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Stroke Literature Synopses: Basic Science (2015/June)

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The inflammasome is a multi-protein complex that regulates innate immunity. Inflammasomes recognize cellular infection and stress, such as pathogen-associated molecular patterns or damage-associated molecular patterns, and then activate caspase-1 to induce secretion of pro-inflammatory cytokines. Thus far, a number of inflammasome proteins is reported, and those identified core components belong to two families: the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) family and the pyrin and haematopoietic interferon-inducible nuclear antigens with 200 amino-acid repeats domain-containing protein (PYHIN) family.

Although accumulating evidence has revealed important molecular mechanisms underlying the inflammasome-mediated processes, roles of inflammasomes in central nervous system still remain unclear. For example, although mechanisms of inflammasome-mediated activation have been extensively studied in hematopoietic macrophages, much less is known about microglia that are resident tissue macrophages in brain. **Burm et al., (Inflammasome-induced IL-1 β secretion in microglia is characterized by delayed kinetics and is only partially dependent on inflammatory caspases. The Journal of Neuroscience. 2015;35:678–687)** compared inflammasome-mediated activation in different types of macrophages. In this study, the authors prepared primary microglia, bone marrow derived macrophages (BMDMs), and blood CD14⁺-derived macrophages (CD14Ms) from adult healthy rhesus macaques. mRNA expression levels of the inflammasome-related proteins were compatible between BMDMs and CD14Ms, but microglia expressed significantly lower levels of some typical inflammasome-related proteins, including NOD1, NOD3, and caspase 1. However, after LPS priming, mRNA expression profile of microglia became closer to that of those hematopoietic macrophages. Importantly, pro-IL-1 β mRNA transcripts were rapidly induced by LPS priming in both microglia and BMDMs. However, the increase of transcript levels in microglia was more sustainable than BMDMs. These cell type-specific differences in the inflammasomes may help us develop novel strategies to modulate innate immune responses in brain.

Inflammasome-mediated processes may contribute to brain dysfunction under diseased conditions. **Denes et al. (AIM2 and NLRC4 inflammasomes contribute with ASC to acute brain injury independently of NLRP3. Proceedings of the National Academy of Sciences of the United States of America. 2015;112:4050–4055)** examined which

inflammasomes participate in brain injury after stroke, using five kinds of knockout mice. Firstly, the authors analyzed three lines of knockout mice; (i) NLR family, pyrin domain containing 3 (NLRP3), (ii) NOD2, and (iii) apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (CARD) (ASC). Both NLRP3 and NOD2 belong to the NLR family, and ASC works as an adaptor protein for the inflammasome complex. After stroke (e.g. middle-cerebral artery occlusion), the knockout mice of NLRP3 or NOD2 did not show any differences in infarction volume, neurological outcomes, and microglial activation compared to wild-type mice. On the other hand, ASC knockout mice were confirmed to be resistance to ischemic stress, indicating that other inflammasome-related proteins contribute to brain damage after stroke. Then, the authors analyzed two additional lines of knockout mice; (iv) NLR family, CARD domain containing 4 (NLRC4) and (v) absent in melanoma 2 (AIM2). NLRC4 belongs to the NLR family, and AIM2 belongs to the PYHIN family of inflammasomes. Compared to wild-type mice, both NLRC4 knockout and AIM2 knockout mice were more resistant to ischemic stress. Although multiple inflammasomes may regulate neuronal injury, these findings indicate that the NLRC4 and AIM2 inflammasomes would be important targets for stroke therapy.

Other inflammasomes also participate in neuronal damage. **Kaushal et al. (Neuronal NLRP1 inflammasome activation of caspase-1 coordinately regulates inflammatory interleukin-1-beta production and axonal degeneration-associated caspase-6 activation. Cell Death and Differentiation. 2015; doi: 10.1038/cdd.2015.16)** examined the roles of neuronal NLRP1 inflammasome, focusing on mechanisms of caspase-6 activation because the active caspase-6 protease is associated with axonal degeneration. In primary fetal human neurons, the NLRP1 inflammasome was responsible for caspase-6 activation via caspase-1 activation after serum deprivation. In addition, the NLRP1 inflammasome also played critical roles in IL-1 β production by serum deprivation. By analyzing NLRP1 knockout and caspase-1 knockout mice, the importance of NLRP1-caspase1-caspase6 pathway was also confirmed in live brains. These data revealed a fundamental mechanism how the inflammasomes contribute to neuroinflammation and axonal degeneration.

These three studies describe novel mechanisms for how the inflammasomes lead to brain dysfunction with implications for potential targets for stroke therapy. Since inflammatory responses are essential in stroke pathology, further investigations of inflammasomes in brain are warranted.