RESEARCH TOPIC MECM_29
MODELING SEX-SPECIFIC LYMPHOCYTE–GLIA INTERACTIONS IN MS USING A HUMANIZED BBB PLATFORM

Curriculum
MECM Standard

Research Area
Neuro

Laboratory name
Laboratory of Pharmacology and Brain Pathology

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Abstract
Multiple sclerosis (MS) susceptibility is influenced by sex. Women are about three times more likely to develop MS and typically mount stronger pro-inflammatory immune responses. However, men often experience a more aggressive and rapidly progressing disease course. This disparity has sparked growing interest in uncovering the biological mechanisms underlying sex-related differences in MS susceptibility, to develop tailored therapies targeting not only relapsing forms but also impacting CNS lesions which drive neurodegeneration and progression.
A key pathological event in MS is the migration of autoreactive lymphocytes across the blood–brain barrier, triggering reactive gliosis, chronic demyelination, and neuroaxonal injury. However, the extent to which this is influenced by biological sex remains largely unexplored. In a previous FISM-funded study, we developed a biomimetic, patient-specific in vitro model of the human BBB to investigate immune cell transmigration in treatment-naïve pwMS. Using this system, we observed that immune cells from female pwMS show increased transmigration rates of Th1 and Th17 subsets—key drivers of autoimmune inflammation—while T follicular helper (Tfh) cells, typically associated with B cell activation in lymphoid tissues, were more abundant in male pwMS.
Our project aims to dissect early immune-glial cross-talk, as it may shape divergent, sex-dependent glial responses that contribute to disease progression. Dissecting immune-glial interactions early in disease due to sex-specific T cell trafficking is critical for identifying mechanisms underlying disease progression and developing targeted interventions.
We will determine whether lymphocyte ability to migrate across brain borders is modulated by biological sex in pwMS with different disease trajectories and how this affects the CNS microenvironment. Specifically, we will investigate whether sex-specific immune infiltration alters microglial phenotypes.
Using the BBB model and immune cells from male and female pwMS we will distill transmigrating single-cell phenotype via high-dimensional cytometry and transcriptomics. We

will then incorporate human iPSC-derived microglia -to assess whether distinct immune profiles differentially program microglial phenotype.

Main technical approaches
Flow cytometry, RNAseq

Scientific references

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4. Fagiani, F. et al. A glia-enriched stem cell 3D model of the human brain mimics the glial-immune neurodegenerative phenotypes of multiple sclerosis. Cell Rep Med 5, 101680 (2024)

Type of contract

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