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

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ABSTRACT

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 (mERaTg) 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 mERaTg mice with a high fat diet (HFD) for 8 weeks. mERaTg 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**: mERaTg 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.