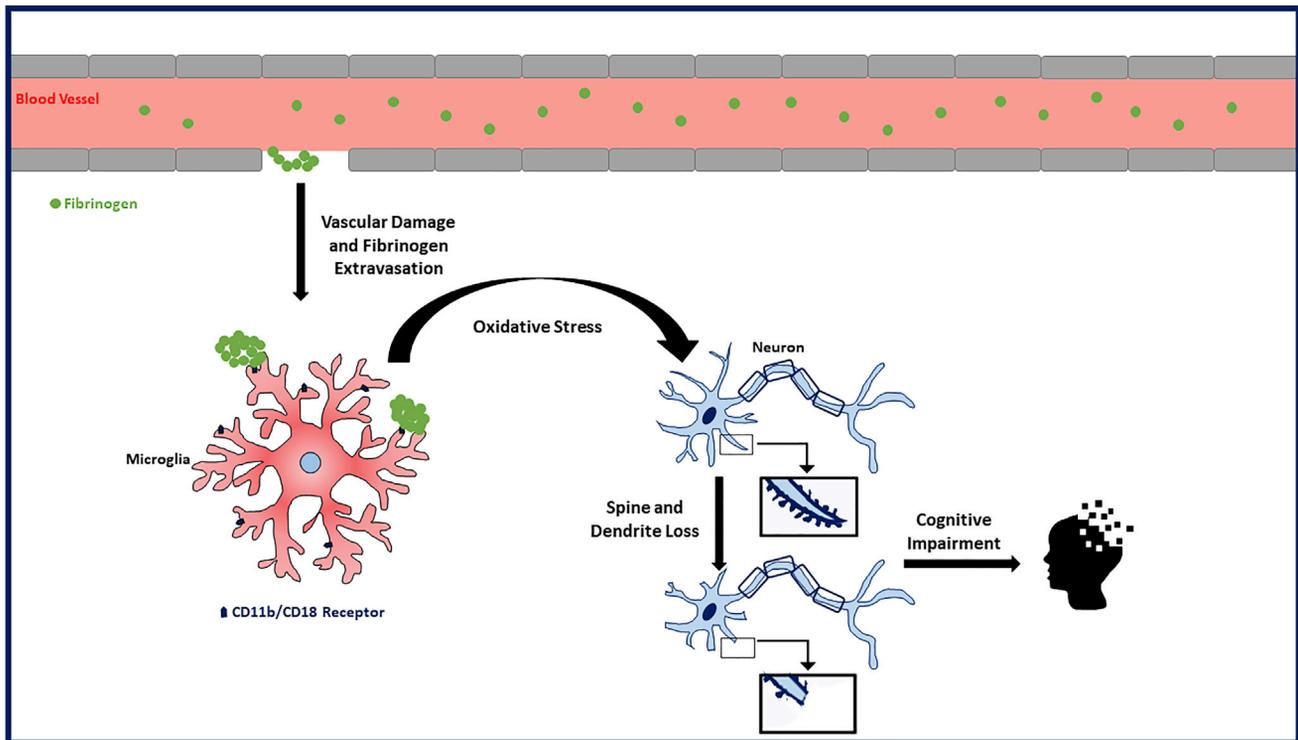
Figure 1. When There Is Damage to Blood Vessels of the Brain, as in AD, Fibrinogen Can Leak into the Parenchyma
Fibrinogen can activate microglia via the CD11b/CD18 receptor, contributing to oxidative stress, dendritic spine loss, and cognitive deficits.

a stronger inflammatory response in AD patient brains (Ahn et al., 2010; Cortes-Canteli et al., 2010). Based on these and other considerations, Merlini et al. (2019) proposed fibrinogen-induced CD11b/CD18 receptor-mediated microglial activation as a major pathway in AD pathogenesis. They found that fibrin deposits in the AD brain can activate microglia via binding to the CD11b/CD18 integrin receptor in areas devoid of Aβ plaques. Genetic elimination of the fibrinogen binding motif to CD11b/CD18 reduced neuroinflammatory activity, synaptic deficits, and cognitive decline in a mouse model of AD.

Indeed, a crucial experiment in this study was the analysis of fibrinogen's effect on spine elimination in the absence of the CD11b/CD18 receptor. The CD11b/CD18 integrin receptor is expressed on monocytes, macrophages, and microglia, and when fibrinogen binds to this receptor, it elicits many cell signaling responses, including cytoskeletal rearrangements, phagocytosis, adhesion, migration, and chemotaxis. The binding of CD11b/CD18 to fibrinogen plays a role in multiple sclerosis, and inhibition

of this binding can eliminate some of the inflammatory demyelinating effects of fibrinogen without affecting its ability to clot (Petersen et al., 2018). The authors also show that mutation of the CD11b/CD18 binding site of fibrinogen to limit its proinflammatory effects preserves cognitive function, supporting the idea that this binding is critical to the pathological effects of fibrin in AD.

Cerebral vascular dysfunction is a key feature of AD (Strickland, 2018), and BBB dysfunction and breakdown occur early in disease, even before signs of neurodegeneration or cognitive impairment are evident (Montagne et al., 2017). The BBB is a complex and dynamic barrier composed of closely aligned endothelial cells, astrocyte endfeet which wrap around the capillaries of the brain, and pericytes in the basement membrane. Endothelial tight junction complexes in the BBB have a major role in keeping neurotoxic plasma proteins, cells, and pathogens like bacteria and viruses out of the brain. However, the BBB must also allow for the exchange of oxygen and carbon dioxide between the vasculature and parenchyma via free diffusion

and the crossing of energy metabolites, nutrients, and regulatory molecules via receptor-mediated transport (Montagne et al., 2017).

More than 45% of early-stage AD patients exhibit increased cerebral microbleeds by magnetic resonance imaging. Furthermore, postmortem analyses of AD patient brains show brain capillary leakages and perivascular accumulation of blood-derived macromolecules such as fibrinogen, thrombin, albumin, immunoglobulin G, and hemosiderin. These findings suggest significant loss of BBB integrity in AD (Montagne et al., 2017). However, it is not clear how accumulation of blood-derived macromolecules induces cognitive impairment in AD patients. The experiments performed by Merlini et al. (2019) show that fibrinogen or plasma injection into the healthy mouse brain induces dendrite and spine loss, but injection of fibrinogen-deficient plasma does not. Furthermore, dendritic spine elimination occurs around fibrinogen deposits even distal from Aβ plaques in the AD mouse brain. This result suggests that among several extravasated blood

proteins in the AD brain, fibrinogen could be a major contributor to spine loss and cognitive deficits.

Dendritic spines are specialized components on neuronal cells that receive input from distinct synapses. These spines are crucial for proper synaptic communication between cells, and the formation and elimination of spines is dependent on signaling pathways in the actin cytoskeleton. Synapse loss is a key feature of AD and may be an indicator of cognitive impairment. In addition, many transgenic AD animal models show age-dependent synapse loss, regardless of degree of Aβ deposition, suggesting that soluble Aβ may be most detrimental to synapses rather than plaque deposition (Knobloch and Mansuy, 2008). Merlini et al. (2019) show that fibrin's detrimental effects contribute to spine loss in areas where there is no obvious Aβ deposition. Since synapse loss could also be caused by oxidative stress mechanisms (Knobloch and Mansuy, 2008), the authors also report that reactive oxygen species are produced in the presence of fibrin deposition, which is dependent on microglial activation.

This study supports the role of fibrinogen in AD and provides evidence that its activation of microglia may be one mechanism acting in parallel to Aβ deposition to stimulate spine elimination, synapse loss, and cognitive deficit (Figure 1).

These intriguing findings prompt several approaches to further probe the role of fibrinogen-induced microglial activation in AD pathology. First, a previous publication from the Akassoglou lab showed that fibrinogen injection induces CD11b/CD18-mediated recruitment of peripheral macrophages into the CNS and activation of myelin antigen-specific type 1 helper T cells in an animal model of MS (Ryu et al., 2015). It will be interesting to investigate how fibrinogen-induced inflammatory cell activation differs between AD and MS and what these two diseases have in common pathologically. Second, as discussed earlier, several genes that are highly expressed in microglia, such as CR1 and TREM2, are AD risk genes. Exploring the relationship between these AD risk genes and fibrinogen-induced effects in AD pathogenesis may help us better understand the role of microglial activation in this devastating disease.

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