Abstract

Ischemic brain injury belongs to the most common cause of death in the developed countries. High complexity of this disorder significantly slows and limits the possible treatment. Currently, there is only one treatment available – the application of the thrombolytic, tissue plasminogen activator, while thousands of other drugs failed during clinical testing. Great expectations were seen in the stroke treatment employing neural stem cells obtained from several external sources; nevertheless, low survival rate, limited favorable outcome and enormous ethical issues complicate the application of such therapy. On the other hand, in the adult mammalian brain exist two endogenous processes - neurogenesis and gliogenesis. These processes need to be fully described and understood, in order to employ them as a source of new cells after injury. Therefore, this thesis focuses on the processes of adult neurogenesis and gliogenesis predominantly after ischemia.

Adult neurogenesis and gliogenesis are processes, by which neurons or glial cells are generated from stem/progenitor cells. Both these processes are strongly influenced by brain injury; nevertheless, their contribution to regeneration after ischemia in the human brain is negligible.

Here, we aimed to describe the role of polydendrocytes in the post-ischemic gliogenesis, which leads to the formation of glial scar after injury. Moreover, we used analyses of gene expression on single-cell level, to unravel the heterogeneity of glial cells around injury. Finally, we also study the neurogenic potential and contribution to post-ischemic regeneration of the cells in the dorsal parts of lateral ventricle – a non-typical place of adult neurogenesis. For all three aims, we utilized transgenic mouse strains, which enabled us to label and visualize cells of our interest. Subsequently, we analyzed phenotype and properties of these cells after ischemic injury using several complementary methods. As a model of focal ischemia, we used middle cerebral artery occlusion with direct vessel coagulation on the brain surface.

Our findings showed that polydendrocytes are the most proliferating glial cells in the vicinity of ischemic core, and that they have the ability to differentiate into reactive astrocytes, which form subsequently the glial scar. Analyses of gene expression on single cell level revealed large heterogeneity of reactive astrocytes during post-ischemic period, which could be caused by their distinct origin. Ischemic injury also significantly influenced the cell population in the dorsal part of the lateral ventricle. These cells expressed neural stem cell phenotype and produced increased number of neuroblast in response to ischemia. However, we disclosed that these newly-derived neuroblasts are not able to migrate towards ischemic lesion and therefore, they do not contribute to the regeneration of damaged nervous tissue following ischemia.

In conclusion, this work shed some light on endogenous neurogenic and gliogenic processes occurring in the adult mammalian brain, whose understanding is essential for developing future treatment of brain ischemia.