1. Neurogenesis after ischemic stroke

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Recent findings in rodents that stroke leads to increased, long-term generation of neurons from neural stem cells (NSCs) in the subventricular zone (SVZ), suggest the ability of brain for self-repair and puts forward an alternative approach of cell therapy in stroke. The newly formed immature neurons migrate into the stroke-damaged area, where they express markers of those mature neurons which died due to ischemic insult. Whether the newly formed neurons are functionally integrated into the existing brain circuitry and contribute to the functional recovery is currently unknown. However, even re-establishment of only a fraction of damaged neuronal circuitries could have significant implications. Whether the microglial response associated with ischemic injury extends into SVZ and influences neuroblast production is unknown. We have recently demonstrate increased numbers of activated microglia in ipsilateral SVZ concomitant with neuroblast migration into the striatum at 2, 6, and 16 weeks, with maximum at 6 weeks, following 2 h middle cerebral artery occlusion in rats. In the peri-infarct striatum, numbers of activated microglia peaked already at 2 weeks and declined thereafter. Microglia in SVZ were resident or originated from bone marrow, with maximum proliferation during the first 2 weeks postinsult. In SVZ, microglia exhibited ramified or intermediate morphology, signifying a down-regulate inflammatory profile, whereas amoeboid or round phagocytic microglia were frequent in the peri-infarct striatum. Numbers of microglia expressing markers of antigen-presenting cells (MHC-II, CD 86) increased in SVZ but very few lymphocytes were detected. Elevated numbers of IGF-1-expressing microglia were found in SVZ at 2, 6, and 16 weeks after stroke. At 16 weeks, 5% of microglia but no other cells in SVZ expressed the IGF-1 protein, which mitigates apoptosis and promotes proliferation and differentiation of NSCs. The long-term accumulation of microglia with proneurogenic phenotype in the SVZ implies a supportive role of these cells for the continuous neurogenesis after stroke.

The molecular mechanisms regulating post-stroke neurogenesis which is probably involved in structural reorganization and functional recovery, are poorly understood. Understanding of these mechanisms will help to develop the ways to modulate this response and hence improve functional recovery after stroke. The adaptor protein LNK suppresses hematopoietic stem cell self-renewal but its presence and role in the brain is unknown. We have recently demonstrate that LNK is expressed in neural stem and progenitor cells in the adult rodent and human subventricular zone and our data indicate that LNK is a stroke-specific, endogenous negative regulator of neural stem and progenitor cell proliferation, and suggest that LNK signaling is a novel mechanism influencing plastic responses in post-ischemic brain.