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## Oligodendroglial (dys)function in alpha-synucleinopathies

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<b>Title:</b> Oligodendroglial (dys)function in $\alpha$ -synucleinopathies			
<b>Abstract</b> <p>The complexity of <math>\alpha</math>-synucleinopathies, which include multiple system atrophy (MSA) and Parkinson's disease (PD), is not entirely understood. It is known that pathological accumulation of <math>\alpha</math>-synuclein (<math>\alpha</math>-syn) into proteinaceous aggregates is a cellular hallmark of these diseases. <math>\alpha</math>-Syn positive aggregates appear in neurons in PD and dementia with Lewy bodies (DLB), and in oligodendrocytes in MSA. Much research has focused on using animal models that pathocopy and phenocopy PD and MSA to investigate the disease pathogenesis. However, as no genetic link has been associated with MSA, it is possible that current transgenic models do not fully reflect the human pathology. The discovery of induced pluripotent stem cells (iPSCs) changed life science, and allowed for the first time to conduct large scale experimental work using patient cells. Since these cells are embryonic pluripotent-like, their use can help to unravel early disease mechanisms, as they can be differentiated into young brain cells. Despite intense research efforts made to understand the pathogenesis of PD and MSA, several questions remain unanswered, in particular the origin of <math>\alpha</math>-syn in oligodendrocytes and possible toxicity to these cells.</p> <p>The work presented in this thesis aims to 1) generate patient iPSC- based models, 2) develop efficient protocols to generate dopaminergic neurons and oligodendrocytes from iPSCs, and 3) study the role of oligodendrocytes in synucleinopathies, to gain insights into oligodendrocyte (dys)function in PD and MSA. Here, we report that during oligodendrocyte development and in the human brain, the <i>SNCA</i> gene encoding for <math>\alpha</math>-syn is differentially expressed in oligodendrocytes. Since neurons expressing pathogenic forms of <math>\alpha</math>-syn exhibit cellular alterations, we hypothesized that oligodendrocytes having the same genetic background should also be affected.</p> <p>For the first time, we show that iPSC-derived oligodendrocytes generated from PD patients carrying the variation p.A53T in <math>\alpha</math>-syn or a triplication of the <i>SNCA</i> locus, and from MSA patients, display impaired differentiation and maturation. This was further supported by observations from experiments involving mouse embryonic stem cell (mESC)-derived oligodendrocytes generated from the M83 transgenic mouse model of PD. Moreover, we demonstrate that p.A53T <math>\alpha</math>-syn and MSA oligodendrocytes exhibit a deviation in their phenotype, adopting an immune-reactive phenotype and not myelinating oligodendroglia. Finally, our transcriptomic data further reveal alterations in innate inflammatory components, with differential expression of complement proteins, MHC-class and immune-proteasome genes in p.A53T <math>\alpha</math>-syn and MSA oligodendrocytes.</p> <p>This thesis is composed of a unique set of studies addressing crucial questions related to the origin of <math>\alpha</math>-syn in oligodendroglia, and focuses on elucidating the cellular alterations in oligodendrocytes in PD and MSA.</p>			
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