Title: *Microglial Activation in Multiple Sclerosis: An in vitro Approach*

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Abstract

Microglia are the immune cells of the brain and play a crucial role in monitoring brain activity, maintaining tissue homeostasis, and responding to environmental cues, including inflammation. In several neurodegenerative diseases, such as multiple sclerosis (MS), microglia are implicated in disease pathogenesis, leading to inflammatory activation and tissue damage. However, the underlying mechanisms remain unclear. Therefore, human-based *in vitro* models are essential for enhancing our understanding of the pathology and developing effective treatments.

This study aimed to explore the inflammatory phenotype of microglia through *in vitro* disease modeling using human induced pluripotent stem cell (hiPSC)-derived microglia from six patients with MS and four healthy controls. We utilized RNA sequencing complemented by functional assays, to demonstrate intrinsic alterations in MS microglia at basal state as well as under inflammatory challenge. Our results revealed a distinct inflammatory transcriptome in MS microglia, accompanied by alterations in functions critical for MS pathophysiology including release of inflammatory factors and increase in phagocytic function.

These findings demonstrate cell-autonomous microglia activation in MS and indicate that disease-specific hiPSCs are an effective model for studying neuroinflammation and microglial activation on a dish. They also highlight the potential to identify novel genes involved in the disease phenotype, which may serve as promising drug targets for MS.