The Kapahi lab focuses on identifying and characterizing the mechanisms by which nutrient signaling pathways modulate aging and age-related diseases. This is being achieved by using an interdisciplinary approach combining genetic, pharmacological, biochemical and genomic approaches in invertebrate model systems *C. elegans*, *D. melanogaster* and mammalian cells. The broader significance of this research is to help uncover the role of nutrition in the etiology of age-related human diseases like diabetes, obesity and neurodegeneration.

Current projects include:

1. One approach we used was to find genes that mediate diet responses. We performed a genetic screen in fruit flies (*Drosophila melanogaster*) to find genes which are important for the benefits of dietary restriction and found one gene, *Oxidation Resistance 1* (*OXR1*), is essential for lifespan extension by dietary restriction. We have found that OXR1 plays an important role in trafficking proteins through the retromer complex and for autophagy.

Our work on this project has taken us in many directions, including understanding how OXR1 and the retromer could be useful to protect against Alzheimer's disease, how we can maximize both retromer function and autophagy at the same time, and how cells with OXR1 mutations become senescent (meaning they do not divide nor do they undergo apoptosis but they do secrete potentially harmful factors). We are using flies, cell culture (human fibroblasts and iPSC-derived neurons), and mouse models to test each of these approaches to understanding the importance of OXR1. We regularly test animal behavior, biochemical interactions, and molecular techniques to identify the function of OXR1 and how it influences protein trafficking and degradation.

2. A by-product of glycolysis is methylglyoxal (MGO), a highly reactive dicarbonyl that can readily and non-enzymatically react with proteins and nucleic acids to generate toxic adducts called advanced glycation end products (AGEs). These toxic adducts build up gradually during an increase in conditions like aging and diabetes.

Research in our lab addresses how aging and hyperglycemia-induced accumulation of AGEs influence age-associated decline in physical and cognitive function in conditions like Alzheimer's disease. Using cell culture, *Caenorhabditis elegans*, and mouse models, we explore the metabolic network altered by methylglyoxal and AGEs. We have identified a cocktail of compounds that can significantly reduce the impact of methylglyoxal and its toxic byproducts We have observed that the combination we identified is multimodal in action and engages many biological pathways involved in aging to extend lifespan, induce caloric restriction and boost exercise tolerance. Our current focus is to understand the compound cocktail mechanism of action using cell culture and mice in aging, diabetes and neurodegeneration.

Desired Skills or Experience: Completed coursework in biology, biochemistry, chemistry, genetics, and neuroscience preferred but not necessary. We welcome students with intriguing scientific questions and curiosity in pursuing challenging ideas.

To learn more about the Kapahi lab, click HERE.

To apply to the Kapahi lab, return to the Internships Homepage.