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Targeting calcium signaling as a novel therapeutic strategy for cardiac hypertrophy and failure

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Identification of novel regulators of cardiac hypertrophy is key in understanding the mechanisms of heart failure. The plasma membrane calcium ATPase 4 (PMCA4) is a ubiquitously expressed Ca2+ pump that is involved in regulating calcium signaling in the heart. Here we investigated a novel role of PMCA4 in controlling myocardial hypertrophy.

We subjected mice with a global knockout of PMCA4 (PMCA4-/-) to transverse aortic constriction (TAC) for 5 weeks. PMCA4-/- mice exhibited a significantly reduced hypertrophic response compared with wild type (WT) mice. This was accompanied by less fibrosis and a lower expression of hypertrophic marker BNP. However, cardiomyocyte specific knockout of PMCA4 did not show any protective effect following TAC prompting us to hypothesize that the protective effect might be due to PMCA4 ablation in fibroblasts. Microarray analysis revealed a ~100 folds upregulation of secreted frizzled-related protein 2 (sFRP2) in PMCA4-/- fibroblasts. sFRP2 is a potent inhibitor of the Wnt/β-catenin pathway. To unravel the clinical relevance of our findings we developed a specific pharmacological inhibitor of PMCA4, which had not previously been available. Using a modified colorimetric ATPase assay we screened a library of medically optimized drug-like molecules and identified Aurintricarboxylic acid (ATA) which has an IC50 of 150 nM for PMCA4. Injection of ATA in mice (5 mg/kg body weight/day ip) treated the pre-established TAC-induced hypertrophy.

Overall, our results demonstrated that specific inhibition of PMCA4 prevents and reverses pressure-overload hypertrophy making the plasma membrane calcium pump a potential target for the treatment of cardiac hypertrophy.

Biography

Tamer Mohamed has completed his Ph.D. at the age of 30 years from University of Manchester, UK and held various Postdoctoral training at the University of Manchester, University of Glasgow, and University of Gottingen. He is currently conducting a collaborative research program between the University of Manchester and the J. David Gladstone Research Institute (UCSF) to identify novel therapies for heart failure. He has published more than 15 papers in reputed journals in the past 10 years and has been awarded several awards including the prestigious Young Investigator Award at the European Society of Cardiology Congress in 2010.

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