Hypoxic signalling in the type 2 diabetic heart – mechanisms for therapeutic modulation

Supervisor name: Dr Lisa Heather & Dr Damian Tyler

Department: Physiology, Anatomy and Genetics

Project details

Background: Cardiovascular disease is the leading cause of mortality in patients with type 2 diabetes, and strategies to improve survival are needed. The type 2 diabetic heart has abnormal substrate metabolism, which contributes to decreased recovery following myocardial infarction in patients with type 2 diabetes. Cardiac glycolysis and glucose oxidation are decreased in diabetes. In contrast, fatty acid metabolism is increased, due to increased circulating fatty acid concentrations that activate the peroxisome proliferator-activated receptor (PPAR) α transcription factor. To survive a myocardial infarction, the heart must adapt metabolically to decreased oxygen availability (hypoxia) by activating the hypoxia-inducible factor (HIF). HIF regulates a plethora of genes to make the cell more oxygen efficient, a large number of which are metabolic enzymes. HIF1α increases transcription of glycolytic genes, resulting in an increase in glycolysis and oxygen-independent ATP production. In addition, HIF1α activation decreases PPARα, resulting in suppression of fat metabolism, and decreases transcription of mitochondrial enzymes to decrease oxygen consumption.

The cardiac metabolic changes in type 2 diabetes are the opposite of those induced by hypoxia and HIF activation. Given that diabetes and hypoxia induce opposite metabolic effects, this raises questions regarding how the diabetic heart responds when exposed to hypoxia, and whether this contributes to the decreased recovery following myocardial infarction

Hypothesis: We hypothesise that changes in hypoxia signalling pathways in the type 2 diabetic heart underpin the impaired recovery following myocardial infarction, and that an inflexibility of metabolism in response to hypoxia is the intermediary in these two processes. Therefore, the aim of this research is to determine whether direct activation of HIF signalling pathways or HIF's downstream metabolic targets may provide a mechanism to increase hypoxic tolerance of the diabetic heart, providing a route to improve recovery post-myocardial infarction.

Work to be undertaken: Our research focusses on the activation of hypoxic signalling pathways and the metabolic adaptation to hypoxia in the type 2 diabetic heart. Using a combination of *in vivo and ex vivo* techniques, including magnetic resonance imaging, isolated heart perfusion and mitochondrial respiration, the relationships between metabolism, hypoxia and cardiac function will be investigated in a rodent model of type 2 diabetes. In addition, we are one of a few groups in the world who have the expertise to investigate cardiac metabolism using dynamic nuclear polarisation (DNP), a ^{13}C spectroscopy technique that measures *in vivo* metabolic flux in the heart. DNP using ^{13}C-labelled metabolites will be used to investigate metabolism in the diabetic heart in real time.

We will be studying cardiac metabolic flexibility in the isolated perfused heart using radioisotopes following housing in chronic physiological hypoxia and in response to an acute hypoxic insult. Changes in response to hypoxia in type 2 diabetes will be investigated at the molecular level to identify the mechanisms underpinning these changes and open up avenues for targeted therapy. Pharmacological approaches that suppress fat metabolism and PPARα activation will be tested to determine if they improve *in vivo* metabolic adaptation prior to chronic hypoxia, and whether they improve recovery following myocardial infarction. Compounds that activate HIF signalling pathways have potential for improving hypoxic tolerance of the diabetic heart, and will be investigated. Exposing the diabetic heart to brief and repetitive burst of hypoxia (hypoxic pre-conditioning) prior to ischemia has been shown to offer some protection post-infarction, but to a lesser extent than in control hearts, therefore we will investigate why diabetes perturbs this acute beneficial response. Finally, using cell culture, molecular genetic approaches and metabolite supplementation of culture media will be used to investigate how the metabolic milieu of diabetes affects HIF signalling and the hypoxic response. This work has potential for translation into man, as initial trials of DNP in diabetic patients are just commencing within the group, making translation to clinical research rapid and achievable.

Recent relevant publications

1. **Heather LC** and Clarke K. Metabolism, Hypoxia and the Diabetic Heart. J Mol Cell Cardiol. Apr 50 (4): 598-605, 2011.
2. **Heather LC**, Pates KM, Atherton HJ, Cole MA, Glatz JFC, Griffin JL, Luiken, JJFP and Clarke K. Sarcolemmal fatty acid and glucose transporter translocation is associated with metabolic remodelling in the ischemic reperfused heart. Circulation: Heart Failure, Sep 1;6(5):1058-66, 2013.
3. Schroeder MA, Cochlin LE, **Heather LC**, Clarke K, Radda GK, and **Tyler DJ**. In vivo determination of pyruvate dehydrogenase activity in the heart using hyperpolarized carbon-13 magnetic resonance. Proc Natl Acad Sci USA. 106: 12051-6, 2008.
4. Mansor LS, Gonzalez E, Cole MA, **Tyler DJ**, Beeson, JH, Clarke K, Carr CA and **Heather LC**. Cardiac metabolism in a new rat model of type 2 diabetes using high-fat feeding and low dose streptozotocin. Cardiovasc Diabetol, Sep 24; 12(1):136, 2013.
5. **Heather LC**, Cole MA, Tan JJ, Ambrose LJA, Pope S, Abd-Jamil A, Carter EE, Dodd MS, Yeoh KK, Schofield CJ and Clarke K. Metabolic adaptation to chronic hypoxia in cardiac mitochondria. Basic Research in Cardiology April 107 (3):268, 2012.