Estrogen Receptor Alpha Controls Mitochondrial Function and Metabolic Homeostasis, and is Critical for Exercise-Induced Improvements in Metabolism

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Skeletal muscle is an important tissue responsible for locomotion, oxidative metabolism, and insulin-stimulated glucose disposal. Because exercise is the most effective means to combat metabolic dysfunction and prevent the progression of type 2 diabetes, our laboratory is interested in understanding the molecular transducers underlying the health benefits of exercise. Previous work by our group has shown that muscle ESR1/ERα expression is correlated with indices of metabolic health, and Esr1 expression in muscle is induced following exercise training. PURPOSE: Determine whether genetic overexpression of Esr1 to mimic transcript induction by physical activity is sufficient to produce favorable metabolic changes comparable to exercise training. METHODS: We generated a conditional gain of Esr1 expression mouse model (mERαTg) using a muscle-specific tamoxifen-inducible promoter. By design, we achieved Esr1 expression levels in skeletal muscle of adult mice comparable to that of age-matched wildtype animals following 30 days of training. To determine whether the induction of muscle Esr1 was protective against metabolic dysfunction, we challenged mERαTg mice with a high fat diet (HFD) for 8 weeks. mERαTg mice were provided with cage running wheels (for 30 days) to determine whether Esr1 induction by genetic means produces synergistic outcomes on metabolism when coupled with exercise training. RESULTS: mERαTg mice were protected against HFD-induced obesity and insulin resistance compared with control animals. Protection of metabolic health during HFD-challenge was associated with improved mitochondrial function and oxidative capacity. In sedentary animals, Esr1-driven improvements in mitochondrial function over control were further enhanced following exercise training. Specifically, Esr1 overexpression coupled with exercise training produced a synergistic effect to increase the expression of TFAM, MTCO3, and mtDNA copy number. CONCLUSION: The data suggests that Esr1 overexpression produces favorable changes in metabolism and protects against metabolic perturbations that contribute to chronic disease. Our research indicates that Esr1 could be targeted by therapeutic means to enhance the effectiveness of exercise and combat chronic diseases associated with metabolic dysfunction.