Project 6: Exercise-triggered mechanisms contributing to beneficial metabolic responses and type 2 diabetes protection.

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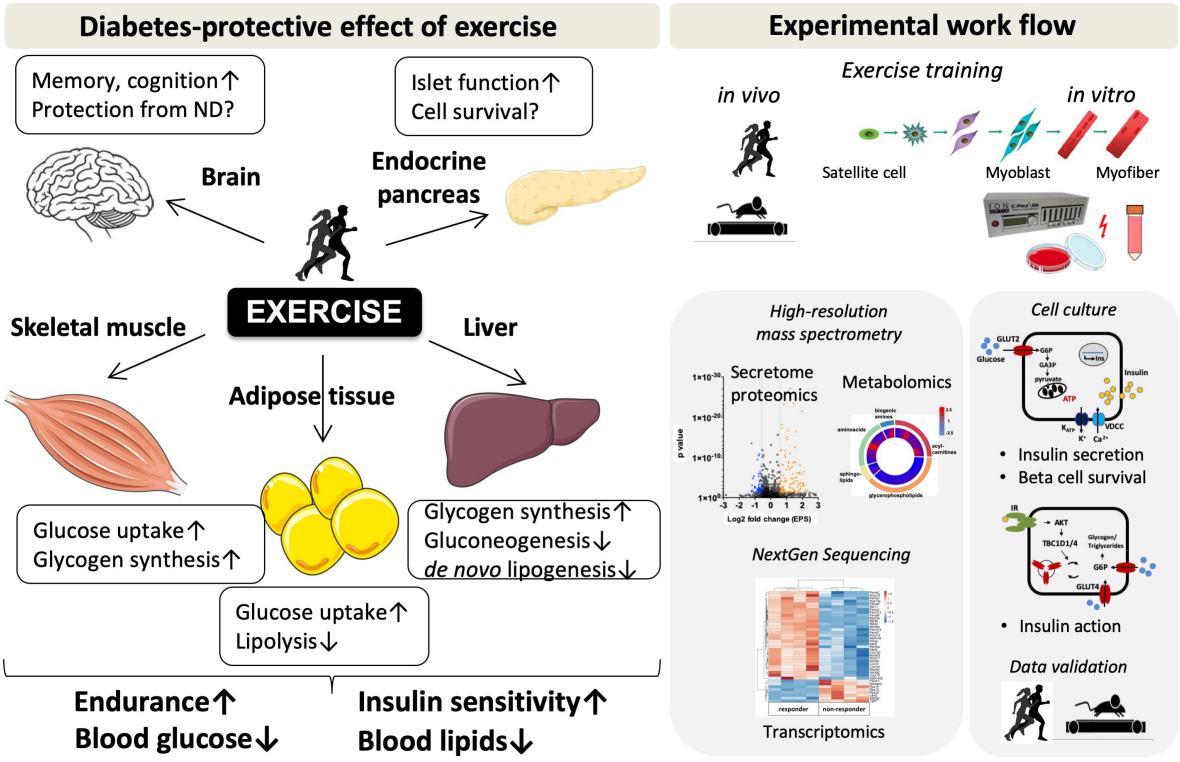
Background: Physical exercise is associated with advantageous systemic metabolic effects on energy substrate metabolism, insulin sensitivity and protection against type 2 diabetes. In fact, exercise training positively affects multiple organ systems implicated in energy homeostasis, including skeletal muscle, liver, adipose tissue, brain and insulin-producing pancreatic beta cells. Hormone-like proteins (myokines) and metabolites secreted from skeletal muscle are thought to mediate the insulin-sensitizing and diabetes-protective effect of exercise training through unknown mechanisms.

Own previous work: We generated different mouse models to study how exercise improves insulin action and glycemic control. We further established protocols for *in vitro* contraction of rodent skeletal muscle and cultured human muscle cells ("training in a petri dish" by electrical pulse stimulation, EPS). Moreover, we identified novel myokine candidates and metabolite patterns associated with insulin sensitivity using high-resolution mass spectrometry.

Aim of the project: We will use models of exercise and muscle contraction to identify regulatory factors, myokines and metabolites that improve i) pancreatic islet/beta cell function and ii) insulin sensitivity of skeletal muscle and adipose cells.

Work program: Cultured muscle cells will be subjected to EPS training in vitro, and analyzed before and after contraction for transcriptional control of glucose and lipid metabolism and contraction-related signaling by RNASeq, real-time qPCR, phosphoproteomics and Western blotting. After the contraction protocol, conditioned skeletal muscle cell media will be used to study their impact on i) glucose-stimulated insulin secretion (GSIS) of cultured insulin-producing beta cells and proliferation for paracrine effects, and ii) insulin-stimulated glycogen synthesis and signaling in cultured skeletal muscle cells, as well as glucose uptake into adipocytes for autocrine effects on insulin action. Myokines/cytokines and metabolites in the conditioned media will be analyzed using high-resolution mass spectrometry.



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