

Toxoplasma Gondii Induces Blood-Brain Barrier Dysfunction in a Human Stem Cell-Derived Model

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Background: *Toxoplasma gondii* is a single-celled obligate intracellular parasite commonly found in cat feces and animal issues and is known to cause cerebral infections in immune-compromised individuals and neonates. Once ingested, *T. gondii* reaches the host's blood supply and reaches the brain, where infection ensues. However, it remains unclear how *T. gondii* crosses the blood-brain barrier to reach the brain. In this study, we utilize a human stem cell-derived BBB model with near *in vivo* properties to investigate the effects of *T. gondii* on critical barrier properties that permit entry into the brain parenchyma.

Methods: Human-induced pluripotent stem cells (iPSCs) were used to derive brain microvascular endothelial cells (BMECs). BMECs were exposed to tachyzoites, the infectious rapid replicating stage of *T. gondii*, at a multiplicity of infection (MOI) of 0.1 and 1.0 for 24 hours. Following exposure, several critical barrier properties were monitored, including trans-endothelial electrical resistance (TEER) and tight junction analysis.

Results: BMECs treated with both MOI of 0.1 and 1.0 showed a significant reduction in all three tight junction proteins (Claudin-5, Occludin, and ZO-1), as indicated by an increase in discontinuous junctions and a decrease in area fraction index. Barrier integrity is directly associated with tight junctional continuity and localization. Furthermore, tachyzoites at an MOI of 0.1 and 1.0 demonstrated a reduction in barrier tightness, as observed by a decrease in TEER.

Conclusion and Potential Impact: These results indicate that *T. gondii* may, in part, have access to the brain by inducing disruption in tight junction proteins, thus increasing barrier leakiness via a para-cellular route. These data may help guide future investigations on *T. gondii*'s ability to evoke blood-brain barrier dysfunction and reach the vulnerable brain tissue.