Andrea L. Hevener, PhD

The impact of ERα on mitochondrial function, metabolic homeostasis, and insulin action

Impaired estrogen receptor (ER)α action drives obesity and metabolic dysfunction in humans and mice; however, the mechanisms underlying this response are inadequately understood. We have established that reduced ERα expression in metabolic tissues is associated with glucose intolerance and adiposity in women and female mice. To study the impact of Esr1 expression on metabolic health, we are the only laboratory in the country to have generated tissue-specific ERα loss and gain of expression mouse models for skeletal muscle, adipose tissue, liver, myeloid cells, endothelial cells, and pancreatic islets. In all KO models we find common abnormalities including the retention of aberrant mitochondria, basal overproduction of reactive oxygen species, alterations in mitochondrial DNA replication, and impairment in basal and stress-induced mitochondrial remodeling. Our findings indicate that ERα is critical in the preservation of mitochondrial health, aerobic capacity, and insulin action as a defense against metabolic disease.

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Highlighted in *Nature Reviews Endocrinology, Nature Metabolism, and JAMA*

The impact of cellular stress resistance and mitochondrial dynamics on metabolic homeostasis and insulin sensitivity

Cellular stress resistance against metabolic insult is critical for disease prevention. Mitochondria, the powerhouse of the cell, undergo a rapid remodeling to combat cellular stress and alter metabolism to meet changing energy requirements. The remodeling process is also critical for

organelle quality control and it plays a critical role as a central hub for coordinating numerous cellular processes beyond ATP production including calcium buffering, iron and heme homeostasis, cholesterol and steroid biosynthesis, mtDNA replication, and apoptosis. We have identified key regulators of mitochondrial remodeling and quality control that modulate metabolic health and cellular resilience in response to stress and aging. Of interest, we obese sexual dimorphism in cellular stress resistance as females are protected against numerous forms of cellular stress that disrupt metabolic homeostasis and insulin action.

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**** = These authors contributed equally to this work***

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Team science and mentoring

I have performed numerous collaborative projects where I have contributed substantively to the development, execution, and overall success of the research. Citations are relevant to this proposal as these publications show the breadth of my expertise and ability to perform large-scale phenotyping projects collaborating with a diverse team of researchers investigating mechanisms regulating metabolism, inflammation and insulin action. I mentored each of the first authors of these manuscripts in which I served as a fellowship or NIH "K" advisory committee member, and importantly, each of these individuals is now independent holding a tenure track professorial position at a major research institution.

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If you want to see more, the link below will take you to Dr. Hevener's complete list of published work. https://www.ncbi.nlm.nih.gov/myncbi/1nMyx9AyRb_QX/bibliography/public/