Multiple sclerosis (MS) is a debilitating disease where the body’s immune system attacks the myelin sheath that protect the nerve fibers. The myelin sheath is comprised mostly of lipids and allow signals to travel faster within the nervous system [1]. The gene LXRA is associated with an increase chance of MS and is highly important on lipid homeostasis, inflammation, and innate immunity [2,3]. It is unknown how loss of the LXRA gene contributes to the onset of MS and in myelination. By understanding how LXRA contributes to myelination in the nervous system, the development of therapeutic avenues to control symptoms and stop progression of MS and other neurological diseases will be realized.

My **primary goal** is to understand how the LXRA gene functions in the myelination of the nervous system. My **hypothesis** is that mutated LXRA causes incorrect cholesterol homeostasis leading to myelin degradation. I will be using the common mouse (Mus *musculus*) and zebrafish (Danio *rerio*) as model systems for studying myelination. Mice are good for studying behavioral effects and zebrafish are good for studying myelination [4]. My **overall goal** is to develop better therapeutic treatments for MS and other diseases associated with demyelination.

**Aim 1: Identify conserved amino acids of LXRA that are critical in myelination.**

**Approach:** I will determine which conserved amino acids are important for myelination. I will use BLAST and ClustalOmega to perform sequence alignment to identify the most conserved amino acids in the ligand binding domain of LXRA. Then, I will mutate these amino acids using CRISPR to see how myelination of nerves is affected by staining mice brain sections with an Osmium Tetroxide protocol [5].

**Rationale:** Not all, but many, patients with MS have a change within the amino acid sequence of the conserved ligand binding domain of the LXRA gene, thus it is important to understand the effect this mutation has on myelination.

**Hypothesis:** Mutating different amino acids in the ligand binding domain in zebrafish and mice will show a reduction in myelination.

**Aim 2: Characterize differentially expressed genes in the central nervous system (CNS) in LXRA deficient mice.**

**Approach:** I will perform RNA-seq on the CNS in WT and LXRA deficient mice. This data will be sorted using GO analysis to identify changes in neuron-specific transcripts which will be compared between WT and LXRA deficient mice. These genes will be knocked out, brains sectioned and stained with an Osmium Tetroxide protocol.

**Rationale:** Genes that are differentially expressed without LXRA are possible targets for identifying novel pathways essential for myelination.

**Hypothesis:** Genes involved in lipid homeostasis will be downregulated in LXRA deficient mice compared to WT mice.

**Aim 3: Determine protein interactions that differ between WT and mutant LXRA.**

**Approach:** Using Co-immunoprecipitation, I can determine the different LXRA protein interactions in WT and ligand binding mutant LXRA from Aim 1. I will determine which interactions are crucial for myelination.

**Rationale:** Understanding which proteins LXRA interact with will allow us to determine which proteins assist in myelination of axons.

**Hypothesis:** LXRA will interact with genes involved in lipid homeostasis in WT but not mutant.

By the end of this study I expect to have a better understanding of the role LXRA plays in myelination due to lipid homeostasis. This research will better identify the protein interactions LXRA has that promote myelination. After determining how LXRA affects myelination, better therapeutic approaches can be developed for MS and other demyelinating diseases.

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