Relieving the epigenetic blockade in progressive MS

Chapter 10

Impact paragraph

The research described in this thesis identified epigenetic signatures underlying impaired oligodendrocyte precursor cell (OPC) differentiation and remyelination within lesions of progressive multiple sclerosis (MS) patients as a first step towards the identification of new targets for the development of novel treatment strategies. Furthermore, it linked brain and peripheral epigenetic marks in view of the potential application of blood methylation profiles as new biomarkers for disease progression in MS.

Societal impact

MS is one of the most common neurological conditions among young adults in the Western world, affecting approximately 2.5 million people worldwide. Around 1 million people are diagnosed as progressive MS patients, including primary progressive (PPMS) and secondary progressive MS patients (SPMS). The relatively high prevalence of MS (1:1000) is accompanied by high costs for patients and their family, as well as for society. In Europe, the annual costs for an MS patient with moderate disease severity is estimated at €37,100. Importantly, these costs increase with approximately 50% as the disease progresses (313, 314). In the early stages of the disease, overall costs are mainly driven by disease-modifying drug treatments. As the disease progresses, the overall cost increase is mainly affected by indirect costs, such as the loss of productivity for patients and their caretakers (315).

Available Food and Drug Administration (FDA)-approved therapies mainly modulate the immune system and temper early disease activity, but have limited efficacy in preventing transition towards the chronic phase and are no longer effective in progressive MS stages (8, 316, 317). Thus, there is a high medical need for novel therapeutic strategies to induce repair mechanisms and prevent or attenuate disease progression during the chronic stages of MS. Notably, the emphasis within MS research has strongly shifted towards understanding the molecular mechanisms underlying progression in MS, as supported by the Progressive MS Alliance (318), which represents a global collaboration of MS organisations, researchers, health professionals, the pharmaceutical industry, companies, trusts, foundations, donors and people affected by progressive MS, aimed at accelerating the development of effective treatments for people with

progressive MS in order to improve quality of life. Accordingly, in the present project, we aimed to uncover new mechanisms and pathways that underly remyelination impairment in order to identify novel therapeutic targets for progressive MS. We identified multiple epigenetic target genes that play an important role in oligodendrocyte precursor cell (OPC) differentiation. Targeting these epigenetic alterations, e.g. by CRISPR-Cas9-based epigenetic editing, could therefore be considered as a potential therapeutic strategy to overcome remyelination failure.

The second aim of this thesis was to investigate whether brain methylation profiles are mirrored in the blood and could serve as a biomarker for disease progression in MS. Unfortunately, in our study, we were not able to discover new biomarkers for progression in MS when it comes to DNA methylation signatures of myelin-related genes. Yet, this does not exclude the possibility of blood-born DNA methylation biomarkers to be of added value in this respect. Such a biomarker would benefit progressive MS patients and the healthcare system on multiple levels. First of all, a new bloodborne surrogate marker to define disease progression is easily accessible and reduces the need of magnetic resonance imaging (MRI), the current golden standard. Moreover, this can lead to an early adaptation of the treatment regimen so that patients will not be unnecessarily treated with ineffective drugs, eventually leading to a cost reduction for both the patients and society. As for the development of new drugs that modulate the disease progression, biomarkers for remyelination impairment can be applied in drug screening phases, as well as in human clinical trials. Such theranostic markers give an accurate and valid indication of the effect of a treatment on patients, thereby enabling and accelerating clinical trials.

Scientific impact

The research described in this thesis is one of its kind, since it is the first to reveal the epigenetic signature within chronically demyelinated lesions of progressive MS patients. Similar research has been conducted in the context of other neurological diseases, such as Alzheimer's disease or schizophrenia, and has revealed innovative targets related to disease development (319, 320). Yet, within the scope of progressive MS, data on the epigenetic imprint of remyelination

impairment was still lacking at this stage. We aimed to explore these new avenues to unravel the molecular links between environmental changes and disease progression in MS. To achieve this, we applied a set of innovative experimental techniques, such as laser-capture microdissection (LCM) and CRISPR/Cas9-based epigenetic editing system, to assess the specificity of our targets and the functional effect on OPC differentiation, respectively. Our work represents a starting point for important research regarding DNA methylation signatures in chronically demyelinated MS lesions with the final aim to discover new targets to restore the remyelination capacity in progressive MS stages.

Even though in our current study, we did not identify new biomarkers for disease progression in MS, blood-based methylation marks may still be assessed and proven useful in view of disease prognosis by e.g. performing an epigenome-wide association study in the blood, as our group has previously shown in other disease domain, including Alzheimer's disease (321). Moreover, our data on myelin-related gene methylation in MS suggest that the degree of DNA methylation in the blood can be affected by long-term sample storage, depending on the gene assessed. This is an important factor that had been neglected before yet might lead to false epigenetic discoveries. Sample storage time should therefore be considered during the initial sample selection stage in future studies.

Altogether, this dissertation provides more insights into the influence of DNA methylation on OPC differentiation and MS pathology. The work in this thesis is a first step in the field of myelin-related epigenetics and lays the foundation for future research on epigenetic changes in relation to progressive MS stages. The data generated in this research is a valuable addition to the current epigenetic data collection on MS brain samples and contributes to the efforts of the scientific community to identify novel markers for disease progression as well as targets for therapeutic drug development.