Fatty Acid Oxidation and Retina:

Webpage with info:
http://www.ohsu.edu/xd/education/schools/school-of-medicine/departments/basic-science-departments/molecular-and-medical-genetics/index.cfm?WT_rank=2

One of the complications of LCHAD deficiency is vision loss because of a degeneration of the retina, a part of the eye that is essential for us to see. This degeneration of the retina is called retinopathy and the cause of retinopathy in children with LCHAD is not known.

Our previous study found a correlation between blood levels of an LCHAD metabolite, long chain 3-hydroxyacylcarnitines and progression of retinopathy. We followed 14 children with LCHAD deficiency over 5 years. Subjects who had high long chain 3-hydroxyacylcarnitines in their blood had a greater progression of retinopathy associated with loss of night and color vision. Long-chain 3-hydroxyacylcarnitines are observed only in patients with LCHAD deficiency. Our hypothesis is that metabolites are toxic to the retina.

We have not been able to test this hypothesis because an LCHADD animal or LCHADD retinal cell culture model do not exist. Recent advances in science have made it possible to directly reprogram cultured skin cells or fibroblasts into stem cells; cells that have the potential to become any type of cell in the body. Fibroblasts are frozen from skin biopsies of patients obtained to diagnosis LCHADD. If patient fibroblasts were reprogrammed, the stem cells would have LCHAD deficiency like the original fibroblast from which they were derived. The LCHAD deficient stem cells can then be programmed to become retina cells.

In this project we propose to generate stem cells from the cultured skin cells of patients with LCHADD. We will then program the LCHAD deficient stem cells to become retinal cells to create an LCHAD deficient retinal cell. We hypothesize that the LCHADD retinal cells will accumulate long-chain 3-hydroxyacylcarnitines. The accumulation of these metabolites will result in cell death. If our hypothesis is true, we will have the first direct evidence for the cause of retinopathy of LCHAD deficiency and we can develop potential treatments. We believe this project will further our understanding of retinal cell energy metabolism and provide insights to develop new treatment options for this LCHAD retinopathy.

Our progress to date is summarized below.

1. We have obtained Institutional Review Board (IRB) approval for this project

2. We have obtained skin cells to use in our experiments from patients with LCHAD deficiency that had skin biopsies at the time of diagnosis.

2. We are testing these skin cells to see how much fat they can burn for energy and how much sugar they burn compared to other skin cells.

3. We have finalized our protocol to transform the skin cells into stem cells and then retinal cells, and we have received Institutional Biosafety Committee (IBC) approval to conduct the experiments.

4. We recently hired a laboratory technician to help conduct these experiments.

Melanie Gillingham, PhD, RD
Assistant Professor
Oregon Health & Science University
Department of Medical & Molecular Genetics
Graduate Programs in Human Nutrition
Mailcode L103

3181 SW Sam Jackson Park Road
Portland, OR 97239
phone: (503) 494-1682
FAX: (503) 494-6886
email: gillingm@ohsu.edu