

Internship Proposal

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Project Title:

Understand the impact of impaired S-acylation in neuron biology through the characterization of the Zdhhc14 knockout mouse

Level:

Master

Project Summary:

S-acylation involves the enzymatic addition of long-chain lipids, most typically palmitate, onto cysteine residues of proteins. Protein acylation represents a post-translational modification that greatly influences the function and/or the localization of the protein. Zdhhc14 belongs to a large family of zinc finger DHHC domain-containing (zDHHC) enzymes with predicted acyltransferase activity. Zdhhc14 is highly abundant in the nervous system, but for which there is limited knowledge of its activity, function, and target proteins. Zdhhc14 is within the microdeletion observed in patients with microdeletion syndrome associated with microcephaly, developmental delay, and hearing loss [1]. More recently, Zdhhc14 was found to palmitoylate PSD93 and Kv1 K⁺ channels in cultured rat hippocampal neurons [2]. In order to understand the in vivo functions of Zdhhc14 and the effects of its deficiency we used CRISPR-Cas9 technology to generate a loss of function mouse mutant.

Work to be developed by the student:

The proposed project involves the characterization of Zdhhc14 KO mice and will entail:

- a) Characterization of Zdhhc14 and the null Zdhhc14 KO allele. Using antibodies against Zdhhc14 determine the expression in nervous tissue (cerebrum, cerebellum, spinal cord) using western blot and immunofluorescence.
- b) Identification of the proteins acylated by Zdhhc14 using the acyl biotinyl exchange (ABE) assay.
- c) Initial characterization of the neuropathology in Zdhhc14 KO mice using histological analysis and electron microscopy.

References:

- 1- Nagamani, S., Erez, A., Eng, C. et al. Interstitial deletion of 6q25.2–q25.3: a novel microdeletion syndrome associated with microcephaly, developmental delay, dysmorphic features and hearing loss. *Eur J Hum Genet* 17, 573–581 (2009). doi: 10.1038/ejhg.2008.220
- 2- Sanders SS, Hernandez LM, Soh H, Karnam S, Walikonis RS, Tzingounis AV, Thomas GM. The palmitoyl acyltransferase ZDHHC14 controls Kv1-family potassium channel clustering at the axon initial segment. *Elife*. 2020 Nov 13;9:e56058. doi: 10.7554/eLife.56058

