Inflammatory cells play an important role in stroke pathophysiology, but how these mechanisms contribute to the delicate balance between injury and repair remains to be fully understood. Three recent studies provide new evidence for crosstalk between inflammation and regeneration in the central nervous system.

Kyristsis et al (Acute inflammation initiates the regenerative response in the adult zebrafish brain. *Science*. 2012;338:1353–1356) proposed that under some conditions, inflammatory cells can be a positive regulator of neurogenesis in the damaged central nervous system. A novel zebrafish model of central nervous system trauma was used because this species can efficiently regenerate lost neurons. Traumatic injury in the zebrafish brain activated microglia and leukocytes, consistent with the development of inflammation. Immunostaining detected proliferating cell nuclear antigen (proliferating cell detection) and S100beta (radial glial cell detection) positive cells, showing that acute inflammation could enhance progenitor cell proliferation in the adult zebrafish brain. Along with the proliferation of glial progenitor cells, reactive neurogenesis was also observed. To identify a mediator of neurogenesis after traumatic brain injury, the authors performed a transcriptome screen and determined that cysteinyl leukotriene receptor 1 (cysLT1) on radial glial cells played a central role for neuronal recovery after brain injury. Even without direct brain lesions, leukotriene C4 (LTC4), one of the cysLT1 ligands, was able to upregulate Gata3 expression and increase neurogenesis. Gata3 is generally induced only after brain damage. Therefore, these findings indicate that the inflammatory response, in part, via the LTC4-cysLT1 cascade, may initiate endogenous regenerative programs for remodeling after brain injury.

Cell–cell signaling is typically bidirectional. If inflammatory cells can promote neurogenesis, is it possible that in turn, neurogenesis can regulate inflammation? A recent study by Mosher et al (Neural progenitor cells regulate microglia functions and activity. *Nature Neurosci*. 2012;15:1485–1487) showed that neuronal progenitor cells (NPCs) possess a secretory protein profile that is distinct from that of other brain cells, and these secretory interactions can modulate microglia. The authors observed that microglial cells were more densely populated and proliferative in neurogenic niches, and seemed to be closely associated with NPCs; 3-dimensional reconstruction of the hippocampus demonstrated that NPCs are encircled by microglia. The authors then conducted in vitro medium-transfer experiments to show that conditioned medium from primary NPCs (1) increased the number, (2) promoted the migration, and (3) accelerated the phagocytosis efficacy of mouse microglia cells. Interestingly, injection of NPCs into mouse brains resulted in microglial activation. To identify the mechanisms of NPC-microglia cross-talk, the authors showed that several factors such as vascular endothelial growth factor were secreted in relatively large amounts by NPCs, and exogenous vascular endothelial growth factor promoted microglial functions in cell culture systems. Finally, the authors showed that injection of conditioned medium from normal NPCs into mouse brains led to microglial activation, whereas conditioned medium from vascular endothelial growth factor–knocked down NPCs did not, again consistent with the idea that NPCs may activate microglia via vascular endothelial growth factor signaling.

Because stroke and neurodegeneration are diseases that are strongly age dependent, it is important to ask whether cross-talk between microglia and NPCs may be affected by age. L’Episcopo et al (Aging-induced Nrf2-ARE pathway disruption in the subventricular zone drives neurogenic impairment in parkinsonian mice via PI3K-Wnt/β-Catenin dysregulation. *J Neurosci*. 2013;33:1462–1485) suggest that these signaling pathways are dampened with increasing age. The authors used an in vivo mouse model of Parkinson disease (MPTP injection) to demonstrate that aging exacerbated neurogenic deficit in the subventricular zone, which is one of the most important brain regions for adult neurogenesis. Using in vitro cell culture systems, the authors showed that cultured microglia prepared from young brains promoted the proliferation and differentiation of NPCs, whereas microglial cells from aged brains did not. With pharmacological and molecular-biological approaches, the authors demonstrated that an imbalance of Nrf2-driven antioxidant/anti-inflammatory genes might be associated with the aging-induced switch of microglial neurogenic phenotype.

Taken together, these 3 recent studies support an age-dependent cell–cell signaling model wherein inflammatory cells regulate neurogenesis and vice versa. How these mechanisms operate in the context of stroke recovery warrants further study.