TNFR2 signaling in oligodendrocyte precursor cells suppresses their immune-inflammatory function and detrimental microglia activation in CNS demyelinating disease

Desu, H. L., *et al*. *Brain, behavior, and immunity, 123, 81–98.*

Presenter: Ming-Hsuan Lin **Date/Time**: 2025/10/16, 16:20-17:10
Commentator: Chih-Yen Wang, Ph.D. **Location**: Rm. 601, Med College Building

Background: Multiple sclerosis (MS) is a chronic autoimmune disease characterized by demyelination. Oligodendrocyte precursor cells (OPCs) are recruited to lesions to generate new, mature oligodendrocytes (OLs); however, this reparative process fails as the disease advances. Tumor necrosis factor (TNF) exists in two bioactive forms: soluble (solTNF) and transmembrane (tmTNF), which signal through TNFR1 and TNFR2, respectively. While TNFR1 promotes inflammation and cell death, TNFR2 mediates pro-survival and reparative signaling. Although within the demyelinated CNS, OPCs undergo a functional shift towards an immune phenotype, whereby they increase cytokine and chemokine production, the mechanisms that drive such a shift are far from being fully understood.

Objective: To determine how TNFR2 signaling in OPCs regulates their immune-inflammatory functions and interactions with microglia during demyelinating disease.

Results: Using transgenic *PdgfrαCre^{ERT}:Tnfrsf1b$^{fl/fl}$:Eyfp* mice with OPC-specific TNFR2 ablation, the study demonstrated accelerated disease onset and peak of experimental autoimmune encephalomyelitis (EAE), accompanied by increased immune cell infiltration and microglial activation in the spinal cord. In contrast, TNFR2 loss did not affect OPC proliferation or differentiation into OLs. In the cuprizone model, TNFR2-deficient OPCs led to reduced survival of newly formed oligodendrocytes and decreased expression of myelin proteins (MBP, MAG, and GSTπ), resulting in impaired remyelination. At the molecular level, OPCs lacking TNFR2 showed upregulated Tnfrsf1a and Ccl2, enhancing their inflammatory profile. These pro-inflammatory factors released by TNFR2-deficient OPCs, in turn, drove surrounding microglia to develop a “foamy” phenotype characterized by excessive lipid droplet accumulation and elevated Nos2 and Plin2 expression, indicative of dysfunctional lipid metabolism and impaired remyelination.

Conclusion: TNFR2 signaling in OPCs plays a protective role in demyelinating diseases by suppressing OPC-derived inflammatory responses and restraining microglial activation. Although TNFR2 does not have a cell-autonomous role in OPC differentiation, it may regulate the survival of newly formed myelinating OLs. These findings suggest that promoting TNFR2 signaling in OPCs has therapeutic potential, as it can both suppress neuroinflammation and promote repair.