Translational multiple sclerosis research in primates

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1.3 Aims and outline of thesis

Despite advances in basic knowledge and development of therapeutics to modify disease, the precise etiology of MS remains unclear. There is a great need to develop refined therapies that halt all forms of disease and have less adverse effects than current treatment options. For both basic and applied research, animal models have contributed to the knowledge of pathogenic mechanisms of disease, and have aided in the development of therapeutics.

The aim of the research described in this thesis was to i) determine how closely non-human primate EAE models reflect MS, thus determining their relevance and limitation for applied and basic research and ii) utilize these models to provide insights into mechanisms driving disease.

Several lines of evidence indicate an important role of lymphocryptovirus (EBV/CalHV3)-infected B cells in MS and marmoset EAE [1]. We hypothesized that the lymphocryptovirus infected B cell plays an important role in the egression of the T cell from the lymphoid organs based upon previous observations. Therefore, we assessed the interaction between EBV-infected B cells and T cells in **chapter 2.1.** Co-cultures of autologous EBV transfected B cells were performed with T cells from MOG34-56/IFA-immunized marmosets and immunological parameters focused on T-cell function were assessed. Since, lymphocryptovirus-infected B cells constitutively secrete the cytokine IL-7, the role of IL-7 in marmoset EAE was assessed in **chapter 2.2** [2]. Induction of EAE by MOG34-56/IFA was performed in twin marmosets, with one twin receiving a mAb directed against the IL-7Rα (CD127). Longitudinal immune profiling was performed during the course of the study and both CNS and secondary lymphoid organs was examined post necropsy.

Peripheral immunization with myelin antigens induced activation of the immune system and the development of CNS specific pathology (**chapter 3.1-3.3**). Understanding the features and limitations of a model with respect to how closely it mirrors human disease is vital for preclinical testing. Therefore, in **chapter 3.1** a pathological analysis of oxidative injury in marmoset EAE models was performed, as this is a crucial pathway in MS. This comprehensive analysis examined mechanisms that induce oxidative stress and injury, and examined the role of iron in pathology development. Oxidative stress and injury impacts mitochondria. Based upon findings in **chapter 3.1**, and the observations that the MS brain is characterized by impairment of neuronal mitochondria function, we determined to which extend these organelles are impacted (discussed in **chapter 4.0)**.

As GM pathology is a prominent feature of MS, and may be caused by mitochondria impairment or axonal degeneration, in **chapter 3.2** we compared cortical pathology of marmoset EAE induction protocols [3,4]. The aim of this chapter was to provide insight into the development of GM injury and to determine if refinement of the model had any effect on the ability to elicit this type of pathology.

In **chapter 3.3** we performed a pathological characterization of the rhesus monkey EAE model, with an emphasis on oxidative stress pathways.

Finally, in **chapter 4,** the implications of the experimental data obtained in this thesis are discussed in terms of pathogenic mechanisms of EAE and MS; both from periphery to the CNS.

References

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Chapter 2

Peripheral mechanisms