BOOK OF ABSTRACTS

18.ª EDIÇÃO

IJUP

Organização

U.PORTO

Apoio

IJUP INVESTIGAÇÃO JOVEM DA UNIVERSIDADE DO PORTO

TÍTULO | *TITLE*

Livro de Resumos do 18º Encontro de Investigação Jovem da U.Porto | *Book of Abstracts Young Researchers Meeting of U.Porto*

UNIVERSIDADE DO PORTO

Professor Doutor Pedro Rodrigues

ijup@reit.up.pt

ISBN

978-989-746-418-8

DESIGN

Serviço de Comunicação e Imagem da U.Porto

22752 | Determining the impact of impaired acylation on the nervous tissue using a novel mutant mice

Guilherme Torres[1,2]; Nygell Alves[1]; Pedro Brites[1]

Neurolipid Biology group, Institute for Research and Innovation in Health (i3S), University of Porto, Porto, Portugal[1]; School of Health (ESS), Polytechnic of Porto, Porto, Portugal[2]

Normal cellular function is tightly controlled by various post-translational modifications. ZDHHC14, a member of the zinc-finger DHHC motif-containing enzymatic family, is predicted to mediate S-acylation of proteins, a process that greatly influences protein localization, association to membranes and stability. ZDHHC14 is highly expressed in the nervous system and its deficiency is often associated with the 6q25 microdeletion syndrome in patients with microencephaly, developmental delay and cognitive impairment. However, there is a knowledge gap with regards to ZDHHC14 activity, function and targets. To address this, a *Zdhhc14* KO mice model was generated, using CRISPR-Cas9 technology, by deletion of exon 5. In this work, we characterized the expression of *Zdhhc14* in WT and *Zdhhc14* KO mice. Using cDNA prepared from brains of WT and *Zdhhc14* KO mice, PCR analysis showed that deletion of exon 5 with its ensuing mutation, i.e., R235Lfs1*, leads to nonsense mRNA decay and virtually undetected Zdhhc14 mRNA in *Zdhhc14* KO mice. We also determined that brain regions including corpus callosum, hippocampus and cortex, display the highest expression of Zdhhc14 mRNA. Following on preliminary neuropathological data, we investigated the effects of Zdhhc14 on central nervous system myelination. Using electron microscopy on optic nerves from WT and *Zdhhc14* KO mice, we unraveled a defect in myelination characterized by reduced myelin thickness and increased number and length of myelin outfoldings. Moreover, measurement of myelin components, using western blot, revealed decreased expression of some myelin markers that could be related to impaired Zdhhc14 activity and may modulate myelin defects. Currently, our aim is to identify the substrates of Zdhhc14 activity (by comparing the palmitoylome of WT mice with that of *Zdhhc14* KO mice) in order to better understand the biological processes and cellular functions of Zdhhc14, and the implications of its deficiency towards neuropathology and disease presentation.

Keywords: S-acylation, Zdhhc14, Nervous system, Myelin, Mouse.

Acknowledgments:

I want to acknowledge i3S, the Electron Microscopy and Histology Unit and the Animal Facility for allowing the conditions for this work to occur and thrive.

References:

S. Mesquita, F., Abrami, L., Linder, M. E., Bamji, S. X., Dickinson, B. C., & van der Goot, F. G. (2024). Mechanisms and functions of protein S-acylation. *Nature reviews Molecular cell biology*, *25*(6), 488-509.

Nagamani, S. C. S., Erez, A., Eng, C., Ou, Z., Chinault, C., Workman, L., ... & Cheung, S. W. (2009). Interstitial deletion of 6q25. 2–q25. 3: a novel microdeletion syndrome associated with microcephaly, developmental delay, dysmorphic features and hearing loss. *European journal of human genetics*, *17*(5), 573-581.

Sanders, S. S., Hernandez, L. M., Soh, H., Karnam, S., Walikonis, R. S., Tzingounis, A. V., & Thomas, G. M. (2020). The palmitoyl acyltransferase ZDHHC14 controls Kv1-family potassium channel clustering at the axon initial segment. *Elife*, *9*, e56058.