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"Retinal degeneration in mice devoid of membrane-type frizzled-related protein or adiponectin receptor 1 results in selective fatty acid synthesis impairments"

Abnormal lipid metabolism is the derivation of multiple retinal degenerative and blinding diseases. The membrane-type frizzled-related protein (MFRP), and adiponectin receptor 1 (AdipoR1) were shown to be vital to the maintenance of a healthy retinal lipidome. The two mice models of retinal degenerations *Mfrp*^{rd6} and *Adipor1* $^{-/-}$ resulted in a reduction of phospholipids containing docosahexaenoic acid (DHA; 22:6) and very long-chain polyunsaturated fatty acids (VLC-PUFAs). In a pathway involving the ω-3 fatty acids eicosapentaenoic acid (EPA; 20:5) and docosahexaenoic acid (DHA; 22:6), the fatty acid elongase-4 (ELOVL4) elongates the fatty acid 28:6 into VLC-PUFAs, which are precursors to potent neuroprotective molecules known as Elovanoids.

Given that these lipids are essential for proper vision, it is important to compare the amount of the total fatty acids in the ω-3 and ω-6 pathways in *Mfrp*^{rd6} and *Adipor1* $^{-/-}$. We isolated retina and RPE-eyecups from 6-week-old *Mfrp*^{rd6}, *Adipor1 -/-*, and control mice and extracted the lipids followed by alkaline hydrolysis and analyzed it via for LC-MS/MS.

Total fatty acids showed a significant decrease in the fatty acids in fatty acids 24:6n3 to 36:6n3 in the retina for both the *Mfrp*^{rd6} and *Adipor1* $^{-/-}$. For the RPE samples, there was a specific decrease in 32:6n3 and 34:6n3. Interestingly, *Mfrp*^{rd6} showed elevated levels of 22:5n3 and 24:5n3 in the retina. In contrast, *Adipor1* $^{-/-}$ showed decreased levels of 22:5n3 and 24:5n3 in the retina. Additionally, arachidonic acid (20:4n6), 22:4n6, and 24:4n6 were elevated in *Mfrp*^{rd6} retina.

Our study demonstrated that both *Mfrp*^{rd6} and *Adipor1* $^{-/-}$ had depleted levels of VLC-PUFAs from 24:6n3 onwards, suggesting a decreased ability to synthesize Elovanoids which require the precursors 32:6n3 and 34:6n3. Given that there was a buildup of 24:5n3 in *Mfrp*rd retina, the conversion of 24:5n3 to 24:6n3 seems to be impaired in animals with *Mfrp*^{rd6}. In contrast, the levels of PUFAs in *Adipor1* $^{-/-}$ retina were low from 20:5n3 to 36:6n3. In *Mfrp*rd retina, there were increased levels of arachidonic acid and its downstream products. Despite the implications of both models in retinal degeneration, there were significant differences along the ω-3 and ω-6 biosynthesis pathways. The next step in our project will attempt to clarify these lipid synthesis pathways using deuterium starting products.