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REVOLUTIONISING MEDICINE - THE NEW FRONTIER

Inhibiting Cardiac Myeloperoxidase Alleviates the Relaxation Defect in Hypertrophic Cardiomyocytes

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Background

Hypertrophic cardiomyopathy (HCM) is characterised by cardiomyocyte hypertrophy and disarray, and myocardial stiffness due to interstitial fibrosis, which result in impaired left ventricular filling and diastolic dysfunction. The latter manifests as exercise intolerance, angina, and dyspnoea. There is currently no specific treatment for improving diastolic function in HCM. Here, we investigated whether myeloperoxidase (MPO) is expressed in cardiomyocytes and provides a novel therapeutic target for alleviating diastolic dysfunction in HCM.

Methodology

Human induced pluripotent stem cells (iPSCs) were generated from a healthy individual and two HCM patients (bearing *MYBPC3* [HCM-1] and *MYH7* [HCM-2] mutations) and differentiated into functional cardiomyocytes (iPSC-CMs), which were validated for clinical phenotypes. An MPO inhibitor, AZD5904, was tested for its ability to improve relaxation in HCM-CMs, and its mode of action was determined through biochemistry and imaging approaches. A *p* value of <0.05 was considered statistically significant.

Results

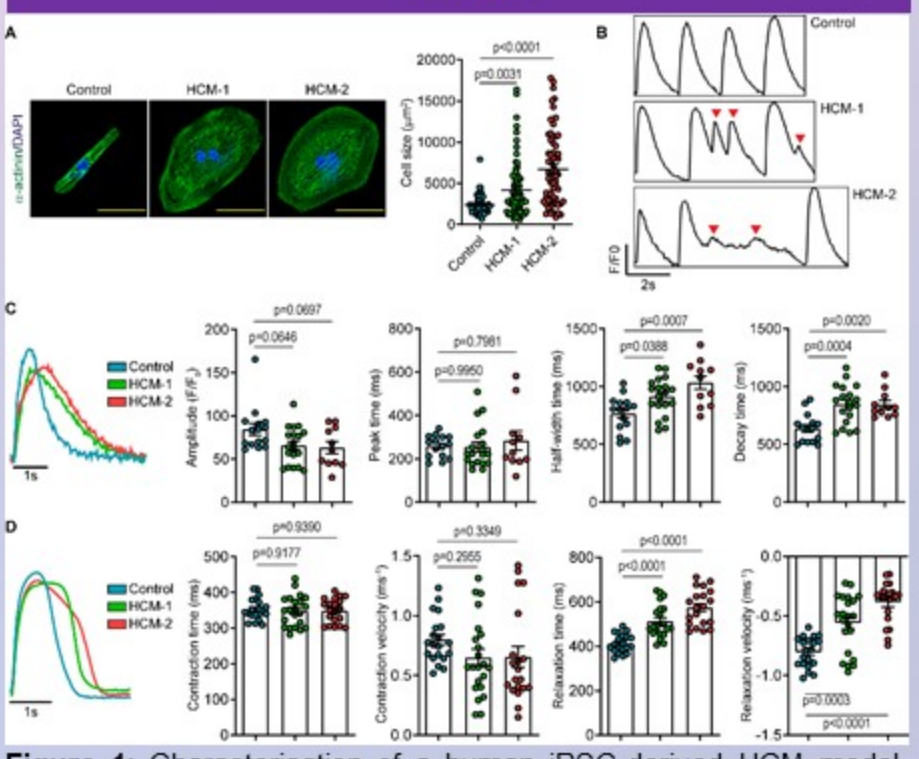

Figure 1: Characterisation of a human iPSC-derived HCM model. HCM-CMs underwent (**A**) cellular hypertrophy, (**B**) displayed arrhythmias (red arrowheads) upon electrical stimulation, (**C**) exhibited prolonged calcium re-uptake [indicated by increased half-width and decay times] and (**D**) relaxation impairment [indicated by increased relaxation time and decreased relaxation velocity].

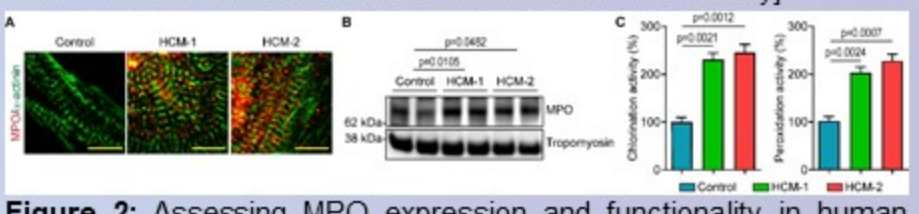

Figure 2: Assessing MPO expression and functionality in human iPSC-CMs. (**A-B**) MPO was expressed in control- and HCM-CMs, and was up-regulated in the latter. (**C**) Cardiomyocyte MPO was deemed functionally active as indicated by chlorination and peroxidation activity, which was increased in HCM-CMs.

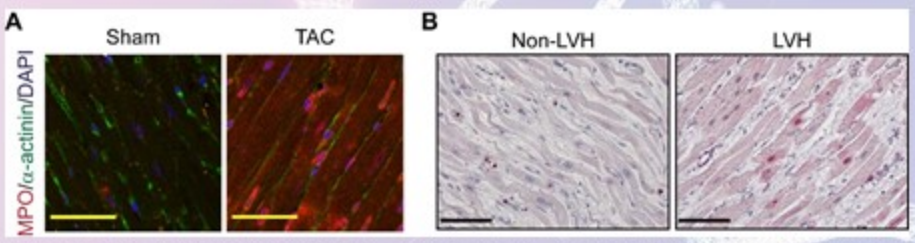

Figure 3: Assessing MPO expression in adult mice and human hearts. (**A**) MPO was up-regulated in mouse hearts subjected to thoracic aortic constriction (TAC) which resulted in pressure overload-induced left ventricular hypertrophy (LVH), and in (**B**) human hearts with LVH (stained pink).

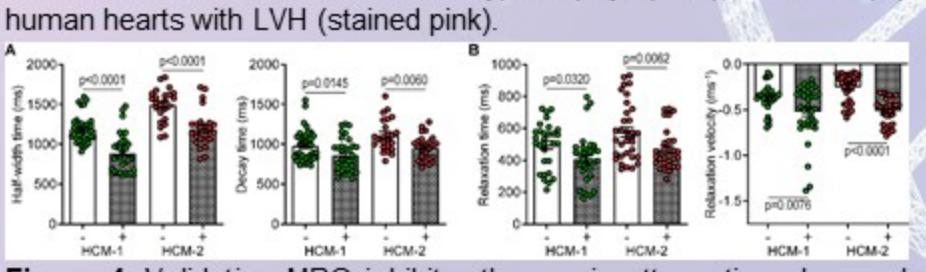

Figure 4: Validating MPO inhibitor therapy in attenuating abnormal calcium handling and relaxation impairment in HCM-CMs. Post AZD5904 treatment (shaded bars), HCM-CMs displayed (**A**) improved calcium re-uptake [indicated by decreased half-width and decay times], and (**B**) improved relaxation [indicated by decreased relaxation time and increased relaxation velocity].

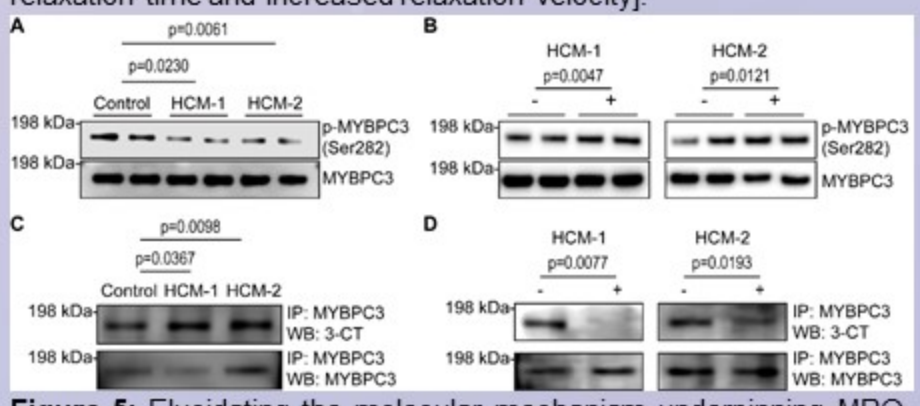

Figure 5: Elucidating the molecular mechanism underpinning MPO-mediated relaxation impairment. HCM-CMs contained (**A**) reduced phosphorylated cardiac myosin binding protein-C (MYBPC3) which (**B**) increased post AZD5904 treatment (+). This reduction in phosphorylation was associated with (**C**) increased MYBPC3 chlorotyrosine (3-CT) levels which (**D**) decreased post-treatment.

Conclusion & Clinical Significance

We show for the first time that MPO is present in and is up-regulated in cardiomyocytes derived from human iPSCs obtained from HCM patients, where it impairs cardiomyocyte relaxation by reducing phosphorylation of cardiac MYBPC3. Treatment with the MPO inhibitor, AZD5904, restored MYBPC3 phosphorylation and alleviated the relaxation defect, demonstrating cardiomyocyte MPO to be a novel therapeutic target for improving diastolic function in HCM, a treatment strategy which can be evaluated in HCM patients given that MPO inhibitors are already available for clinical testing.

Acknowledgments

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