Investigating the Role of IL-37 in Brain Endothelial Cells and Blood–Brain Barrier Regulation in Multiple Sclerosis

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IL-37 is a member of the IL-1 cytokine family and functions as a broad anti-inflammatory mediator through suppression of pro-inflammatory cytokines and modulation of immune signaling pathways. Uniquely, IL-37 signals through both extracellular receptor-mediated mechanisms (IL-18R1 and IL-1R8 (SIGIRR)) and intracellular pathways (SMAD3-mediated nuclear translocation) that broadly reduce inflammatory pathway activation. The protective effects of IL-37 in EAE occur through its extracellular function, specifically binding IL-1R8, thereby inhibiting pro-inflammatory signaling cascades such as NF- B, MAP kinases, and mTOR pathways. IL-37 has been studied in cardiovascular endothelial cells, where it inhibits atherosclerosis, reduced endothelial apoptosis, and protects against coronary endothelial damage, suggesting therapeutic potential in inflammatory endothelial pathologies. However, the expression and function of IL-37 in human brain endothelial cells remains poorly characterized. These cells are implicated in Multiple sclerosis (MS), a chronic neuroinflammatory disease affecting around 2.9 million people worldwide. The disease results from immune cell infiltration across the blood-brain barrier (BBB), which disrupts neuronal signalling by promoting inflammation, demyelination, gliosis and neuroaxonal degeneration. Transgenic mouse studies that introduced IL-37 in experimental autoimmune encephalomyelitis (EAE), the standard animal model for MS, demonstrated significantly reduced clinical scores and decreased demyelination. In addition, IL-37 expression reduced immune cell accumulation in the spinal cord and shifted cytokine profiles toward a more anti-inflammatory phenotype. Because human brain endothelial cells regulate immune trafficking and inflammatory signaling at the BBB and are associated withMS pathology, this project aims to investigate IL-37 signaling in human brain endothelial cells and determine whether this pathway contributes to immune regulation at the BBB. Understanding IL-37 in this context may provide insight into mechanisms that limit neuroinflammation in MS and identify potential therapeutic targets.