Universität Basel

Research Project

Schw. Diabetes-Stiftung (Echo)

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The prevalence of type 2 diabetes is reaching epidemic proportions in Western societies and constitutes a major burden on healthcare systems. Hallmarks of this metabolic disease are increased blood glucose levels and reduced insulin sensitivity of peripheral tissues. Unfortunately, the molecular dysregulations leading to the development of insulin resistance and ultimately type 2 diabetes remain unclear. The prevalence of type 2 diabetes correlates with increased body fat mass (obesity) and physical inactivity. Strikingly, exercise is one of the most efficient interventions to prevent and treat the disease. Again, the exact mechanisms underlying the therapeutic effects of exercise are unknown. Our proposal aims at increasing the knowledge regarding the pathological changes leading to insulin resistance in skeletal muscle and the molecular adaptations that mediate the therapeutic effects of exercise. The strength of the project lies in the integration of data from cell cultures, animal models and patient exercise trials.

We investigate of the transcriptional co-activator peroxisome proliferator-activated receptor g co-activator 1a (PGC-1a) in the etiology of type 2 diabetes and as a potential target that mediates the beneficial effects of exercise. PGC-1a is a strong promoter of mitochondrial function, oxidative metabolism and glucose uptake in skeletal muscle. PGC-1a transcription is controlled by motor neuron activity and accordingly, higher PGC-1a levels are observed in trained muscle, whereas inactivity causes a drop in PGC-1a transcript and protein levels. Interestingly, ectopic expression of PGC-1a in skeletal muscle promotes a muscle fiber-type switching towards oxidative muscle fibers and improves the muscular fatigue resistance. On the other hand, mice with a specific ablation of PGC-1a in skeletal muscle exhibit abnormal glucose and insulin homeostasis as well as reduced exercise tolerance. In skeletal muscle biopsies of type 2 diabetic patients and of pre-diabetic individuals, a significant reduction in PGC-1a mRNA levels has been reported, suggesting that dysregulation of PGC-1a is an early event in the causation and progression of insulin resistance. Interestingly, reduced PGC-1a levels are also observed in skeletal muscle of elderly individuals and correlate with diminished insulin-stimulated glucose uptake and oxidation. Finally, specific inhibition of the protein-protein interaction between PGC-1a and the estrogen-related receptor a (ERRa) precipitates a type 2 diabetes-like state in skeletal muscle cells in vitro.

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