Hypoxia-inducible factor-1 α and RIP3 triggers NLRP3 inflammasome in ischemic stroke

Despite the enduring status of ischemic stroke as a major cause of morbidity and mortality worldwide, a deficiency of effective therapies currently exists to treat this deadly disease. It is therefore essential that research continues to be conducted into the molecular mechanisms that precipitate injury following strokes. These mechanisms may, one further elucidated, yield the therapeutic targets that have eluded clinical practice thus far.

It is for this reason that inflammation, a major component of the damage produced by ischemic stroke, is of interest to our group. The molecular basis of poststroke inflammation has been enriched in recent years by the growing body of evidence implicating activation of inflammasomes in aggravation of brain damage.[1,2] Inflammasomes are intracellular complexes consisting of multiple proteins that may include pattern-recognizing NOD-like or absent in melanoma-2-like receptors (NLR and AIM2, respectively), an adaptor protein, and caspase-1; damage-associated molecular pattern sensation by the complex leads to the activation of caspase-1, which results in the release of the proinflammatory cytokines interleukin 1 (IL-1) β and IL-18.[2] Of the inflammasomes, NLRP3 appears to be especially relevant to the pathophysiology of stroke: it is thought to the most important inflammasome sensor in the brains of stroke patients,[3] and Yang *et al*. found that NLRP3 mRNA and protein expression is significantly increased after 12h poststroke.[4]

Inflammasome activation appears to promote cell death in ischemic stroke by multiple mechanisms. In addition to the cell death pathway mediated by pyroptosis, necroptosis also plays an important role. Necroptosis is mediated by the activation of receptor-interacting protein kinase-1 (RIPK1) and RIPK3, which leads to phosphorylation of the effector mixed lineage kinase domain-like protein (MLKL).[5] The activation of MLKL then causes its translocation to the membrane, resulting in cell rupture. In addition, it has been shown by Conos *et al*.,[6] and Gutierrez *et al*.[7] that MLKL directly activates NLRP3, resulting in an inflammatory response due to the release of mature IL-1 β.

Hypoxia-inducible factor 1 (HIF-1), a key transcription factor that is composed of HIF-1α and HIF-1 β protein subunits and regulated by oxygen, also appears to be involved in this pathway. Under hypoxic conditions, HIF-1α serves the adaptive purpose of inducing the transcription of genes that may be involved in the mitigation of brain injury.[8] Some studies indicate, however, that activation of HIF-1α promotes cell death after ischemic stroke.[9] Reactive oxygen species (ROS), which are known to be elevated following ischemic stroke, appear to induce HIF-1α accumulation, resulting in cell death. In addition to this ROS-driven mechanism, Yang *et al*. recently demonstrated that HIF-1α might be activated in the course of RIP3/MLKL-mediated necroptotic brain injury: compared to control cells, those subjected to oxygen-glucose deprivation significantly upregulated the expression of RIP3 and HIF-1α, and RIP3 siRNA decreased the protein level of HIF-1α under ischemic conditions. Additionally, HIF-1α siRNA did not affect the expression of RIP3 or MLKL, but did result in decreased ischemic injury.[8]

In summary, poststroke inflammation induces RIP3/MLKL activation, and MLKL triggers the NLRP3 inflammasome, which elaborates the proinflammatory cytokines IL-1 β and IL-18 that promote brain damage.[10] In addition, HIF-1α appears to be involved in the RIP3/MLKL pathway, and the expression of HIF-1α increases after ischemic stroke. It is currently not clear whether HIF-1α is involved in the activation of the NLRP3 inflammasome, however. Our group hopes, by investigating its involvement with NLRP3 inflammasome activation, to clarify the manner in which HIF-1α is involved in the pathophysiology of ischemic stroke, and thus to contribute to the discovery of novel interventions against the damage wrought by this disease.

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