Abstract: P95

**Heterozygous mutation of PMCA1 might serve a protective role in the heart following myocardial infarction**

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Introduction Coronary artery disease and its main consequence-myocardial infarction (MI) are the UK’s biggest killers. A large proportion of these deaths occur as a result of post-MI cardiac remodelling eventually leading to heart failure. Recent genome-wide association studies elucidated a potential link between the PMCA1 gene, atp2b1, and these diseases. Purpose PMCA1 has been associated with many of the key features of heart failure and I found that PMCA1 expression is significantly increased 1 week post-MI in mouse models. This study therefore aims to investigate the potential role of PMCA1 in the post-MI remodelling process.

Methods MI via permanent ligation of the LAD coronary artery, alongside a sham procedure was induced in either wild type (WT) or mice carrying a heterozygous mutation of the PMCA1 gene (PMCA1Ht). Occurrence of ischemia was confirmed by evaluation of plasma levels of cardiac troponin I (cTnI), conscious electrocardiography (ECG) and histologically. Post-surgery the animals were kept for either 1 or 4 weeks. Unconscious ECG and echocardiography were performed in vivo to assess cardiac function. To further characterise the cardiac response in vitro, histological and molecular analysis were performed at both time points.

Results LAD coronary artery ligation led to ST-segment elevation and a significant increase in the plasma cTnI levels 24 hours post-surgery in both WT and PMCA1Ht-MI mice. However, overall survival 4 weeks post-surgery was significantly lower in WT-MI mice when compared to PMCA1Ht-MI mice and both WT and PMCA1Ht-sham control groups. Interestingly, whilst both WT and PMCA1Ht-MI mice showed a significant deterioration in cardiac function 1 week post-surgery, there were differences seen in cardiac structure suggesting WT-MI mice experienced an exacerbated pathological remodelling characterised by development of eccentric hypertrophic response. For example, the WT-MI hearts had significantly bigger endocardial circumferences, left ventricular (LV) lumens and LV mass to body weight ratios when compared to their PMCA1Ht counterparts. Unconscious ECG revealed a significantly lower proportion of arrhythmic events among the PMCA1Ht-MI mice. In addition, a significant difference in infarct size was observed when WT-MI hearts were compared to their PMCA1Ht counterparts 1 week post-surgery. This was accompanied by an increased expression of Bax, Bad and p53 in the WT-MI mice and a significantly higher proportion of apoptotic cells in the WT-MI hearts when compared to PMCA1Ht-MI hearts.

Conclusion Heterozygous mutation of PMCA1 might serve a protective role in the heart post-MI. The protective mechanism most likely develops in the sub-acute post-operative phase, as an MI of similar extent is associated with higher mortality rates and an exacerbated pathological remodelling response in WT mice. Heterozygous mutation of PMCA1 might facilitate protection post-MI through modulation of apoptosis sub-acute post-MI.
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Introduction

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Purpose

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Methods

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