Internship Proposal

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Project Title:
Unravelling the pathology and disease mechanisms of the newly identified leukodystrophy caused by impaired choline transport

Level:

Master Student

Project Summary:

For proper development and function, nervous tissue synthesizes various key components but also relies on essential nutrients. Choline is one such nutrient necessary for the synthesis of phospholipids and the production of the neurotransmitter acetylcholine. SLC44A1 serves as the sole sodium-independent high-affinity choline transporter expressed in nervous tissue. The recent discovery of SLC44A1 mutations in patients exhibiting dysarthria, ataxia, tremor, and cognitive decline underscores the critical role of choline in nervous system function and the prevention of neurodegeneration. Using CRISPR-Cas9 technology, we generated 2 mouse mutants deficient in Slc44a1. A knockout (KO) allele was created by deleting exon 5, while a conditional allele was generated by inserting loxP sites flanking exon 5. These mutant mice models will be instrumental in elucidating the neuropathology, disease mechanisms, and therapies.

Work to be developed by the student:

The proposed project involves the characterization of Slc44a1 mutant mice and will entail:
-Measurement of choline transport/uptake using propargyl-choline (a fluorescent derivative of choline) in target primary cells of WT and Slc44a1 KO mice.
-Initial characterization of the neuropathology in mice using histological analyses and electron microscopy.
-Validation of key targets identified in a proteomic survey, using western blot and immunohistochemistry
As such, you will acquire hands-on experience in several techniques including biochemistry (e.g. choline measurements, western blot), cell biology (e.g., cell culture, light microscopy, electron microscopy, histology), and training in laboratory mouse manipulations (including

isolation of mouse primary cells).

References:

-Traiffort E et al. The choline transporter-like family SLC44: properties and roles in human diseases. Mol Aspects Med 2013 34(2-3):646-54.

-Traiffort E et al. Molecular characterization of the family of choline transporter-like proteins and their splice variants. J Neurochem 2005 92(5):1116-25.

-Michel V et al. The ubiquitous choline transporter SLC44A1. Cent Nerv Syst Agents Med Chem. 2012 12:70-81.

-Fagerberg CR et al. Choline transporter-like 1 deficiency causes a new type of childhood-onset neurodegeneration. Brain 2020 143:94-111.

-Inazu M et al. Molecular and functional characterization of an Na+-independent choline transporter in rat astrocytes. J Neurochem 2005 94:1427-37

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