PROINFLAMMATORY PROFILE AND MECHANISMS OF INDUCTION OF REACTIVE NEURAL STEM CELLS

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In the hippocampus of most mammals including humans, neural stem cells (NSCs) generate newborn neurons throughout adulthood. Newborn neurons integrate into the dentate gyrus participating in memory, learning, pattern separation and the regulation of anxiety and stress. Hippocampal NSCs are multipotent, with both neurogenic and gliogenic potential, and adapt swiftly to different physiopathological stimuli, especially to those related to changes in neuronal activity. Further, NSCs adapt their response differentially to different levels of neuronal hyperexcitation. Using two models of mesial temporal lobe epilepsy (MTLE) we found that NSCs transform into reactive NSCs (React-NSCs) that characterize by: 1) elevated rate of activation (entry into the cell cycle); 2) switch to symmetric cell division; 3) the development of a multibranched and thickened morphology with overexpression of nestin and GFAP; and 4) production of proinflammatory cytokines such as IL-1ß. React-NSCs ultimately transform into reactive astrocytes and neurogenesis is abolished. After traumatic brain injury (TBI) NSCs transform transiently into React-NSCs. Neurogenesis, however, is actually increased although with profound alterations. New neurons born (from days to months) after TBI have abnormal morphology, migration and electrophysiological properties. We have found two signaling pathways involved in the transformation of NSCs into React-NSCs: 1) The epidermal growth factor receptor (EGFR) which is essential for the activation of NSCs and also participates in the differentiation of astrocytes into reactive astrocytes. Blocking pharmacologically the EGFR after seizures we partially preserved the population of NSCs and neurogenesis. 2) ATP via purinergic 2X receptors (P2XR). NSCs express P2XR in vitro and in vivo and respond to ATP, via calcium signaling, by transforming into React-NSCs. Together our results show the high level of plasticity of NSCs and how they react as much as astrocytes and microglia to brain damage. In addition we provide two novel signaling pathways to explain the induction of React-NSCs.