Vorschlag für ein Promotionsprojekt im Rahmen des VorSPrUNG-Programms

Hauptbetreuer (VorSPrUNG-Konzept): Prof. Dr. Martin Weber

Titel des Projektes: "Analysis of $CD20^+$ T cells in the CSF of multiple sclerosis patients as prognostic factor and therapeutic target"

Abstract

The pathogenic mechanisms of multiple sclerosis (MS) remain unknown, still. There are various treatments for disease management available, however it is not yet curable. One of the currently most successful treatments are anti-CD20 monoclonal antibodies (mabs), such as rituximab, ocrelizumab, and ofatumumab. These mabs have been proven to deplete mature B cells. Recently, it was discovered that they also deplete $CD20^+$ T cells, a subset of T cells that develop during pathogenic B cell-T cell interactions by trogocytosis and exhibit pathogenic properties in MS. $CD20^+$ T cells were shown to be increased in the blood of untreated MS patients compared to healthy controls. Furthermore, in untreated MS patients, $CD20^+$ T cells are even more prominent in the cerebrospinal fluid (CSF) compared to the blood. These findings indicate the importance of $CD20^+$ T cells in MS development and progression and the additional benefit of their depletion in anti-CD20 mab therapy.

In this project, we plan to analyze the potential correlation of the amount of $CD20^+$ T cells in the blood and CSF of MS patients with the disease duration and severity. For that purpose, peripher blood mononuclear cells (PBMCs) and immune cells from CSF samples will be collected, isolated, and analyzed via flow cytometry. Additionally, NFL levels will be measured in the serum of the same patients. The generated data will then be correlated to the patient's disease duration and/or other disease related factors. Since fresh CSF samples are not always available, a part of this project will be to establish a protocol for the analysis of immune cells from frozen CSF samples.

Another aim of this project will be to compare two anti-CD20 mabs, Ocrelizumab and Ofatumumab, in their depletion of $CD20^+$ T cells. Ocrelizumab is administered in high doses, i.v., every 6 months, while Ofatumumab is given s.c. once a month at a much lower dosage. These differences in dosage and application might impact their depleting functions. To our knowledge, there is no study comparing both antibodies in their depletion capacity for $CD20^+$ T cells. Their different applications might also impact their potential to deplete $CD20^+$ T cells in the CSF, which remains challenging, since mabs from the periphery are rarely able to cross the blood-brain barrier. The subcutaneous application might enable Ofatumumab to reach $CD20^+$ T cells in the CSF and MS lesions, where they seem to be even more abundant compared to the periphery and in all likelihood exert their pathogenic functions. For this part of the project, PBMCs and immune cells from the CSF will be collected from MS patients before and during Ofatumumab or Ocrelizumab therapy and analyzed via flow cytometry.

The results of this project may enable clinicians to better differentiate, which of these anti-CD20 mabs are best suited to which MS patient. In addition, the establishment of a protocol to analyze immune cells from frozen CSF samples, will provide another easily usable tool to research MS development and progression and the effects of various available and newly developed medications.