Estrogen receptor in the heart found to regulate obesity in postmenopausal women

March 10 2023

Credit: Pixabay/CC0 Public Domain

Estrogen is known to play an important role in the protection of women's hearts, but once women are postmenopausal and estrogen levels drop, they are at an increased risk of a number of diseases and conditions,

including heart disease, obesity and diabetes.

Published in *Nature Cardiovascular Research*, the study found that reduced ERα in the cells responsible for heart contraction (cardiomyocytes) led to moderate heart dysfunction and increased rates of obesity in female mice, but not in male mice.

Professor Julie McMullen from the Baker Heart and Diabetes Institute said the team identified a sex hormone receptor in the heart that can regulate adiposity (obesity) in females.

"We've been interested in trying to understand the role of this estrogen receptor in the heart for some time, to see how it provides protection to the heart," Professor McMullen said.

"When we blocked this estrogen receptor, we were expecting to see changes and damage largely to the heart. But rather than seeing a dramatic heart phenotype, what we saw was an adiposity phenotype. So, we observed that the female mice were heavier and had more fat mass, which we weren't expecting at all."

Genes that are important for contractility of the heart and metabolic function of the heart were also lower in the female heart when ERα was reduced, explaining why the female study hearts did not pump as well.

Associate Professor David Greening, an expert in extracellular vesicle biology at La Trobe University said particles, called extracellular vesicles, that were released from the female hearts with reduced ERα also contained proteins that differed from both the control group and male hearts.

"We found that reducing ERα in heart muscle cells (cardiomyocytes) of female mice leads to transcriptional, lipidomic and metabolic

dysregulation in the heart, together with metabolic dysregulation in skeletal muscle and adipose tissue," Associate Professor Greening said.

"Furthermore, the extracellular vesicles that are released from heart cells with reduced ERα had the capacity to reprogram skeletal muscle cells in cell culture.

"These changes to tissues, the extracellular vesicles proteome and reprogrammed skeletal muscle cells altered the cells' molecular landscape and function. So rather than energy being expended, energy is instead stored, which explains the increased adiposity in female mice in the absence of Erα," Associate Professor Greening said.

This important work has implications for preventing and treating heart and metabolic disease in postmenopausal women, but also cardiotoxicity in premenopausal women receiving therapies that may inhibit or reduce ERα in the heart.

"Females who have drugs which can interact with or inhibit this particular receptor, including some chemotherapies, often become obese," Professor McMullen said.

"Now we have a better understanding of ERα, we've got a better chance of identifying therapies to prevent the obesity from occurring."

Associate Professor Greening said this study demonstrated that "extracellular vesicles—nanovesicles with their packaged molecular cargo—are systemic signaling regulators that can travel to, and impact other organs in the body, including adipose tissue and skeletal muscle."

"Extracellular vesicles thereby provide a new paradigm in crosstalk between cells, tissues and organs in health and disease," Associate Professor Greening said.

More information: David Greening, Estrogen receptor alpha deficiency in cardiomyocytes reprograms the heart-derived extracellular vesicle proteome and induces obesity in female mice, *Nature Cardiovascular Research* (2023). DOI: 10.1038/s44161-023-00223-z. www.nature.com/articles/s44161-023-00223-z