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Stroke Literature Synopses: Basic Science (2015/April)

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Microglia/macrophage play critical roles for immune defense in brain. After stroke, microglia/macrophage accumulation may last for weeks, which contributes to both deleterious and beneficial cascades. Three recent studies provide new information on novel beneficial mechanisms of microglial/macrophage function after central nervous system (CNS) injury.

Kawabori et al. (Triggering receptor expressed on myeloid cells 2 (TREM2) deficiency attenuates phagocytic activities of microglia and exacerbates ischemic damage in experimental stroke. *The Journal of Neuroscience*. 2015;35:3384-3396) used both in-vitro and in-vivo stroke models to examine the roles of triggering receptor expressed on myeloid cells 2 (TREM2) on microglia in phagocytosis of damaged brain cells. In vitro cell culture experiments showed that control microglia took up injured neurons, but blunted phagocytosis was observed in TREM2-deficient microglia. In vivo studies using mouse stroke model confirmed that compared to wild-type mice, TREM2 knockout mice showed decrease in activated microglia and phagocytes after stroke. Concomitantly, TREM2 knockout mice with ischemic brain damage exhibited worsened neurological recovery and less brain resorption than wild-type mice. TREM2 is known to bind anionic ligands on various bacterial and yeast, thus was originally described as an important receptor for phagocytosis of various pathogens. But it was reported that there would be unknown ligands for TREM2 in brain. So finally, this study explored to find endogenous ligand for TREM2 in ischemic brains and showed that nucleic acids from injured neurons was capable of eliciting TREM2 signaling to enhance phagocytosis.

Other cell types than neurons may also regulate phagocytosis in brain. Gadani et al. (The glia-derived alarmin IL-33 orchestrates the immune response and promotes recovery following CNS injury. *Neuron*. 2015;85:703-709) demonstrated that damaged oligodendrocytes would secrete a regulator of innate immune response after CNS injury. This study focused on the roles of interleukin-33 (IL-33), which is known as a nuclear alarmin of the IL-1 cytokine family released by cell damage. By immunofluorescence analysis, the authors first showed that post-mitotic oligodendrocytes or gray matter astrocytes are a primary CNS source for IL-33, and after spinal cord injury, IL-33 was immediately released. Then the authors used IL-33 knockout mice to examine the roles of IL-33 after CNS injury. IL-33 knockout mice showed no deficits in baseline motor function,

but after spinal cord injury, IL-33 knockout mice showed significant impaired recovery relative to wild-type counterparts. The M2-microglia/macrophage are thought as beneficial for neuronal survival/recovery, and indeed, there were significant decrease in expression of several M2-associated genes in the lesion site of IL-33 knockout mice. However, expressions of M2 genes in microglia were not changed after injury both in wild-type and IL-33 knockout mice. Instead, there was a reduction in the number of infiltrated peripheral circulating cells including monocytes/M2-macrophages in the IL-33 deficient spinal cords after injury. The authors finally showed that released IL-33 upregulated chemokine production in glial cells, which would increase protective myeloid cell recruitment after injury.

Drugs that can switch microglia/macrophage phenotype from M1 (deleterious) to M2 (beneficial) would be effective treatments for injured brain. Wang et al. (HDAC inhibition prevents white matter injury by modulating microglia/macrophage polarization through the GSK3 β /PTEN/Akt axis. *Proceedings of the National Academy of Sciences of the United States of America*. 2015;112:2853-2858) tested the efficacy of Scriptaid, a histone deacetylase (HDAC) inhibitor, using in-vitro and in-vivo models of traumatic brain injury (TBI). Scriptaid is a novel inhibitor of class I/II HDACs, and the same research team previously reported that Scriptaid protected gray matter against experimental TBI model. In this study, the authors first showed that Scriptaid preserved myelin sheath and axonal function in white matter after TBI, and Scriptaid also enhanced recovery of motor function. Scriptaid did not protect myelin-producing oligodendrocytes against oxygen-glucose deprivation (OGD) in vitro. However, conditioned media from Scriptaid-treated microglia supported oligodendrocyte survival under the OGD conditions, but culture media from control-treated microglia did not. To support the findings, the authors then confirmed that Scriptaid shifted the microglia/macrophage polarization toward beneficial M2 phenotype via PI3K/Akt pathway.

The findings described above provide new insight into beneficial roles of microglia/macrophage after brain injury. Further investigation of these pathways may lead to therapeutic ways to modulate microglia/macrophage in stroke.