CNS myelination: a role for autophagic function

N. Ktena[1,2#], S-I. Kaplanis[1,2], I. Kolotueva[4], A. Georgilis[2], V. Stavroulaki[2], V. Nikoletopoulou[3], D. Karagogeos[1,2], M. Savvaki[1,2*]

[1] Foundation for Research and Technology, Institute of Molecular Biology and Biotechnology, Heraklion, Greece

[2] University of Crete, School of Medicine, Heraklion, Greece

[3] University of Lausanne, Department of Fundamental Neurosciences, Lausanne, Vaud, Switzerland

[4] University of Lausanne, Electron Microscopy Facility (PME), Lausanne, Vaud, Switzerland

Presenting author: Niki Ktena, email: niki_ktena@imbb.forth.gr

* Corresponding author: Maria Savvaki, email: msavaki@imbb.forth.gr

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 central nervous system (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 OLs, remains poorly characterized.

We will present data on the significance of macroautophagy in the CNS, focusing on OLs and myelin homeostasis. To this end, we have used both *in vitro* and *in vivo* approaches. *In vitro*, using both pharmacological and genetic inhibition of the autophagic machinery, we provide evidence that autophagy is an essential mechanism for oligodendrocyte maturation. Our study reveals that two core myelin proteins, namely proteolipid protein (PLP) and myelin basic protein (MBP) are incorporated into autophagosomes in OLs, resulting in their degradation. Furthermore, we ablated *atg5*, a core gene of the autophagic machinery, specifically in myelinating glial cells *in vivo* by tamoxifen administration (*plp-Cre^{ERT2}; atg5$^{F/F}$*). Biochemical and ultrastructural analysis of this mouse line has revealed differences in myelin protein levels, morphological alterations as well as behavioral deficits in conditional mutant animals compared to age-matched controls.

In summary, our data highlight that the maintenance of adult myelin homeostasis in the CNS requires the involvement of a fully functional autophagic machinery.

We acknowledge funding from the Hellenic Foundation for Research and Innovation (HFRI grant agreement 1676), the National Multiple Sclerosis Society (NMSS, pilot Research Grant), the Hellenic Society for Neuroscience (travel Award to attend FENS Forum Paris 2022), and from The Company of Biologists (Travelling Fellowship).