Universität Basel

Research Project

Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (SSEM)

Third-party funded project

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The transcriptional coactivator peroxisome proliferator-activated receptor g coactivator 1a (PGC-1a) is a key mediator of skeletal muscle adaptations to motor neuron activity. Subsequent to transcriptional induction by innervation-induced calcium signaling, PGC-1a controls the expression of metabolic, myofibrillar, neuromuscular junction and other genes. Ectopic expression of PGC-1a in skeletal muscle of transgenic mice results in a fiber type switch towards oxidative, high endurance muscle fibers. Furthermore, PGC-1a muscle-specific transgenic animals are resistant against disuse-induced muscle atrophy in denervated hind legs. Thus, even in the absence of a functional motor neuron, forced expression of PGC-1a is sufficient to maintain a phenotype resembling exercised muscle indicating that PGC-1a regulates many, if not all of the adaptive changes following increased physical activity. For obvious reasons, skeletal muscle of dystrophic patients exhibits a gene expression pattern that is in part identical to disused muscle. Moreover, expression of a subset of genes directly controlled by PGC-1a is reduced in a number of muscular dystrophies. Recent experiments in mdx mice, a mouse model for Duchenne muscular dystrophy (DMD), revealed a beneficial effect of transgenic expression of PGC-1a on fiber damage, muscle necrosis and muscle function. In particular, elevated levels of PGC-1a in skeletal muscle of mdx mice reduced circulating creatine kinase levels, decreased histological markers for fiber damage and dramatically enhanced the ability of these mice to run on a treadmill. However, the molecular mechanisms underlying the therapeutic effect of PGC-1a in this mouse model for DMD remain elusive. The project described in this research grant proposal aims at elucidating the upstream and downstream signaling events as well as gene expression changes that account for the amelioration of the muscle dystrophy mediated by PGC-1a. Moreover, we aim at testing pharmacological agents that persistently modulate PGC-1a expression in muscle cells in vitro and in vivo. We hope that by combining in vivo approaches using different mouse lines with ex vivo experiments in isolated muscle fibers and primary muscle cells in culture, we are able to pinpoint the molecular basis for the PGC-1a effect on DMD and also find potential drugs for pharmacological manipulation of PGC-1a in DMD. Finally, because of the strong potency of PGC-1a to promote exercise-induced adaptations, we are convinced that manipulation of the PGC-1a pathway provides a promising avenue for any skeletal muscle-associated disease that shows a muscle disuse-related phenotype, including atrophy due to prolonged hospitalization or limb immobilization, sarcopenia and many of the muscular dystrophies.

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