Botch

The neuroprotective gene 7 (NPG7) is also known as Chac, cation transport regulator homolog 1, and is identified in functional screen for neuroprotective proteins. Currently, the NPG7 is renamed Botch (Blocks Notch), which was widely expressed in multiple organs, including brain. Botch could prevent cell surface presentation of Notch1 by inhibiting the S1 furin-like cleavage of Notch1 and maintain Notch1 in the immature full-length form (Notch1-FL).

Notch1 up-regulation participates in inflammatory responses after cerebral ischemia-reperfusion (I/R) injury, and it has been reported that Botch binds to and blocks Notch1 maturation. In this study, we investigated the role of Botch during cerebral (I/R) injury and explored its potential mechanisms. A middle-cerebral-artery occlusion/reperfusion (MCAO/R) model was established in adult male Sprague-Dawley rats in vivo, and cultured neurons and microglia were exposed to oxygen-glucose deprivation/reoxygenation (OGD/R) to mimic I/R injury in vitro. The results showed that protein levels of Botch and the Notch1 intracellular domain (NICD) were increased after MCAO/R. Furthermore, after overexpression of Botch, the generation of the activated form of Notch1, NICD, was decreased, while Botch knockdown or mutation led to an increase in NICD generation. As a result, Botch overexpression exhibited neuroprotective effects by significantly decreasing neurobehavioral phenotypes, improving infiltration of activated microglia, ameliorating inflammatory cytokine release, and inhibiting neuronal cell death. Conversely, Botch knockdown and mutation induced opposite effects. In addition, NICD was found to translocate to the mitochondria after OGD/R in neurons and microglia, which stimulated accumulation of reactive oxygen species in mitochondria and resulted in neuronal cell death and microglial activation. Botch overexpression inhibited the generation of NICD and decreased the translocation of NICD to the mitochondria, which inhibited neuronal cell death and ameliorated neuroinflammation. In conclusion, we found that Botch exerts neuroprotective effects via antagonizing the maturation of Notch1-induced neuronal injury and neuroinflammation, which may provide insights into novel therapeutic targets for the treatment of I/R injury [1].

1)
Li H, Ma J, Fang Q, Li H, Shen H, Li X, Xue Q, Zhu J, Chen G. Botch protects neurons from ischemic insult by antagonizing Notch-mediated neuroinflammation. Exp Neurol. 2019 Aug 1:113028. doi: 10.1016/j.expneurol.2019.113028. [Epub ahead of print] PubMed PMID: 31377404.