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"Investigating the role of AdipoR1 in pro-homeostatic fatty acid metabolism pathways"

Docosahexaenoic acid (DHA, 22:6) is a substrate widely accepted as necessary for synthesizing very-long-chain polyunsaturated fatty acids (VLC-PUFAs), a class of lipids found in high concentrations in the retina. VLC-PUFAs are formed from 28:6 derived in the omega-3 fatty acid pathway involving eicosapentaenoic acid (EPA, 20:5) and docosahexaenoic acid (DHA, 22:6) by a series of reactions catalyzed by the elongase ELOVL4 within the inner segments of the photoreceptor cells (PRCs). VLC-PUFAs are precursors to elovanoids (ELVs), which have been indicated to maintain homeostasis in the retina in response to inflammation and uncompensated oxidative stress (UOS). During these conditions, elovanoids are formed when VLC-PUFAs are cleaved from the phosphatidylcholines (PCs) in the retinal epithelial cells (RPEs), which then induce anti-apoptotic and pro-survival protein expression to prevent retinal degeneration. In *AdipoR1 -/-* mice, previous studies show a significant decrease in both DHA and VLC-PUFAs in the retina and RPE cells. This genetic anomaly is medically significant, as clinical studies have correlated mutation of the *Adipor1* gene with patients suffering from retinitis pigmentosa and age-related macular degeneration.

We intend our research efforts to help elucidate the mechanisms of fatty acid elongation and desaturation pathways necessary to generate VLC-PUFAs and ELVs in the retina. Specifically, our goal is to determine tissue specificity for the fatty acids generated by these reactions and the enzymes which facilitate them. The design of our project primarily revolves around liquid-liquid extraction of lipids from retina and RPE tissues harvested from wild-type and double knockout mice (aged either 5 weeks or 9 days for developmental comparison) and the media which they were incubated in. Contained within the media are deuterated fatty acids intermediates within the biochemical pathways thought to generate VLC-PUFAs, causing fatty acids downstream to these precursors to also contain deuterium. After completing our extraction protocol, we analyzed the samples via mass spectrometry to quantify the concentrations of deuterated fatty acids. Comparisons of fatty acid profiles between wild-type samples and double knockout samples were made to determine sites of fatty acid metabolism and help infer the mechanism AdipoR1 participates in.

Preliminary results have gone against the grain of previous research, which show significantly lower concentrations of EPA in *AdipoR1 -/-* tissues compared to wild-type tissues, whereas DHA has no significant difference between either genetic line. This difference may be due to AdipoR1's higher affinity for EPA over DHA, although further experimentation and replication of preliminary results is needed to support this claim. Additionally, we plan to complement our final findings with the evaluation of the relative expression of elongases and desaturases throughout the pathways of the omega-3 and omega-6 fatty acids by employing Western blotting and immunohistochemistry studies.