Relieving the epigenetic blockade in progressive MS

Summary

The work presented in this thesis investigates the influence of DNA methylation on oligodendrocyte biology, both in physiological conditions, as well as in the context of progressive multiple sclerosis (MS).

Chapter 2 offers in-depth information on how epigenetic mechanisms influence oligodendrocyte differentiation and myelination. It provides first of all a general overview of the transcriptional network that regulates the differentiation process. Then, the epigenetic mechanisms, comprising DNA methylation, histone modifications, and miRNAs, are each discussed separately based on how they are known to play a role during physiological oligodendrocyte precursor cell (OPC) differentiation. Finally, the implication of epigenetic dysregulation related to OPC differentiation on demyelinating disorders and ageing is discussed.

Even though the literature suggests that DNA methylation enzymes strongly influence OPC cell fate commitment and (re)myelination, it remained undisclosed which genes are actually targeted by the DNA methylation enzymes during OPC differentiation. In Chapter 3, I investigated the direct influence of DNA methylation on the transcriptional network that regulates myelin gene expression and OPC differentiation. I did not only confirm that DNA methylation is crucial for the differentiation process, but also showed that the negative transcriptional regulators, Id2 and Id4, are mainly affected by DNA methylation going from OPC to oligodendrocyte stages. Moreover, I showed that in the pathological context of MS, methylation and gene expression levels of both ID2 and ID4 are altered compared to control human brain samples. Based on these data, we can conclude that DNA methylation is crucial to suppress ID2 and ID4 during OPC differentiation, a process that appears to be dysregulated during MS. These results do not only reveal new insights into oligodendrocyte biology, but could also lead to a better understanding of myelin disorders, such as MS.

Chapter 4 is based on a perspective, in which we discuss the importance of causality assessment in neuroepigenetic research. We propose a workflow, starting from epigenome-wide association studies (EWAS), all the way to applying CRISPR-Cas9 based epigenetic editing as a tool to investigate the potentially causal associations between epigenetic modifications of top hit genes and the pathophysiology of neurodegenerative disorders.

In the work described in Chapter 5, I applied the proposed workflow from chapter 4 in the context of progressive MS. Starting from epigenomic and transcriptomic profiles of chronically demyelinated MS lesions, I identified target genes that are differentially expressed and differentially methylated in these lesions, in comparison to the surrounding normal-appearing white matter (NAWM). Cell-specific validation of one of the strongest differentially methylated genes in relation to myelination, MBP, in laser-captured OPCs showed that OPCs within the lesion exhibit a hypermethylated profile of this essential myelin gene. By applying the epigenetic editing toolbox, I validated the causal relationship between the methylation of MBP and the differentiation capacity of human induced pluripotent stem cell (iPSC)-derived oligodendrocytes.

In the final study, presented in Chapter 6, I investigated whether the brain methylation pattern of progressive MS patients is mirrored in the blood and could thus be applied as a biomarker for disease progression in MS. The dysregulated epigenetic signature of the myelin genes, observed in the EWAS study from chapter 5, was not reflected in the blood samples of progressive MS patients. However, we did observe a strong correlation between DNA methylation of these genes and the storage time of the samples. Our data from this study suggests that the blood DNA methylation signature can be affected by long-term storage, an important factor that should be taken along in future studies.

To conclude, this dissertation provides more insights into the influence of DNA methylation on OPC differentiation and MS pathology. The studies presented in this thesis contribute to a better understanding of the molecular mechanisms underlying remyelination impairment and set the stage for future research on epigenetic changes in relation to progressive MS stages.