Estrogen-related receptors and their role in skeletal muscle metabolism

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Skeletal muscle plays key roles in glucose and lipid homeostasis, and contributes to whole body energy expenditure. Poor physical fitness and inactivity are risk factors for developing type 2 diabetes. Conversely, physical activity is effective in improving metabolic health, by enhancing insulin sensitivity and improving lipid parameters. Notably, the capacity for exercise and the metabolic benefits and responses to exercise vary greatly among individuals and are decreased in some disease states. Thus, elucidating the molecular mechanisms that determine skeletal muscle function and fitness (and thereby enable exercise), and mediate exercise-induced skeletal muscle responses, is important for finding new ways to target muscle and improve metabolic health.

The family of estrogen-related receptors (ERRα, ERRβ and ERRγ) regulates oxidative metabolism and other pathways important for energy homeostasis. The three ERRs are expressed in skeletal muscle, with higher levels in slow/oxidative fiber- than fast/glycolytic fiber-rich muscles, and are induced by endurance exercise. Our group studies the molecular mechanisms by which muscle ERRs integrate physical activity cues to control the expression of genes important for muscle metabolic and contractile properties. We also use mice lacking ERRs specifically in skeletal muscle to dissect the roles of ERRs for muscle function and physiology. *In vitro* and *in vivo* studies suggest that the three ERRs act largely complimentary to each other (additively or in a redundant fashion) to control oxidative metabolism, but carry isoform-specific functions in controlling other programs. Interestingly, the ability of ERRs to affect broad expression programs relies on the induction of key downstream effectors, such as Perm1. We have identified Perm1 as a PGC-1- and ERR-induced gene that is expressed specifically in muscle and is important for basal and PGC-1/ERR - enhanced respiratory capacity. Consistent with being a PGC-1/ERR regulated gene, Perm1 levels in humans are enhanced by physical activity and decreased in disease states. Overexpression of Perm1 in the skeletal muscle of mice enhances the expression of OxPhos complexes. The molecular mechanisms by which Perm1 impacts gene expression and mitochondrial function, and the physiological consequences of Perm1 expression are currently unclear.

We expect that elucidation of the mechanisms by which Perm1 and ERRs impact skeletal muscle health may enable therapeutic approaches for states where muscle function and metabolism are compromised, such as disease-associated muscle atrophies and/or age-related muscle degeneration.