On the cause of multiple sclerosis

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INTRODUCTION AND SCOPE OF THIS THESIS

In the central nervous system (CNS), oligodendrocytes (OLGs) insulate axons of neurons by means of myelination, which enables the saltatory propagation of action potentials, thereby strongly increasing the speed of electrical impulses along the axon. Multiple sclerosis (MS) is a chronic disease of the CNS in which inflammation, loss of myelin and loss of axons are the main pathological features [1–3]. Myelin regeneration (remyelination) can occur as a result of the differentiation of endogenous oligodendrocyte progenitor cells (OPCs), a process which ultimately fails in MS [4–6]. Indeed, failure of remyelination is associated with axonal loss, and the progression of clinical disability. For *de novo* biogenesis and maintenance of the myelin sheath, a continuous, coordinated synthesis and subsequent polarized transport of myelin components in maturing OLGs is necessary. Myelin is composed of lipids and proteins, most of which are specific to the myelin sheath. The biogenesis and maintenance of the myelin membrane is dependent on a complex intracellular trafficking machinery, the mechanism of which are gradually emerging, i.e., myelination by OLGs is a tightly regulated undertaking in which proteins and lipids are transported to distinct locations within the cell in a specific and carefully controlled order. Thus, individual myelin components are expressed, sorted and transported via different mechanisms. Proteolipid protein (PLP) for instance is sorted and transported via a vesicular transcytotic route [7–11]. Myelin basic protein (MBP), on the other hand, is transported as mRNA in granules via microtubule dependent transport, and translated 'on-site', i.e., at the myelin membrane [12–14]. Galactolipids are enriched at specific locations of the plasma membrane, interacting with myelin specific proteins like PLP and MBP [7,11,15,16]. It is anticipated that a better understanding of the complex mechanisms behind myelin formation will be essential to allow us to develop tools to control and regulate myelin biogenesis in demyelinating and neurodegenerative diseases, such as MS. Therefore, the aim of this work was to further the knowledge of the regulation of myelin formation at a molecular level.

In **Chapter 1**, current knowledge on sorting and trafficking in OLGs with a focus on the major myelin proteins PLP and MBP, and the role of galactolipids, specifically sulfatide, is reviewed, including several findings obtained in this thesis. This review underscores the polarized nature of OLGs and the similarities with (endocytic) transport systems in other polarized cell types like epithelia. The focus of **Chapters 2 and 3** was to clarify the involvement and underlying mechanisms of regulatory proteins in polarized trafficking, as occurs in myelin biogenesis. In **Chapter 2**, the polarized distribution of syntaxins 3 and 4, components of the SNARE-dependent transport machinery, was examined in OLGs, as well as their functional role in myelin biogenesis. Most interestingly, the t-SNARE syntaxin 4 that mediates docking and fusion of transport vesicles, appeared to be involved in regulating the onset of MBP transcription. The role of the timely expression of MAL, a well-known regulator of polarized trafficking in epithelial cells, was examined in **Chapter 3**.

In most MS lesions, remyelination fails as the local environment prevents OPC differentiation [4,5]. However, evidence is gradually emerging that the trafficking machinery in OLGs responds to extracellular signals, such as extracellular matrix (ECM) molecules, thereby influencing myelin biogenesis [7,17–20]. MBP is the only myelin-specific protein known to be imperative for myelin biogenesis. Therefore, in the next two chapters the effect of extracellular factors, known to be important for myelination and/or their presence in MS lesions, was examined on MBP expression and localization. **Chapter 4** aimed at elaborating the effect of galactolipids on MBP dynamics in the presence of physiologically relevant, myelin-promoting laminin-2, and in the presence of myelination-inhibiting fibronectin, known to be present in MS lesions. The results revealed a role of the galactolipid sulfatide, an important constituent of membrane microdomains, in the relay of signals from the aforementioned ECM molecules to initiate OLG maturation and myelin formation. **Chapter 5** aimed at examining the influence of TNFα, an inflammatory mediator released in MS lesions [21,22], on MBP expression and localization in mature OLGs. **Chapter 6** summarizes the work presented in this thesis, and based upon the findings as presented, outlines perspectives and directions for future research in clarifying the underlying cause of remyelination failure in MS.