

The main purpose of the project is to investigate myelinating and migrating properties of glial progenitors (GRPs) with overexpression of neuregulin-1 (NRG-1).

Demyelination is the first process occurring during the course of many diseases such as multiple sclerosis (MS) or leukodystrophies. Demyelinating diseases are one of the most common causes of mortality within neurological disorders. Demyelination process comprises the destruction of myelin sheath that is responsible for signal conduction along the axon and consequently leads to degeneration of neurons. Oligodendrocytes are the cells responsible for production of myelin with proper composition and thickness. Those cells that belong to glia family are also responsible for nutrition of neurons. There is a direct and precise communication between the neurons and glia, thus disturbances in interactions between them leads to damage of myelin sheath and neurodegeneration. Ongoing studies are focused on the use of stem cells in treatment of demyelinating diseases. Mostly mesenchymal or neural stem cells are used; however their acting is based on release of factors stimulating the endogenous repair processes. Recently, the scientists are emphasizing the role of glia in the degeneration of neurons. Therefore intriguing concept seems to be based on replacement of malfunctioning glia with the functional oligodendrocytes and astrocytes that are able to create stabile contacts with neurons. We are able to obtain those cells from glial progenitors that may be isolated from different sources such as embryonic, fetal or adult tissues. For the purpose of basic research we proposed to isolate GRPs from mouse fetuses, the method that is employed by our team. Preliminary results of our group documented myelinating potential of canine glial progenitors. Those cells were also able to prolong the life of transplanted shiverer mice - a model of demyelination. However, the other group transplanted allogenic GRPs into the same model revealed that egzogenous cells were not able to migrate on long distances nor did prolong the survival of the recipients. Therefore it seems crucial to enhance the migratory and myelinating properties as well as survival of GRPs after their transplantation. We would like to accomplish this aim with overexpression of neuregulin-1 in GRPs. NRG-1 is a mitogen responsible for migration and differentiation of glial progenitors during development. This protein is also crucial in myelination processs and survival of oligodendrocytes and Schwann cells. We plan to accomplish long-term overexpression of NRG-1 using the lentiviral transduction of GRPs that would stimulate the cells to neuregulin-1 production. Modified GRPs (nrg-GRPs) will be characterized in terms of the presence of proteins, typical for glial progenitors. The migratory and myelinating properties of GRPs overexpressing neuregulin-1 will be investigated in vitro and in vivo. In vitro research will cover recording of migration of the glial progenitors and the co-culture of GRPs with neurons in order to evaluate the myelinating properties. The in vivo experiments will involve transplantation of nrg-GRPs and non-modified GRPs (m-GRPs) into the brain of shiverer mice. In the following step migratory and myelinating properties will be estimated using magnetic resonance imaging, electron and confocal microscopy. In this project we would also like to evaluate if nrg-GRPs are able to prolong the life of transplanted mice.

Demyelination process leads to malfunctioning of central and peripheral nervous system and results in development of neurodegenerative diseases. Thus, intriguing issue is to elucidate the mechanisms responsible for myelination and remyelination. Our preliminary results documented the myelinating properties of glial progenitors, therefore the absorbing question remains to be resolved, namely if we are able to increase the potential of GRPs to rebuilt the damage myelin and thereby enhance the functional properties of the cells after their transplantation.