C5aR1 mediates progression of inflammatory responses in brain of rats after ischemia and reperfusion

Yunwei Shi[1], Ying Jin[1], Xing Li[2], Chen Chen[1], Zhi Hong Zhang[1], Xiao Yu Liu[1], Yi Jun Deng[2], Xing Juan Fan[3], and Cai Ping Wang[1]

[1]Nantong University
[2]No 1 People's Hospital of Yancheng
[3]Affiliated Hospital of Nantong University

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Abstract

C5a receptor 1 (C5aR1) can induce strong inflammatory response to injury. Targeting C5aR1 has emerged as a novel anti-inflammatory therapeutic method. However, the role of C5aR1 in cerebral ischemia and reperfusion (I/R) injury and the definitive mechanism have not been elucidated clearly. Here we determine whether C5aR1 signaling is essential to the development of post-ischemic inflammation and brain injury and whether it is a valid target for therapeutic blockade with soluble receptor antagonist PMX53. In an in vitro model (oxygen and glucose deprivation and reperfusion, OGD/R) and in vivo model (middle cerebral artery occlusion and reperfusion, MCAO/R) of I/R, neuronal cells of rats showed significantly up-regulated gene expression of C5aR1, and notable inflammatory response demonstrated with elevated tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6. Inhibition of C5aR1 by PMX53 treatment significantly reduced cell injury and inflammation, and promoted brain function recovery. The further mechanism studies showed that inhibiting C5aR1 by PMX53 protected rats from MCAO/R injury, decreased cell inflammation and apoptosis via inhibiting TLR4 and NF-ϰB signaling pathway and reducing the production of TNF-α, IL-1β, and IL-6 in MCAO/R rats. In addition, manipulation of the C5aR1 gene expression in vitro displayed that the inflammatory cascades signals including TLR4, TNF-α, IL-1β and IL-6 were coincidently regulated with the regulation of C5aR1 expression levels. Thus, our results demonstrated a pathogenic role for C5aR1 in the progression of brain injury and inflammation response following I/R injury. Our study clearly demonstrated that C5aR1 inhibition might be an effective treatment strategy for ischemic stroke.

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