INDUCTION OF THE CYTOSKELETON LINKER PROTEIN RADIXIN IN THE ADULT BRAIN

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Abstract

Neural stem and progenitor cells (NSPCs) proliferate throughout life in two regions of the brain, namely the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of dentate gyrus in the hippocampus. In the adult SVZ, NSPCs give rise to neuroblasts that leave the SVZ for long distance migration along the rostral migratory stream (RMS), on their way to the olfactory bulb where they mature and are integrated in the neural network. Understanding how adult neuronal migration is regulated is of importance for the development of new therapeutic interventions using endogenous stem or progenitor cells for brain repair strategies. Long distance migration of neuroblasts in the RMS requires a highly dynamic cytoskeleton with the ability to respond to surrounding stimuli. In this thesis, we hypothesized that cytoskeleton rearrangement in the RMS is mediated by the ERM (Ezrin/Radixin/Moesin) family of proteins. ERM proteins regulate actin polymerization through interaction with actin and transmembrane adhesion molecules in many different parts of the body, however, limited studies exist of ERM proteins in the adult brain. In the first paper, our studies demonstrate the specific expression of radixin in neuroblasts in both the ventricular and hippocampal neurogenic niches. We also demonstrate the presence of radixin in Olig2 expressing cells throughout the adult brain. In the second study, the function of radixin was inhibited using a selective quinocarmycin analogue which interrupts the ability for radixin to link the actin cytoskeleton to the membrane. Inhibition of radixin in SVZ explant cultures selectively blocked the migration of neuroblasts, whereas glial migration remained unaltered, suggesting that these populations use different ERM proteins for actin polymerization. In addition, intracerebroventricular infusion of the radixin inhibitor resulted in aberrant neuroblast chain formation and decreased neuroblast proliferation in the RMS.

In the third paper, EGF infusion revealed elevated levels of radixin expression in the SVZ and RMS. EGF treatment is known to greatly reduce the migratory population in the SVZ and RMS. Accordingly, a new radixin expressing population was present in the RMS after EGF treatment and these cells also expressed Olig2. Proliferation of the radixin/Olig2$^+$ population occurred already after 24h, even in parts of the RMS that are distal to the SVZ, suggesting local activation by EGF throughout the RMS rather than migration from the SVZ. The radixin/Olig2$^+$ cells in the RMS were arranged in chains and migrated in explant cultures *in vitro*. Being negative for NG2 and CNPase, these radixin/Olig2$^+$ cells are likely not oligodendrocyte progenitors.

In the fourth study, radixin expression was induced in the peri-infarct region after cortical stroke. Unexpectedly, the number of cortical radixin/Olig2$^+$ cells decreased after stroke and radixin was instead present in a subpopulation of activated microglia. In the healthy brain and in the contralateral cortex, microglia did not express radixin. A new dual concept of microglial activation suggests the presence of classically activated M1 microglia and an alternatively activated M2 microglia population, which has more beneficial effects for the survival of neurons under inflammation conditions. The expression profile of radixin after stroke implies similarities with the type M1 microglia and radixin might be useful as a new microglia activation marker.

Taken together, these data suggest a role for radixin in NSPC proliferation and migration in the adult brain, as well as in activation of microglia after stroke.

Keywords: Neural stem cells, rostral migratory stream, ezrin/radixin/moesin, EGF, Olig2, microglia, stroke

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