Universität Basel

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Dysfunction of the systems that control basal muscle function or that are required for muscle adaption results in severe pathological consequences. Similarly, inadequate physical activity is a strong and independent risk factor for many chronic diseases and thus results in a shortened life expectancy. Disequilibrium of one of the key factors, namely decreased or absent expression of the peroxisome proliferator-activated receptor g coactivator 1a (PGC-1a) in skeletal muscle of mice leads to a fiber-type shift towards glycolytic IIx and IIb fibers, reduced mitochondrial function, dysregulated glucose and insulin homeostasis, impaired exercise capacity, muscle fiber damage and elevated systemic inflammation. Thus, in general, the phenotype of PGC-1a muscle-specific heterozygous or knockout animals closely recapitulates that of pathologically inactive individuals. Accordingly, abnormally low PGC-1a gene expression has been observed in muscle biopsies of inactive populations, e.g. type 2 diabetic or sarcopenia patients. In contrast, elevation of PGC-1a expression results in a muscle phenotype similar to an endurance-exercised muscle. Even in the absence of functional motor neuron signaling, preventing the normally occurring drop in PGC-1a expression in an inactive muscle by transgenic expression drastically reduces muscle atrophy and maintains fiber properties of an exercised muscle. Importantly, many diseases are associated with inactive skeletal muscle and therefore, increased levels and/or activity of PGC-1a is beneficial in a range of pathologies with completely different etiologies. Thus, in addition to the prevention of disuse-induced muscle atrophy, maintaining or inducing PGC-1a expression has been described to be therapeutically beneficial against muscle wasting caused by the statin-class of drugs and to ameliorate Duchenne muscular dystrophy. Clearly, elevation of PGC-1a provides symptomatic relief in a variety of muscle-associated diseases, even those caused by mutations of muscle or motor neuron genes. However, all these findings have been made in mouse models using transgenic techniques to modulate PGC-1a expression and obviously, this approach is not an option in human patients. For many muscular dystrophies, that is, muscular diseases caused by mutations of key genes in muscle or motor neurons, no treatment is known. The goal of our project is the development of new avenues to modulate PGC-1a levels in skeletal muscle in vivo.

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