Interferon Beta Modulation of Brain Endothelial Cell Activation in Ischemic Stroke

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Background and Hypothesis:

Every year, more than 690,000 people in the United States suffer an ischemic stroke. Many survivors are left with long-term disability. While the initial insult to the brain is caused by hypoxia resulting from cerebral artery occlusion, a secondary insult is caused by peripheral immune cell infiltration across the blood brain barrier (BBB) and subsequent cytotoxic insult. Previous studies have demonstrated that interferon beta (IFNβ) limits peripheral immune cell infiltration across the BBB and reduces brain infarction volume. We hypothesize that during ischemic stroke IFNβ suppresses brain endothelial cells (bECs) activation to reduce their expression of adhesion molecules as one of the mechanisms by which it decreases peripheral immune cell infiltration across the BBB.

Experimental Design:

In this project, bEnd.3 cells, a cell line of bECs, were activated by TNF-α, a pro-inflammatory cytokine. Tissue plasminogen activator (tPA), an FDA-approved thrombolytic for ischemic stroke, was included in the study. bEnd.3 cells were treated with IFNβ at 1.5 hours prior TNF-α or TNF-α + tPA stimulation to evaluate its modulation of adhesion cell expression. The adhesion molecule expression was determined by flow cytometry. Results were further confirmed by in vivo studies in which stroke animals were subjected to tPA treatment in the presence or absence of IFNβ.

Results:

Our results showed that TNF-α induced ICAM-1, VCAM-1, E-selectin, and P-selectin expression. Importantly, we found IFNβ suppressed the expression of aforementioned adhesion molecules in bEnd.3 cells treated with TNF-α or TNF-α+tPA. Our in vivo results demonstrated that IFNβ treatment reduced ICAM-1 and E-selectin, but not VCAM-1 or P-selectin expression in the ischemic brain

Conclusion and Potential Impact:

Our study demonstrates that IFNβ modulates bEC expression of adhesion molecules in vitro and in vivo of ischemic stroke, suggesting IFNβ, an FDA-approved drug for Multiple Sclerosis, shows potential to improve ischemic stroke outcomes.