Scientific Paper:

Translational Stroke Research (2022) 13, 462-482

Erythropoietin Abrogates Post-Ischemic Activation of the NLRP3, NLRC4, and AIM2 Inflammasomes in Microglia/Macrophages in a TAK1-Dependent Manner

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Abstract:

Inflammasomes are known to contribute to brain damage after acute ischemic stroke (AIS). TAK1 is predominantly expressed in microglial cells and can regulate the NLRP3 inflammasome, but its impact on other inflammasomes including NLRC4 and AIM2 after AIS remains elusive. EPO has been shown to reduce NLRP3 protein levels in different disease models. Whether EPO-mediated neuroprotection after AIS is conveyed via an EPO/TAK1/ inflammasome axis in microglia remains to be clarified. Subjecting mice deficient for TAK1 in microglia/ macrophages (Mi/MΦ) to AIS revealed a significant reduction in infarct sizes and neurological impairments compared to the corresponding controls. Post-ischemic increased activation of TAK1, NLRP3, NLRC4, and AIM2 inflammasomes including their associated downstream cascades were markedly reduced upon deletion of Mi/MΦ TAK1. EPO administration improved clinical outcomes and dampened stroke-induced activation of TAK1 and inflammasome cascades, which was not evident after the deletion of Mi/MΦ TAK1. Pharmacological inhibition of NLRP3 in microglial BV-2 cells did not influence post-OGD IL-1β levels, but increased NLRC4 and AIM2 protein levels, suggesting compensatory activities among inflammasomes. Overall, we provide evidence that Mi/MΦ TAK1 regulates the expression and activation of the NLRP3, NLRC4, AIM2 inflammasomes. Furthermore, EPO mitigated stroke-induced activation of TAK1 and inflammasomes, indicating that EPO conveyed neuroprotection might be mediated via an EPO/TAK1/inflammasome axis.

Keywords: stroke, microglia, inflammasomes, TAK1, EPO, neuroinflammation