Vorschlag für ein Promotionsprojekt im Rahmen des VorSPrUNG-Programms

Hauptbetreuer (↗ VorSPrUNG-Konzept):

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Titel des Projektes:

Calcium metabolism influences T cell-driven MS pathogenesis – a novel target in MS?

Abstract:

The exact cause of MS is still unknown; however, it is considered to be an autoimmune-mediated disease triggered by environmental, genetic or infectious factors or a combination of these. First lines of evidence indicate that also calcium influences the course of MS. Calcium ions are essential second messengers involved in the activation of calcineurin and nuclear import of NFATc proteins, which regulate immune-response genes encoding for cell proliferation, differentiation, migration and production of cytokines. Several studies suggest that extracellular calcium influx, via voltage-gated calcium channels contributes to white matter damage in acute spinal cord injury and stroke. In EAE, administration of calcium channel blockers ameliorated disease, decreased microglial proinflammatory activity, fostered remyelination and induced microglia-specific apoptosis. Furthermore, in a recently published case series of 21 MS patients hypercalcemia after high dose vitamin D treatment was associated with neurologic deterioration including new relapses and enhanced MRI activity. This is in line with our own work in which a set of experiments suggested that calcium directly enhances activation and pro-inflammatory differentiation of T cells. In light of the above mentioned findings and this preliminary work calcium seems to play an important role in the pathogenesis of EAE and MS and in other T cell-driven diseases.

In this present project, we will specify the role of calcium in the pathogenesis of MS. First, we will investigate whether lowering calcium levels may have a direct effect in preventing of pro-inflammatory B cell, monocyte and T cell development. For this purpose, we will isolate blood B cells, monocytes and T cells from healthy donors. Upon incubation with increasing calcium concentrations in vitro, we will analyze calcium-influx, immune cell activation and differentiation using flow cytometry and ELISA. Second, we will investigate whether calcium by itself enhances activation and pro-inflammatory differentiation of T cells and other immune cells in vivo by analyzing PBMCs ex vivo from patients receiving a calcium antagonist therapy vs. healthy controls with normal calcium serum levels.

In perspective, to control calcium level could prove to be a promising new therapeutic target in MS patients as it has no side effects, is easy to perform and is cost-effective.