Isoleucine is an essential dietary protein. Our lab has found that by reducing isoleucine intake by 2/3 (Low Ile), mice exhibit tremendous improvements in metabolism and lifespan. This project studies the effects of Low Ile in mice starting at 20-months-old, the mice-equivalent age of 60 human years. 

• Even at this advanced age, Low Ile remains effective in improving metabolism.
• We found significant rejuvenation of the heart structure and function by Low Ile. This benefit was specific to females.
• In the female heart, Low Ile suppressed the group of lipids named phosphatidylglycerols, a mitochondrial component that increases with age.
• In the liver, the two sexes exhibited mostly different set of aged-induced differentially expressed genes. Notably, the female liver had more than twice of the age-driven gene changes as males, and most of these were sensitive to Low Ile treatment.

These results demonstrate that Low Ile can have profound influences on metabolism, cardiac health, and liver function even in aged mice, suggesting that dietary interventions are translationally promising for promoting healthy aging even in older people.

**Low Ile Diet Increases Lifespan in UM-HET3 mice** (Green et al. 2023)

**Late-life Low Ile Diet Induces Beneficial Metabolic Adaptations**

**Dietary Interventions Rejuvenates the Heart Lipid Profile**

**Gene Expression Analysis of the Low Ile Liver in Aged Mice**

Liver transcriptomic analysis found a large number of age-driven differentially expressed genes (DEGs) which were sensitive to the Low Ile dietary intervention. Colored outer ring = diet-sensitive aged gene changes. The number of expression changes is more than doubled in the females.

**Changes in Gene Expression Pathways are Sex-Dependent**

**In conclusion**: A diet with 2/3 reduced isoleucine content (Low Ile) is effective in improving metabolic health in aged mice and we found rejuvenation effects of the lipid profile in the heart. But, various changes were highly sex-dependent and follow-up studies will highlight the specific effects of this diet and their consequences.

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