Internship Proposal

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Project Title:
Determine how very long chain fatty acid accumulation impairs myelination in giant axons

Level:

Master Student

Project Summary:

Leuko-axonopathies represent inherited white matter disorders characterized by intricate etiology and interplay between neurons and oligodendrocytes. Disruptions in lipid homeostasis are predicted to exacerbate pathology in nearly a third of white matter disorders. Nevertheless, there is a significant gap in our understanding of how lipids modulate cellular, molecular, and signaling pathways underlying pathology and disease. Impaired beta-oxidation of very-long-chain fatty acids (VLCFA) stands as the hallmark of X-linked ALD and ACBD5 deficiency, two peroxisomal disorders characterized by severe white matter involvement. Using CRISPR-Cas9 technology, we generated a novel mutant mouse, Acbd5 Gly357*, to elucidate how VLCFA disrupt cellular functions. Characterization of Gly357* mutants unveiled a distinct and severe phenotype with ataxia, tremors, and premature lethality. Histological analyses unveiled a pronounced axonopathy featuring giant axons and loss of myelin.

Work to be developed by the student:

The proposed work is set to unravel how Acbd5 function impacts on oligodendrocytes and myelin and cellular mechanisms by which the accumulation of VLCFA impairs myelination, and it will involve:

1-Analyze myelination in WT and Gly357* mice using confocal and electron microscopy.

2-Using an in vitro system (mixed cultures of cortical neurons with oligodendrocytes cultured in the presence or absence of VLCFA evaluate myelination and axon development.

3-Data mining of the proteomic analysis of spinal cords from WT and Gly357* mice, for players involved in oligodendrocyte/myelin function, and validation of the identified targets using western blot and immunofluorescence.

As such, you will acquire hands-on experience in several techniques including biochemistry

(e.g., 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:

1- Granadeiro L, Zarralanga VE, Rosa R, Franquinho F, Lamas S, Brites P. Ataxia with giant axonopathy in Acbd5-deficient mice halted by adeno-associated virus gene therapy. Brain. 2023 Dec 8:awad407. doi: 10.1093/brain/awad407.

2- Ferdinandusse S, Falkenberg KD, Koster J, Mooyer PA, Jones R, van Roermund CWT, Pizzino A, Schrader M, Wanders RJA, Vanderver A, Waterham HR. ACBD5 deficiency causes a defect in peroxisomal very long-chain fatty acid metabolism. J Med Genet. 2017 May;54(5):330-337.

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