Familial Alzheimer's Disease Mutation *PSEN2* Exacerbates *Toxoplasma gondii*-mediated Human Blood-Brain Barrier Damage

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Background and Hypothesis

Toxoplasma gondii is an obligate intracellular parasite that infects one-third of the global population. *T. gondii* transmission to humans primarily occurs from the consumption of contaminated meats, water, or produce. Unfortunately, *T. gondii* will evade the host clearance, allowing it to cross the blood-brain barrier (BBB), infecting neurons where it transitions into slow-growing cysts, leading to a life-long chronic infection. Recently, studies have suggested that *T. gondii* infection may exacerbate the decline of cognitive function. The BBB is critical for restricting neurotoxic blood-derived products, leukocytes, and pathogens from entering the brain. Studies have shown that BBB dysfunction and damage to the barrier integrity may also contribute to cognitive impairment. Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disease and its neuropathology is associated with β-amyloid plaques. Familial Alzheimer's Disease is associated with the proteins, presenilin-1 and presenilin-2, encoded by *PSEN1 and PSEN2*. Mutations in these two genes contribute to early onset AD. Furthermore, dementia has been linked with an increased breakdown of the BBB. Therefore, we hypothesized that *T. gondii* infection will exacerbate barrier damage and dysfunction in brain microvascular endothelial cells (BMECs) containing familial AD mutations compared to healthy controls.

Experimental Design

To test our hypothesis, we infected human induced pluripotent stem cell (iPSC)-derived BMECs, which display near *in vivo* like BBB properties, containing the familial AD *PSEN2* mutation or healthy controls with *T. gondii.*

Results

Using immunofluorescence and transendothelial electrical resistance, our results show that BMECs containing the *PSEN2* mutation have a quicker onset of barrier damage, but we observed no difference in the loss of tight junctions ZO-1, Occludin, and Claudin-5 compared to healthy controls after infection.

Potential Impact

These data suggest that a *T. gondii* infection can exacerbate the breakdown of the BBB in patients with the *PSEN2* mutation, worsening the prognosis of familial AD patients.