SWACSM Abstract

Exercise and Esr1 Control Mitochondrial Content and Function to Regulate Adiposity

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ABSTRACT

Mechanisms that underlie adipose tissue remodeling to enhance metabolic health in response to exercise training remain inadequately understood. **PURPOSE:** We utilized mouse genetics and human GWAS to determine the impact of exercise training on mitochondrial DNA copy number, and interrogate the relationship between Esr1 and adipose tissue health. **METHODS:** We performed RNAseq on adipose tissue from 100 strains of inbred mice following exercise training and determined mitochondrial content by qPCR. We performed deep phenotyping of mice harboring conditional Esr1 overexpression selectively in adipose tissue. Adipose specific Esr1 overexpression and control mice were fed a high fat diet and placed in metabolic chambers to interrogate the effects of Esr1 on whole body metabolism. **RESULTS:** We determined that exercise training significantly increased adipose tissue mtDNA content in mouse and man and that increased mitochondrial content correlated with reduced adiposity. Adipocyte health was associated with increased expression of transcripts involved in mitochondrial cristae formation including OPA1, Polg1, and Dnm1l. Since Esr1 is a transcription factor negatively associated with adipose tissue mass, and since deletion of Esr1 disrupts mitochondrial function and reduces expression of Polg1, OPA1, and Dnm1l, we interrogated in impact of conditional Esr1 overexpression on mitochondrial function and adipose tissue health. Adipocyte-specific Esr1 overexpression increased expression of mitochondrial gene targets, increased mtDNA copy number and mitochondrial respiration, and enhanced whole body energy expenditure of animals challenged by high fat diet feeding. Adipocyte-specific Esr1 overexpression protected mice against HFD-induced obesity. **CONCLUSION:** Exercise promotes remodeling of adipose tissue mitochondria and is associated with fat mass reduction. Overexpression of Esr1 drives a similar adipose tissue remodeling and weight loss as exercise training, and protects against adipose tissue weight gain in the context of overnutrition. These data suggest that exercise responsive transcripts in adipose tissue can be selectively targeted to enhance weight loss and improve metabolic health.