An integrative genetic and experimental study of hypertrophic heart disease

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Project outline

Background: Hypertrophic cardiomyopathy (HCM) is the most common genetic disorder of the heart and manifests as aberrant hypertrophy resulting in increased risk for heart failure (HF) and sudden cardiac death¹–². Mutations in sarcomere genes (e.g., MYH7, MYBPC3, and ACTC1), proteasome related gens (e.g., FHL1 and LAMP2) mitochondria-related genes PRKAG2 and GLA are believed to cause the disease³–⁴. Our recent study in HCM mouse models reveals a significant reduction of mitochondrial genes and proteins in mutant hearts. Thus, targeting mitochondria by restoring mitochondrial function may be a feasible therapeutic option for HCM. Work by us and others over the past decade has laid the groundwork for identifying the key roles of p21-activated kinases (PAKs), a group of serine/threonine protein kinases, in cardiac physiology and their therapeutic potential in cardiac hypertrophic disease and HF⁵–⁹, stimulating PAK signalling genetically or pharmacologically showed a beneficial effect in hypertrophic and HF mouse hearts.⁸–¹⁰. Therefore, PAKs are likely potential new druggable targets for defending against the development of cardiac hypertrophy, heart failure associated with HCM.

Hypothesis: Modulating mitochondrial oxidative stress signalling provides a novel therapeutic intervention for the development of HCM and other forms of cardiac hypertrophy

Aims: (1) Delineate mitochondrial metabolomic and redox signalling molecules and genes that are involved in the (causal) pathways of development and disease progression of HCM (2) Determine the role of modulating PAKs on mitochondrial oxidative stress as a therapeutic option for the management of HCM.

Description of the work to be undertaken:

Study #1: Delineate mitochondrial metabolomic and redox signalling molecules and genes that are involved in the (causal) pathways of development and disease progression of HCM, we will determine the role of these pathways in the risk of HCM and mortality using large-scale human omics data (GWAS, eQTL & pQTLs). We will evaluate the role of the PAK genes and their signalling pathway in relation to cardiac hypertrophy (HCM as a genetic model of cardiac hypertrophy) and heart failure. To achieve this, we will initially identify genetic associations shared between cardiac
hypertrophy and heart failure risk loci and quantitative traits which highlight disease related intermediate phenotypes, using genome-wide association studies (GWAS). We will use in-house tools/pipelines, such as fine mapping/colocalization, Mendelian randomisation and rare variant analysis in order to determine if PAK genes are the underlying causal genes for cardiac hypertrophy, contractility and heart failure risk. Finally, we aim to determine both the directionality for therapeutic modulation and potential adverse effects. Collectively, these approaches help to prioritise genetic support for PAK genes in relation to HCM and HF.

Study #2: We will establish the efficacy of PAK activators on HCM and mechanisms of action. Once the target tissue therapeutic concentration has been established, chronic treatment of the lead compound will be conducted in mouse models carrying human HCM mutation. The therapeutic efficacy of the compound and clinical endpoints will be assessed by echocardiography, MRI, histology and biomarker assessment. Plasma will be taken for compound concentration, histology on LV tissue sections will quantify the hypertrophic remodeling at the cardiomyocyte level and fibrosis measured by histology (e.g. Picrosirius Red staining) and real-time RT-PCR for expression of hypertrophic genes. We will determine the signalling mechanisms of activation of PAK on mitochondrial oxidative stress including key signalling molecules in regulating mitochondria function and its respiratory chain complex protein phosphorylation.

Contributions of Oxford and NNRCO supervisors:

Oxford Supervisors: HCM GWAS data and downstream bioinformatic and functional analyses to dissect common variant contributions to cardiac hypertrophy and contractility; HCM mouse model and expertise in HCM pathogenesis. PAK activators and their efficacy in HCM mouse model and action of mechanisms investigation. Oxford supervisors will be responsible for the daily supervision of the fellow.

NNRCO Supervisors: Joanna Howson’s group will provide expertise in statistical and computational analysis of genetic variants for cardiac hypertrophy and related traits including ID genetic associations for HF for PAK gene region. Subsequently determine if PAK genes play an underlying role in HF using advanced genetic tools and explore adverse effects and additional indications. Joanna Howson’s group will supervise the progress of the fellow in regular meetings with Oxford supervisors.

References:

Prof Hugh Watkins, Division of Cardiovascular Medicine Oxford


Associate Prof Ming Lei, Department of Pharmacology Oxford


