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Cyclooxygenase (COX)-1 takes control of adult hippocampal neurogenesis

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The subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the dentate gyrus (DG) of the hippocampus are well-characterized germinal niches of the central nervous system (CNS), in which stem cells support neurogenesis and gliogenesis throughout adult life. The maintenance and differentiation of brain stem cells is orchestrated by cellular contacts to the basal lamina, which acts as a scaffold, sequestering and/or modulating soluble factors derived from local cells.[1]

While investigating the molecular basis of the cognitive decline that follows cranial radiation as adjuvant treatment of primary brain tumors in humans, Monje et al. first observed that experimental cranial irradiation significantly altered neurogenesis in the rat DG. The irradiation-disrupted stem cell niche had a remarkable decrease of blood vessel-associated clusters of proliferative neural progenitors as well as a significant increase of activated microglia. This microglial phenotype led to the hypothesis that inflammation may perturb the endogenous stem cell compartment and, ultimately, neurogenesis.[2] The same authors developed a model of lipopolysaccharide (LPs)-induced inflammation characterized by a significant impairment of hippocampal neurogenesis mediated by activated microglia releasing interleukin-6 in the DG.[3] Striking restoration of DG neurogenesis was achieved by either decreasing microglial activation with the non-selective inhibitor of cyclooxygenase (COX)-1 and COX-2 indomethacin[3] or with metabolites/chaperones that protect mitochondrial function.[4]

Following these first reports, we showed that in chronic experimental autoimmune encephalomyelitis (EAE), persistent CNS inflammation impaired the proliferative and migratory properties of SVZ-resident stem cells, leading to significant accumulation of non-migratory neuroblasts within the SVZ.[5] However, when challenged within a relapsing-remitting EAE model, the SVZ stem cell compartment underwent significant acute increase of proliferation, migration and oligodendrogenic potential. This was lost along with progression towards more chronic disease stages. Interestingly, activated microglial cells were found closely associated with CNS stem and progenitor cells in the dysfunctional EAE SVZ, and delayed (i.e., started 20 days after immunization) treatment with the microglial modulator minocycline reduced the number of microglia while increasing the proliferation in the SVZ.[6]

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These data indicate that adult neural stem cell physiology is greatly influenced by the cross-talk between the immune system and the CNS, and suggest that both states of persistent, hyper- or underactivation (e.g., under immune deficiencies) of the immune system may lead to dysfunction of the CNS stem cell compartments.

Beyond the holistic (but true) view that soluble factors released by immune cells greatly affect stem cells, there is also parallel evidence that CNS stem cells express functional immune-like molecules, such as cell adhesion molecules, chemokine receptors and Toll-like receptors (TLRs), that enable them to interact with the inflamed CNS microenvironment. Interestingly, TLR2 and 4 also orchestrate proliferation and differentiation of CNS stem cells, with TLR2 being a positive regulator of neurogenesis only and TLR4 acting as a negative regulator of both proliferation and neurogenesis.[7]

COX-1 is another very interesting candidate to study when looking at neuro-immune interactions at prototypical CNS stem cell niches. A previous study from Bosetti and colleagues investigated the critical role of *COX-1* in the neuroinflammatory response to intracerebroventricular LPs and established that either gene ablation or pharmacological inhibition of *COX-1* significantly reduced microglial activation, release of pro-inflammatory and oxidative stress mediators as well as blood-brain barrier disruption and recruitment of peripheral leukocytes.[8]

In a previous issue of *Cell Cycle*, Russo and colleagues revealed a role of *COX-1* in the impairment of hippocampal neurogenesis and proliferation following LPs-induced inflammation. The authors showed that LPs reduces progenitor proliferation and neurogenesis in wild-type but not in *COX-1*$^{-/-}$ mice, pointing to an essential role for *COX-1* in propagating the inflammatory response and modulating the neurogenic niche.[9] Hence, *COX-1* emerges as a potential therapeutic target in inflammatory neurodegenerative diseases. Intriguingly, the epidemiological data indicating that non-steroidal anti-inflammatory drugs (NSAIDs) can affect the pathophysiology of major inflammation-driven neurodegenerative diseases, such as Alzheimer disease and multiple sclerosis, indirectly suggest that some of their protective effects may be related to *COX-1* inhibition.[8] Further investigations will be required to elucidate the downstream effectors of this modulation of neurogenesis and how neuro-inflammation relates to the pathophysiology of neurodegenerative diseases.

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