PGC-1α in muscle links metabolism to inflammation

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Skeletal muscle has an enormous capacity to adapt to external stimuli. Most prominently, changes in protein biosynthesis and degradation rates, alterations in contractile and metabolic properties and modulation of signal transduction pathways regulate muscle fiber plasticity induced by physical activity. The transcriptional coactivator peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) is appreciated as one of the central regulators of gene expression in the exercised muscle (Lin *et al.*, 2005; Handschin & Spiegelman, 2006, 2008). In fact, ectopic expression of PGC-1α is sufficient to boost mitochondrial biogenesis and function, stimulate a fiber-type switch towards oxidative muscle fibers, promote a high-endurance muscle phenotype and prevent disuse-induced muscle atrophy. Furthermore, increased PGC-1α levels therapeutically ameliorate Duchenne muscular dystrophy, statin-induced fiber damage and one form of a mitochondrial myopathy in the respective rodent models. In contrast, experimental ablation of PGC-1α gene expression results in lower mitochondrial gene expression, a fiber-type switch towards glycolytic muscle fibers, reduced exercise capacity, abnormal glucose and insulin homeostases and activity-dependent fiber damage.

The molecular events that mediate the protective effects of PGC-1α on muscle fiber integrity remain enigmatic. Several candidate pathways have been proposed: PGC-1α-mediated stabilization of the neuromuscular junction, improvement of the energy crisis, inhibition of ubiquitine ligase expression and upregulation of reactive oxygen species (ROS) detoxification potentially contribute to the therapeutic effect of PGC-1α in diverse contexts of muscle wasting. We now present evidence that PGC-1α in skeletal muscle also has significant anti-inflammatory properties. Pro-inflammatory gene expression in muscle is elevated and increased levels of circulating tumor necrosis factor α (TNFα) and interleukin 6 (IL-6) have been detected in muscle-specific PGC-1α knockout mice. Importantly, these animals exhibit abnormal pancreatic islet morphology and decreased insulin secretion in vivo indicating an increase in detrimental circulating factors in the context of specifically ablated PGC-1α gene expression in skeletal muscle. These factors subsequently lead to phenotypic alteration of the physiological functions of non-muscle tissues, including pancreatic β-cells. We thus propose that a pathological reduction of PGC-1α levels in skeletal muscle is the molecular link between physical inactivity, persistent, low-grade inflammation and the increased risk for many chronic diseases.

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