



Hypoxia-Inducible Factor: a unifying mechanism underpinning multiple diabetes complications

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Project outline

Background: In response to ischaemia, the Hypoxia-Inducible Factor (HIF) transcription factor is activated, and drives a plethora of cellular adaptations that allow the cell to survive in the low oxygen (hypoxic) environment. HIF1 α regulates a large number of different processes, including angiogenesis, metabolism and cell death, and at last count was believed to regulate over 1000 genes. We have shown that type 2 diabetes impairs the activation of HIF1 α in response to ischemia in the heart. This impaired HIF activation occurs because of high levels of fatty acids that accumulate within the heart in diabetes. As a consequence, the downstream beneficial adaptive processes are blunted, resulting in impaired function of the heart in diabetes. However, ischemia is not unique to the heart, many tissues are similarly affected by ischaemia in diabetes, contributing to complications in multiple different organs. Similarly, all tissues are exposed to the high levels of circulating fatty acids in diabetes. Thus, impaired HIF activation and blunted adaptation to ischemia may underpin complications in multiple organs in diabetes.

Hypothesis: Abnormal HIF signalling occurs in multiple tissues in diabetes, mediated by high levels of circulating fatty acids, providing a systemic mechanism uniting multiple diabetes complications.

Work to be undertaken: Taking advantage of human cell systems, we will investigate the response to hypoxia using cells derived from the liver, skeletal muscle, kidney and heart. We will determine if fatty acids impair HIF signalling and the downstream beneficial response to hypoxia in these different cell types. We will investigate the mechanisms linking fatty acids with HIF signalling, by using metabolomics, CRISPR technology and single cell sequencing. In addition, these cells will be cultured with other components of the diabetic milieu (substrates, hormones, adipo/myokines), to screen whether factors other than fatty acids can also modulate the response to hypoxia. These human cell systems will allow us to determine if the mechanism linking diabetes to abnormal HIF signalling are conserved between different tissues. Key downstream mRNA changes will be further probed in biopsies obtained from healthy and diabetic individuals.

Rodent models of diabetes demonstrate evidence of fatty liver disease, nephropathy, cardiomyopathy and myopathy, therefore, liver, kidney, heart and skeletal muscle will be studied in type 2 diabetes. We will investigate the chronic effects of diabetes on HIF signalling at baseline, in response to hypoxia

and to ischemia in these tissues. Lipid lowering therapies will be utilised to determine if reducing fatty acid availability within these tissues restores HIF signalling and the response to ischaemia. We will investigate whether this slows the development of multiple diabetes complications. Ultimately, impaired HIF signalling may unite complications across multiple tissues in diabetes, and may provide a systemic therapeutic target for the pan-complications of diabetes.

Aims:

1. Determine whether HIF signalling and the response to hypoxia is impaired across multiple different tissues in diabetes.
2. Determine whether this is mediated by conserved mechanisms, driven by fatty acids.
3. Determine whether lipid lowering strategies have potential to restore HIF signalling and hypoxic adaptation in multiple complications associated with diabetes.

Supervisor's recent relevant publications:

1. Kerr M, Miller JJ, Thapa D, Stiewe S, Timm KN, Aparicio CNM, Scott I, Tyler DJ and **Heather LC**. Rescue of myocardial energetic dysfunction in diabetes through the correction of mitochondrial hyperacetylation by honokiol. *JCI Insight*, 2020, Sep 3; 5(17): e140326. PMID: 32879143
2. Faulkner A, Tamiato A, Cathery W, Rampin A, Caravaggi CM, Jover E, Allen S, Mellor H, Hauton D, **Heather LC**, Spinetti G and Madeddu P. Dimethyl-2-oxoglutarate improves redox balance and mitochondrial function in muscle pericytes of individuals with diabetes mellitus. *Diabetologia*, 2020, Oct; 63 (10): 2205-17. PMID: 32728894
3. Dodd MS, Sousa Fialho Md L, Montes Aparicio CN, Kerr M, Timm KN, Griffin JL, Luiken JJFP, Glatz J, Tyler DJ and **Heather LC**. Fatty acids prevent Hypoxia-inducible Factor 1 α signalling through decreased Succinate in Diabetes. *J Am Coll Cardiol: Basic Transl Sci*, 2018, 28;3(4):485-498. PMID: 30175272
4. Mansor LM, Mehta K, Aksentijevic D, Carr CA, Lund T, Cole MA, Le Page L, Sousa Fialho MdaL, Shattock MJ, Aasum E, Clarke K, Tyler DJ and **Heather LC**. Increased oxidative metabolism following hypoxia in the type 2 diabetic heart, despite normal hypoxia signalling and metabolic adaptation. *J Physiol*. 2016 Jan 15;594(2):307-20. PMID: 26574233
5. Mansor LM, Sousa Fialho M da L, Yea G, Coumans W, West JA, Kerr M, Carr CA, Luiken J, Glatz J, Evans RD, Griffin JL, Tyler DJ, Clarke K and **Heather LC**. Inhibition of sarcolemmal FAT/CD36 by sulfo-N-succinimidyl oleate rapidly corrects metabolism and restores function in the diabetic heart following hypoxia/reoxygenation. *Cardiovascular Research*, 2017 Jun 1;113(7):737-748. PMID: 28419197