A critical role for autophagy in oligodendrocyte maturation and myelin sheet formation

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ABSTRACT

(Macro)autophagy comprises a conserved lysosome-dependent catabolic pathway, facilitating degradation of cytoplasmic proteins and damaged organelles. Through its role in energy production and cellular homeostasis, autophagy is crucial during development as shown in many tissues and organisms, while its dysregulation has been linked to several disorders, including neurodegenerative diseases and more recently, demyelinating disorders. Myelin, produced by oligodendrocytes (OLs) in the CNS, provides mammals with an evolutionary advantage that insulates the axon, provides trophic support and ensures the rapid and efficient propagation of action potentials along its length. Its disruption, namely demyelination, may occur as a consequence of aging, from genetic alterations in genes encoding myelin proteins (dysmyelination) or from an inflammatory response against myelin producing cells, as is the case in Multiple Sclerosis (MS). Although a few studies implicate autophagy in CNS demyelinating pathologies, its role, particularly in oligodendrocytes, remains poorly characterized.

In our study, we aim to shed light on the significance of autophagy in CNS myelin and oligodendrocytes. We observed significant CNS hypomyelination in a Nestin-Cre; Atg5 $^{fl/fl}$ mouse line where autophagy is ablated in all CNS cells. In parallel, *in vitro* studies of Nestin-Cre; Atg5$^{fl/fl}$ oligodendrocytes showed increased differentiation index of these cells, which, however, present morphological defects in their myelin sheet. Pharmacological inhibition of autophagy, using the highly selective autophagy kinase ULK1 inhibitor SBI-0206965, similarly increased differentiation index, and resulted in a maturation delay of myelin-producing oligodendrocytes over the three basic morphological categories that was restored by DIV8. At that time point, SBI-treated, myelin-producing oligodendrocytes showed a significantly altered morphology. We are currently examining the role of autophagy in both oligodendrocyte primary cultures as well as in vivo utilizing a new conditional mutant mouse line, in which autophagy is specifically ablated in the CNS myelinating glial cells after tamoxifen administration (Plp-Cre^{ERT2}; Atg5 $^{fl/fl}$). Our findings suggest that autophagy is an indispensable mechanism for oligodendrocyte maturation and myelin sheet formation.

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