GFPT1 deficiency is a novel cause of a dilated cardiomyopathy and is required for myocardial adaptation to chronic pressure-overload stress-induced heart failure

A.A. Nabeebaccus¹, S. Verma¹, N. Catibog¹, R. Thompson¹, A.M. Shah¹

¹King’s College London, London, United Kingdom of Great Britain & Northern Ireland

Funding Acknowledgements: Type of funding sources: Public Institution(s). Main funding source(s): British Heart Foundation and Professor Anthony Mellows Fellowship

Background: GFPT1 is the rate-limiting enzyme of a pathway called the hexosamine biosynthesis pathway (HBP) that turns fructose 6-phosphate derived from glucose into another monosaccharide called N-acetylglucosamine (GlcNAc). GlcNAc is an important substrate for modifying diverse cellular proteins on their serine and threonine residues termed O-GlcNAcylation often competing with phosphorylation and altering their activity or stability (Bond & Hanover; 2015). Increased GFPT1 activity is known to stimulate the cellular integrated stress response improving protein quality control and cell survival (Denzel et al 2014). In the heart, GFPT1 expression and O-GlcNAcylation increases in the early stages of chronic cardiac stress but the physiological role of GFPT1 in regulating heart function including its role during chronic stress remains unclear. Identifying molecular pathways that promote adaptive cardiac remodelling is a promising approach to discover novel therapies for heart failure.

Methods: Cardiomyocyte-specific GFPT1 knockout mice were generated to study the effects of GFPT1 deletion in hearts. Heart function was examined by echocardiography. HBP activity was quantified using Western blotting of O-GlcNAc-modified proteins. Abdominal aortic banding (AAB) was used to induce chronic pressure-overload heart failure.

Results: Homozygous GFPT1 KO mice spontaneously develop a dilated cardiomyopathy (DCM) with a 30% mortality rate (ejection fraction 32% compared with 62% for floxed controls and end diastolic volume 125 microL versus 60 microL; n=5-6 per group; p <0.05). Hearts showed reduced levels of total protein O-GlcNAcylation suggesting impaired hexosamine biosynthesis pathway activity. Heart function could be rescued by supplementing their diets with oral glucosamine bypassing GFPT1 to provide metabolites required for hexosamine biosynthesis and normalising O-GlcNAcylation (ejection fraction improved to 40% in KO with supplementation versus KO without; n=4-6 per group; p <0.05). Heterozygous KO mice do not develop a DCM but when subject to pressure-overload cardiac stress, develop worse heart failure with a 50% mortality rate over 9 weeks of pressure-overload (ejection fraction 43% in het KO versus 53% in floxed control; n= 3-6 per group; p = 0.0025).

Conclusion: Deficiency of GFPT1 is a novel cause of a spontaneous dilated cardiomyopathy. GFPT1 is required for physiological growth of the heart that may in part involve the O-GlcNAcylation of proteins. Partial GFPT1 deficiency is associated with adverse cardiac remodelling following pressure-overload stress. Increasing GFPT1 activity may be a key therapeutic target in developing novel heart failure treatments.