Peroxisomal Fatty Acid Metabolism and Kidney Aging
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Abstract

The U.S. population is aging, and patients lose almost 50% of their renal function between their 20s and age 70. Nearly 15% of Americans suffer from chronic kidney disease (CKD) and age-related kidney dysfunction is an important contributor, along with hypertension and diabetes. Progressive CKD leading to end-stage kidney disease (ESKD) places a huge economic burden on the healthcare system and imparts significant mortality and morbidity on patients. Those with CKD who do not progress to ESKD still have an increased risk of cardiovascular disease and death from other causes (e.g., COVID-19). Metabolic dysfunction is a common feature of age-related dysfunction and aging-associated diseases (e.g., Alzheimer's disease, Parkinson's disease).

Most studies have focused on the role of mitochondria in metabolic dysfunction, but the overlooked peroxisome also plays an important role, particularly with fatty acid oxidation (FAO). The proximal tubule, highly metabolically active due to its reabsorptive capacity, prefers FAO to generate the required ATP to support its functions.

This proposal investigates the role of peroxisomal FAO in kidney aging and tests the hypothesis that impaired peroxisomal FAO contributes to the pathophysiology of kidney aging. The proposal has two aims:

- Aim 1: The first aim will determine how peroxisomal FAO affects the aging of primary proximal tubule-enriched (PT) cells by multiple passages in culture, an *in vitro* model that has similar molecular signatures to *in vivo* aging. Primary PT cells generated from mice lacking tubular ACOX1, the rate-limiting enzyme for peroxisomal FAO, will be compared to PT cells from floxed control mice. Both male and female mice will be used to assess sex-specific differences, and some mice will be fed a high-fat diet prior to generation of primary PT cells.
- The second aim will investigate how drugs known to promote FAO, including SGLT2 inhibitors, alter the aging response of primary PT cells and whether the response is dependent upon intact peroxisomal FAO (i.e., ACOX1).

Concurrent with these studies, we will start the process of aging mice with and without tubular ACOX1. Based on data from this pilot project, we will treat the mice in the final three to four months with the drugs (identified in Aim 2) deemed most promising to slow the aging-related tubular injury. This pilot project will generate the necessary preliminary data for an R01 grant to the National Institute of Aging.