Immuno-metabolic modulation of skeletal muscle insulin sensitivity

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**Background.** The goal of this project is to integrate discoveries in clinical and molecular medicine to understand the biological basis of insulin resistance. Specifically, we will identify and validate molecular signatures of skeletal muscle that are associated with the maladaptive response to systemic factors characteristic of overt type 2 diabetes, including but not limited to inflammatory factors. Changes in circulating factors/biomarkers may influence the metabolic profile of skeletal muscle through cell-to-cell communication to modify gene regulatory and metabolic responses. Type 2 diabetes is associated with chronic low-grade systemic inflammation and patients usually show increased levels of endothelin, as well as several cytokines, such as interleukin (IL) 6, tumour necrosis factor (TNF) α and reduced levels of the insulin sensitising adipokine adiponectin. To probe the role of these factors in the modulation of skeletal muscle insulin sensitivity, we will adopt multi-disciplinary approaches integrating clinical cohorts, cell-based systems, and animal models with molecular approaches using secretome, epigenome, transcriptome, proteome and metabolome platforms. This integrated approach will provide non-biased genome-wide profiles to reveal the next generation of candidate genes that we will analyze using cell based systems and animal models of type 2 diabetes.

**Hypothesis:** We will test the hypothesis that circulatory factors (ranging from metabolites to cytokines to miRNA) influence insulin sensitivity and the risk for developing diabetes.

**Aims:** Determine the effect of systemic factors characteristic of the diabetic phenotype (for example changes in metabolic and inflammatory factors) on the epigenome, transcriptome, proteome and metabolome profile and coupling this to changes to insulin sensitivity. Pathways and targets will be validated for a role in insulin sensitivity.

**Description of the work to be undertaken:** To identify a skeletal muscle “secretome” we will analyse *vastus lateralis* muscle samples and blood samples from male and female type 2 diabetic patients and age- BMI-matched healthy people, at baseline and in response to exercise or glucose challenge. Additionally we will use primary cultures of human muscle, or muscle biopises incubated in vitro. These will be analysed for secreted factors, including
cytokines/myokines as well as potential signalling metabolites and miRNA species. We will also confirm results in vivo in circulation. We have established a large and unique collection of primary human skeletal muscle cultures from well characterised donors. These include healthy men and women as well as subjects with type 2 diabetes and/or obesity. This provides a platform for mechanistic studies to explore the signalling pathways engaged by the different factors identified.

References for the project:


H Kirchner, I Sinha, H Gao, MA Ruby, M Schönke, JM Lindvall2, R Barrès, A Krook, E Näslund, K Dahlman-Wright, JR Zierath. Altered DNA methylation of glycolytic and lipogenic genes in liver from obese and type 2 diabetic patients in press, Molecular Metabolism

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