Damage-associated molecular pattern mediators (DAMPs), also known as alarmins, are evolutionarily conserved biomolecules that can initiate and perpetuate a sterile/noninfectious inflammatory response after tissue injury. Three recent studies reported how DAMPS/alarmins are involved in stroke pathology.

Shichita et al (MAFB prevents excess inflammation after ischemic stroke by accelerating clearance of damage signals through MSR1. Nat Med. 2017;23:723–732. doi: 10.1038/nm.4312) examined the mechanisms of clearance of DAMPs after stroke. High-mobility-group box 1 (HMGB1), peroxiredoxins, and S100A8/A9 proteins are well-characterized DAMPs that are involved in brain injury. The authors isolated cells from day 3 postischemic mouse brain (male C57BL/6; 8–14 weeks; 60 minutes middle cerebral artery occlusion by filament insertion) and incubate the cells with fluorescence-labeled recombinant peroxiredoxins, HMGB1, and S100A8/A9. Immunostaining and fluorescence-activated cell sorter experiments confirmed that those DAMPs were selectively internalized by infiltrating mononuclear phagocytes. Then, using a macrophage-like cell line RAW264.7, the authors established mutant clones that were deficient in the internalization of those DAMPs. By comparing the gene expression profiles of parental RAW264.7 and the mutant lines, MSR1 (macrophage scavenger receptor 1) was identified to play a critical role in DAMP internalization. In ischemic mouse brain, DAMP internalization was indeed mediated by MSR1, and the elevation of MSR1 expression in infiltrating myeloid cells after stroke in mice was dependent on the transcription factor Mafb. Importantly, mice with Mafb deficiency in macrophage/neutrophil (Lysm-Cre;Mafb-flox/flox mice) showed larger amounts of DAMPs in brain and worse stroke outcomes compared with wild-type mice. Because the retinoic acid receptor agonist Am80, which can increase the expression of Mafb, exhibited efficacy in these mouse stroke models, enhancing DAMP clearance may be a therapeutic target for ischemic stroke.

DAMPs may contribute to injury mechanisms in hemorrhagic stroke as well. Wang et al (Anti-high mobility group box-1 (HMGB1) antibody inhibits hemorrhage-induced brain injury and improved neurological deficits in rats. Sci Rep. 2017;7:46243. doi: 10.1038/srep46243) aimed to show a proof-of-concept that treatment with neutralizing anti-HMGB1 monoclonal antibody (mAb) is effective for hemorrhage-induced brain damage. Intracerebral hemorrhage (ICH) is one of the most lethal stroke subtypes and is well accepted as a serious clinical problem lacking effective treatment. This study used male Wistar rats for an animal model of ICH by local injection of collagenase IV into striatum. Anti-HMGB1 mAb (1 mg/kg) or class-matched control mAb (1 mg/kg) was administered through tail vein immediately and 6 hours after collagenase IV injection. Although the hematoma size was similar between the control and anti-HMGB1 mAb-treated rats at 24 hours after collagenase IV injection, anti-HMGB1 mAb attenuated ICH-induced motor deficits at day 2 to 3 and BBB disruption/brain edema at day 3. Inflammation-related factors and reactive oxidative species were involved in the ICH-induced brain injury, and ICH rats with anti-HMGB1 mAb treatment exhibited less expression levels for those deleterious factors. Therefore, intravenous injection of neutralizing antibody for HMGB1 may have potential as a therapeutic strategy for ICH.

Interleukin-33 (IL-33) is a member of the IL-1 family. It is known as a nuclear alarmin, which is released after cell damage. Yang et al (ST2/IL-33-dependent microglial response limits acute ischemic brain injury. J Neurosci. 2017;37:4692–4704. doi: 10.1523/JNEUROSCI.3233-16.201) examined the roles of IL-33 receptor ST2 in ischemic brain injury. ST2 is a member of the IL-1 receptor family, and the membrane-bound
ST2 isoform forms heterodimers with IL-1 receptor accessory protein to serve as a receptor for IL-33. In this study, male ST2 knockout mice were subjected to transient or permanent focal ischemia (transient, 60-minute middle cerebral artery occlusion by filament insertion; permanent, distal minutes middle cerebral artery occlusion plus ipsilateral common carotid artery occlusion). Regardless of types of ischemic injury, male ST2 knockout mice exhibited enlarged brain infarct volumes at day 3 after stroke. Also, in female mice, lack of ST2 expression enlarged the brain infarct sizes. In addition, ST2 deficiency aggravated neurological deficits and tissue loss at day 7 after transient focal ischemia. Flow cytometry analyses showed that microglia was one of the major cell types for ST2 expression in brain, and after ischemic insults, ST2 expression in microglia was increased. ST2 deficiency enhanced the expression of M1 markers in microglia but impaired one of the M2 markers. In vitro cell culture experiments also confirmed that IL-33/ST2 signaling shifted the microglial phenotype from M1 to M2, which is neuroprotective via partly releasing neuroprotective factors such as IL-10. Therefore, endogenous IL-33/ST2 signaling is an important mechanism to mitigate ischemic brain injury after stroke.

Taken together, these 3 papers describe novel mechanisms as to how inflammation may contribute to stroke pathology. Further investigations into DAMPs/alarmins may eventually lead to new therapeutic targets for stroke.
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