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Lipid signalling via phosphoinositides in autosomal dominant leukodystrophy with autonomic disease (ADLD)

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Autosomal dominant leukodystrophy with autonomic disease (ADLD) is an extremely rare and late onset letal progressive neurological disorder. It is characterized genetically by Lamin B1 gene duplication [1] and clinically by autonomic abnormalities and age associated demyelination in the central nervous system (CNS), without any effective treatment up to date. Myelin preserves the integrity of nerve fibers and influences the transmission of impulses in both peripheral nervous system (PNS) and CNS. Interestingly, lipids play active roles in myelination: aberrant expression of lipids are evident in various pathologies such as Alzheimer's and Huntington's disease. For this reason, our study is focused on a specific group of lipids, i.e. Phosphoinositides (PI), and on PI metabolizing enzymes known as Phospholipases (PLCs). PI are highly expressed in the brain, they mediate both cytoplasmic and nuclear signaling associated with brain function [2,3]. In this study, we have investigated a panel of PLCs (mainly PLC-β1a, PLC-β1b and PLC-γ1) in fibroblasts from ADLD patients using Real-Time PCR for evaluation of mRNA expression, Immunocytochemistry and Western blot for protein expression and Flow Cytometry for cell cycle analysis in comparison to control human fibroblasts. Furthermore, we have created an ADLD experimental model using MO3.13 and U87-MG cell lines, with oligodendrocytic and astrocytic origins respectively, to reproduce in vitro the effects of abnormal Lamin B1 expression in the cells that are typically involved in CNS myelination processes. With Lentiviral transduction, we overexpressed Lamin B1 in our cell line models and human fibroblasts to study the PI network at mRNA and protein level. Moreover, Flow Cytometric analysis were performed to study the effects of Lamin B overexpression on the cell cycle of ADLD cell line models. Our preliminary data suggest that PI might play regulatory roles in ADLD disorder.

References

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Key words

ADLD, Lamin B[1], Phopsphoinositides, Cell signaling.