Leukemia Inhibitory Factor Confers Neuroprotection during Ischemic Stroke through Enhanced LIFR Expression and Membrane Localization

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Background: Leukemia inhibitory factor (LIF) is an anti-inflammatory cytokine that protects neural cells during ischemic stroke. Upon binding to the LIF receptor (LIFR)/glycoprotein 130 complex, LIF increases Akt signaling to activate the neuroprotective transcription factors, including specificity protein 1 (Sp1) and myeloid zinc finger-1 (MZF-1). These transcription factors bind to the promoter of the antioxidant enzyme superoxide dismutase 3 (SOD3), which is upregulated by LIFR signaling. Previously, this lab demonstrated that immune cells from the spleen migrate to the ischemic hemisphere and cause neurodegeneration. Regulatory mechanisms of LIFR signaling during stroke have not yet been described. Furthermore, it is not known whether LIF alters the splenic response after stroke.

Purpose: The purpose of this study is to determine whether LIF treatment increases expression and membrane localization of LIFR in the brain and the spleen during ischemic stroke.

Methods: Focal ischemic stroke was induced in young male rats using the middle cerebral artery occlusion (MCAO) model. Animals were administered LIF (125 µg/kg) or PBS at 6, 24, 48 h after MCAO. Western blotting was used to measure LIFR expression in brain and spleen tissue. Immunohistochemistry was used to examine the expression and localization of LIFR, MZF-, Sp1 and SOD3 in the cerebral cortex. Genomatix software was used to identify transcription factor binding sites in the promoter of the LIFR gene.

Results: LIFR expression was significantly higher in the brains of LIF treated rats compared to PBS-treated and sham-operated rats at 72 h post-MCAO. In the absence of LIF treatment, neuronal LIFR was localized to the nucleus. At 72 h post-MCAO LIF treatment caused LIFR from the nucleus to the plasma membrane. A binding site for Sp1, a LIF-dependent transcription factor, was identified in the LIFR promoter. Furthermore, Sp1 and MZF-1 co-localized with SOD3 in the brain at 72 h after MCAO. LIFR expression significantly decreased after MCAO, but there was a trend towards increased LIFR expression among LIF-treated rats. LIF treatment also significantly increased spleen size compared to PBS-treated rats at 72 h after MCAO.