SRP Diabetes Postdoctoral Fellowship Program 2024

Project title: Discovery of Molecular Signal Transducers Conferring Insulin-Induced Adaptations on Glucose Transport in Type 2 Diabetes

Background

Skeletal muscle is the primary site of whole-body insulin-mediated glucose uptake. My team has reported that people with type 2 diabetes are characterized by reduced insulin-mediated whole-body glucose uptake[1], which arises from reduced insulin-stimulated glucose transport in skeletal muscle[2]. The glucose transporter 4 (GLUT4) is expressed in skeletal muscle, cardiac muscle, and adipose tissue, and is the rate-limiting transporter for glucose uptake. We reported that people with type 2 diabetes have reduced glucose uptake due to impaired GLUT4 translocation to the skeletal muscle cell surface[2]. Moreover, we reported that acute exercise and contraction, as well as *in vitro* exposure to energetic stressors that mimic the effects of exercise, increase skeletal muscle glucose transport and cell surface GLUT4 content via an insulin-independent mechanism, even in people with severe insulin resistance and type 2 diabetes[2,3]. Thus, pharmacological agents that mimic the effects of exercise on GLUT4 translocation may be efficacious in the treatment of insulin resistance. This project is designed to test the role of signal transducers to improve glucose homeostasis by targeting skeletal muscle glucose transport.

Objectives

To explore the molecular signal transducers involved in the regulation of glucose transport to restore glucose uptake in skeletal muscle from people with type 2 diabetes.

Methodology

We will have mapped the proteome and phosphoproteome of skeletal muscle from >120 men and women with normal glucose tolerance or type 2 diabetes, with varying degrees of insulin sensitivity[4]. Leveraging deep *in vivo* phenotyping, we reveal that fasting proteome and phosphoproteome signatures strongly predict insulin sensitivity[4]. Furthermore, the insulin-stimulated phosphoproteome revealed both dysregulated and preserved signaling nodes - even in individuals with severe insulin resistance. While substantial sex-specific differences in the proteome and phosphoproteome were identified, molecular signatures of insulin resistance remained largely similar between men and women[4]. From this initial study[4], we have identified several candidates that may play a direct role in glucose transport. In this project, the postdoctoral fellow will validate the role of novel signal transducers in the regulation of glucose transport and insulin sensitivity using knock-down and over-expression approaches in primary human skeletal muscle cells. Promising candidates will be further validated in *in vivo* models through electroporation approaches.

Work plan

The postdoctoral fellow will test novel signal transducers identified in a screen of basal and insulin-stimulated skeletal muscle from men and women with normal glucose tolerance or type 2 diabetes[4] for a role in glucose transport. Furthermore, a novel GLUT4 photolabeling technique[2] and assays of signal transduction[1,2] will be utilized. The involvement of signal transducers including Rac1, NADPH oxidase 2 ROS production, AS160, Rab proteins and cytoskeletal modification will be explored using appropriate phospho-specific antibodies.

Relevance of project for diabetes

This program is designed to fill a therapeutic void by optimizing interventions to enhance glucose transport in skeletal muscle, while concomitantly identifying and validating new type 2 diabetes prevention and therapeutic targets. Molecular insight derived from this work may be used by health care practitioners to identify people at risk for metabolic or muscular diseases. The long-term goal is that novel molecular transducers to control insulin sensitivity developed through this work may one day form the basis of a new class of therapies to mitigate secondary aging and prevent insulin resistance and type 2 diabetes mellitus. Through this, we will provide pre-clinical insight into the feasibility of skeletal muscle specific therapeutics to improve glucose homeostasis in type 2 diabetes.

References

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3. Cartee, G.D., Hepple, R.T., Bamman, M.M. & Zierath, J.R. Exercise promotes healthy aging of skeletal muscle. *Cell Metab* **23**, 1034-1047 (2016).
4. Kjærgaard Larsen, J.*, et al.* Personalized molecular signatures of insulin resistance and type 2 diabetes. *bioRxiv*, 2024.02.06.578994 (2024).
5. Furuzono, S.*, et al.* A xanthene derivative, DS20060511, attenuates glucose intolerance by inducing skeletal muscle-specific GLUT4 translocation in mice. *Commun Biol* **4**, 994 (2021).

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