



Marie Curie Host Fellowships for Early Stage Research Training:

Interdisciplinary, international PhD-program of the
Center for Systems Neuroscience Hannover
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Project No. 8:

Molecular basis of the axon-oligodendrocyte interaction during remyelination

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Aims:

The aim of this project is to better understand the molecular mechanisms required for successful remyelination. Employing a toxic model of CNS demyelination, the expression of various molecules on both the axon and the oligodendrocyte will be studied. Knowledge of the regulation of the required signals will help to delineate the reasons for incomplete repair in diseases like multiple sclerosis (MS). These data will also be the basis for experimental approaches to improve remyelination and repair. Ultimately such an approach may lead to the design of regenerative treatment strategies in MS.

Background:

Demyelination in the central nervous system (CNS) is the neuropathological hallmark in multiple sclerosis (MS), the most common cause of disability in young adults. Remyelination by oligodendrocytes can be observed in 40 – 50% of lesions, but it is usually incomplete. Enhancement of remyelination as a regenerative treatment is thus desperately needed, but currently not available. The exact molecular mechanisms for remyelination are only partly understood [1, 2]. The interaction between axon and myelinating oligodendrocytes is essential for this repair process. However, only little is known about the molecular mechanisms that regulate this interaction. We have established an animal model of toxic demyelination and remyelination that allows to study these processes.

Research plan:

Experimental demyelination of the corpus callosum will be achieved by feeding of the copper chelator cuprizone, an established model for toxic demyelination. Withdrawal of cuprizone from the diet leads to spontaneous remyelination. During this process, the expression of adhesion molecules like PSA-NCAM, integrins, and others will be studied using various methods like immunohistochemistry, in situ hybridization, and rtPCR. Where applicable, the functional importance of these findings will be studied in vivo in transgenic animals.

Additional tissue culture experiments with glial cells will allow to study intracellular pathways

and the regulation of the factors found to be of importance for remyelination. Both the animal model and tissue culture techniques are established methods in the lab.

Own previous work:

Our group has a strong interest in the investigation of mechanisms of remyelination. During the last year we have established an animal model to study de- and remyelination in the CNS (induced by cuprizone). Current projects use this model to analyze the role of cytokines and chemokines during remyelination. Furthermore there is a large background in the cell culture of glial cells, in particular oligodendrocyte precursor cells and microglia. These have been used in the past to characterize chemokine receptors on oligodendroglia [3, 4] and to investigate the mechanism of action of intravenous immunoglobulins [5, 6, 7, 8, 9], a potential treatment to induce remyelination.

Literature:

1. Stangel M, Hartung H-P (2002) Remyelinating strategies for the treatment of multiple sclerosis. *Prog Neurobiol* 68: 361-376
2. Stangel M (2004) Remyelinating and neuroprotective treatments in multiple sclerosis. *Expert Opin Invest Drugs* 13: 331-347
3. Nguyen D, Stangel M (2001) Expression of the chemokine receptors CXCR1 and CXCR2 in rat oligodendroglial cells. *Dev Brain Res* 128: 77-81
4. Nguyen D, Höpfner M, Zobel F, Henke U, Scherübl H, Stangel M (2003) Rat oligodendroglial cell lines express a functional receptor for the chemokine CCL3 (macrophage inflammatory protein-1alpha, MIP-1alpha). *Neurosci Lett* 351: 71-74
5. Stangel M, Boegner F, Klatt CH, Hofmeister C, Seyfert S (2000) A placebo-controlled pilot trial to study the remyelinating potential of intravenous immunoglobulins in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 68: 89-92
6. Stangel M, Compston A, Scolding NJ (2000) Oligodendroglia are protected from antibody mediated complement injury by normal immunoglobulins ("IVIg"). *J Neuroimmunol* 103: 195-201
7. Stangel M, Compston A (2001) Polyclonal immunoglobulins (IVIg) modulate nitric oxide production and microglial functions in vitro via Fc receptors. *J Neuroimmunol* 112: 63-71
8. Pul R, Nguyen D, Schmitz U, Marx P, Stangel M (2002) Comparison of intravenous immunoglobulin preparations on microglial function in vitro: More potent immunomodulatory capacity of an IgM/IgA-enriched preparation. *Clin Neuropharmacol* 25: 254-259
9. Stangel M, Bernard D (2003) Polyclonal IgM influence oligodendrocyte precursor cells in mixed glial cell cultures: implications for remyelination. *J Neuroimmunol* 138: 25-30

The Project belongs to the main topic of ZSN: Movement Disorders