CAPSTONE

A literature review of interleukin-6 family cytokines regulation of oligodendrocytes following demyelination

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Multiple sclerosis (MS) is the most common of the demyelinating diseases affecting more than 1 million diagnosed patients worldwide.[1] Twice as many women as men are diagnosed with MS, and initial clinical presentation is typically between the ages of 15 to 55. The chronic immune-mediated disease leads to inflammation, demyelination, and eventually axonal loss in the central nervous system (CNS). Presentations of MS are wide-ranging and include weakness, tingling and numbness, vision problems, balance problems, bladder issues, sexual dysfunction, pains and spasms, and cognitive difficulties. MS follows a relapsing and remitting course of action. However, MS can be progressive and the intervals between relapses are inconsistent. The etiology of MS is complex, with interactions between multiple genetic and environmental factors attributed to its development.[2] While there is no cure for MS, it has been proposed that remyelination can protect against axonal loss.

One mechanism implicated in the restoration of remyelination is ciliary neurotrophic factor family cytokine (CNTF) activation of adult oligodendrocyte progenitor cells. Oligodendrocyte cells mature through distinct stages of development via growth factor and cell fate signaling pathways. Upon maturation, adult oligodendrocytes maintain the myelin sheaths that wrap axons.[3] CNTFs have been reported to promote oligodendrocyte survival and differentiation in experimental models of demyelination.[4] Although endogenous factors produce CNS neurons and glia, progenitor cells cannot exclusively replace cells and restore normal functioning in MS patients. Therefore, it is important to identify exogenous factors that increase the progenitor cell's response to inflammatory myelin destruction.[5] Such factors have been studied because of their therapeutic potential for slowing the progression of demyelinating diseases, which can be determined by measuring the time elapsed between exacerbations. In early-onset MS, researchers found the mean duration of the first and second remission to be 71.32 and 58.07 months, respectively.[6] Existing immunomodulatory treatments reduce the interval between relapses by merely 60%.[7] This review explores the signaling pathway by which interleukin (IL)-6 family cytokines regulate oligodendrocytes to protect against the progression of MS.

Activation of jak-dependent stat3 signaling pathway

IL-6 family cytokines include CNTF and leukemia inhibitory factor (LIF).[8] The binding of CNTF or LIF to the IL-6 receptor triggers the association of the IL-6 and signaling subunit glycoprotein 130 (gp130). Stimulation of the receptor complex induces the dimerization of the gp130 subunit which activates associated Janus kinases (JAKs). Activated JAKs phosphorylate tyrosine on the cytoplasmic region of the gp130 protein.[8] Tyrosine-phosphorylation of the gp130 subunit attracts the SH2 domain of signal transducer and activator of transcription 3 (Stat3), which is necessary for receptor association and tyrosine phosphodimer formation.[9] The phosphorylated Stat3 dimer is then imported into the nucleus via importin-α/importin-β1-Ran-mediated active transport.[10] In the nucleus, Stat3 activates gene expression which has been implicated to regulate oligodendrocytes and promote remyelination.[4] Therefore, the JAK-dependent Stat3 signaling

pathway has been studied in experimental models of demyelination. Previous studies used the western blotting technique to determine levels of Stat3 and phosphorylated Stat3 in the developing rodent brain. According to Steelman et al., Stat3 was expressed in the cerebrum of rodents from embryonic day 16 to postnatal day 30, and phosphorylated Stat3 was also expressed starting on postnatal day 13. Expression of myelin basic protein was also evident starting on postnatal day 13, indicating that Stat3 activation correlated with myelinogenesis in the developing rodent brain.[4] Furthermore, postnatal day 14 rodent brain sections immunostained for Stat3 and oligodendrocyte marker CC1 revealed their colocalization in the cingulate gyrus and corpus callosum.[4] The evident colocalization of Stat3 and oligodendrocyte cells, correlated with myelinogenesis, points to the regulation of oligodendrocytes via the Stat3 signaling pathway. In another study, Nobuta et al. wanted to identify the role of reactive astrocytes in the loss of premyelinating oligodendrocytes during development.[11] Their study found that STAT3 was activated in postmortem brains of neonatal white matter injury, which is characterized as loss of premyelinating oligodendrocytes. Nobuta et al. also used an experimental mouse model for neonatal white matter injury to ablate STAT3 in reactive astrocytes and identify molecular changes. The STAT3-deficient astrocytes promoted the production of transforming growth factor beta 1 in microglia, which the study found functions to delay oligodendrocyte maturation, and essentially impedes myelination.[11] In addition, it is important to consider limiting factors of the Stat3 signaling pathway. One endogenous inhibitor of the Stat3 signaling pathway is the suppressor of cytokine signaling 3 (SOCS3).[12] Ablation of SOCS3 enhanced axonal regeneration via the JAK-dependent Stat3 signaling pathway.[12] Based on the literature, reactive astrocytes may modify the STAT3 signaling pathway to promote oligodendrocyte maturation, which is important for myelination during development.

Regulation of oligodendrocyte survival and differentiation following demyelination

It is important to identify exogenous factors that activate the JAK-dependent Stat3 signaling pathway and lead to the regulation of oligodendrocytes survival and differentiation in experimental models of demyelination. Slaets et al., used western blotting analysis to determine the levels of Stat3 and phosphorylated Stat3 following exogenous LIF treatment in mature oligodendrocytes.[13] The expression of phosphorylated Stat3 increased 10-fold in the oligodendrocyte culture that was treated with LIF for 10 min, compared to the culture in the control condition of the study.[13] Another study interested in the relationship between exogenous CNTF treatment and oligodendrocyte viability measured changes in cell count after 2, 4, and 6 days of treatment, as well as the level of phosphorylated Stat3. The results showed that CNTF treatment activated Stat3 and significantly increased the number oligodendrocyte cells in vitro.[4] The effect of LIF treatment on oligodendrocyte viability is consistent with the effect of CNTF treatment. Butzkueven et al. were also interested in the relationship between an exogenous LIF treatment and oligodendrocyte viability.[14] The study found that, compared to the control condition, oligodendrocyte viability was significantly reduced in the induced demyelination condition. However, oligodendroglial survival was potentiated and baseline conditions were restored in the LIF treatment condition following induced inflammatory demyelination.[14] Finally, researchers have shown that LIF treatment enhances myelin protein expression and node of Ranvier formation.[5] One study used an immunostaining assay to assess myelin protein expression in the hippocampal CA3 region of mice under different conditions. The study found that mice in the 12-week demyelinating condition showed a reduction in myelin protein expression compared to the untreated condition. While mice in the 12-week demyelinating condition followed by 6-weeks of LIF treatment showed restoration of baseline myelin conditions.[5] In addition, LIF impacts other cell types, such as astrocytes, to produce factors which stimulate oligodendrocytes.[15] Albrecht et al found that oligodendrocyte progenitor cells

treated with CNTF did not proliferate in greater numbers than cells not treated with CNTF.[15] However, the researchers found that CNTF treated astrocytes released mitogens for oligodendrocyte progenitors which increased their viability compared to the control condition in the study.[15] In overview, experimental models of demyelination treated with either LIF or CNTF increased phosphorylated STAT3 to potentiate oligodendrocyte viability and restore baseline myelin conditions.

Conclusion

Previous studies have shown that IL-6 family cytokines regulate oligodendrocytes following demyelination via the JAK-dependent Stat3 signaling pathway. In experimental models of demyelination, CNTF binds to the low-affinity receptor complex IL-6R/gp130/LIFR.[16] Stimulation of the receptor complex then activates the JAK-dependent Stat3 pathway which changes gene expression in the cell to promote oligodendrocyte survival and differentiation. In demyelinating diseases, such as MS, oligodendrocyte progenitor cells cannot exclusively replace cells and restore normal functioning in patients.[5] Therefore, it is important to identify exogenous factors that increase oligodendrocyte progenitor cells' response to inflammatory myelin destruction. CNTF and LIF treatments in rodent brains have been shown to increase oligodendrocyte viability and restore myelin following demyelination. The mechanism responsible for oligodendrocyte proliferation following changes in gene expression induced by Stat3 has not been studied extensively. Future research should focus on the induced changes in gene expression via the JAK-dependent Stat3 signaling pathway in the CNS of experimental models exhibiting demyelination. In addition, LIF treatment in the CA3 stratum radiatum of the hippocampus has shown to enhance $Na_v1.6$ and Caspr restoration.[5] However, the mechanism by which the sodium channel $Na_v1.6$ and paranodal protein Caspr are restored has not been clearly identified, making it an avenue for future research. Overall, exogenous CNTF and LIF treatments might be of therapeutic interest to promote remyelination in MS patients.[17]

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