Abstract

The role of the Wnt signaling pathway in the regeneration following ischemic brain injury

Focal cerebral ischemia results in the loss of neural cells, which may cause permanent disability. At the same time, there are precursor cells (neural stem/progenitor cells and NG2 glia) that naturally reside in the postnatal brain and may proliferate and give rise to other cell types. Their fate is to a large extent influenced by morphogens of the Wnt and Shh family. However, the role of these cellular pathways in differentiation of precursor cells is still enigmatic. For this reason, we employed transgenic mice that enabled us to inhibit or hyper-activate the canonical Wnt signaling pathway, or to map the fate of NG2 cells. The induction of ischemia was achieved by the occlusion of the middle cerebral artery. The changes in the differentiation potential were characterized at the mRNA, protein, and functional levels. First, we evaluated neural stem/progenitor cells isolated from neonatal mice under physiological conditions and found out that Wnt signaling promotes neurogenesis and suppresses gliogenesis. Next, we focused on adult mice and detected a smaller impact of Wnt signaling on their differentiation potential. Nonetheless, its effect was more profound after the induction of ischemia, as we identified changes that resembled those found in neonatal mice. Finally, we confirmed NG2 cells as oligodendrocyte precursor cells under physiological conditions, while they differentiated mostly to astrocytes after the induction of ischemia. Additionally, we identified Shh signaling as the factor responsible for this transition. These findings might be of particular interest to therapeutic approaches examining the regeneration of nervous tissue after ischemia. The importance of this thesis also consists in the use of transgenic animals that may serve as convenient tools to manipulate cellular signaling pathways in neural precursors for further projects and experiments.

Key words: Wnt/Shh signaling, transgenic mouse, neural stem/progenitor cells, NG2 glia, focal cerebral ischemia, neurogenesis/gliogenesis