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MOLECULAR MECHANISMS IMPLICATED IN INHIBITION OF ANGIOGENESIS MEDIATED BY THE CALCIUM TRANSPORTER PLASMA MEMBRANE CALCIUM ATPASE 4

Reshma Naomi¹, Satishkumar Kurusamy¹, Nicholas Stafford², Elizabeth J Cartwright², James Cotton³, Angel L Armesilla¹

¹Cardiovascular Molecular Pharmacology Laboratory, School of Pharmacy, Research Institute in Healthcare Science, Faculty of Science and Engineering, University of Wolverhampton, Wolverhampton, UK; ²Division of Cardiovascular Sciences, University of Manchester, Manchester, UK; ³Department of Cardiology, Heart and Lung Centre, New Cross Hospital, Wolverhampton, UK

INTRODUCTION: Ischaemic heart disease is a leading cause of death worldwide. Myocardial Infarction (MI) is caused by insufficient or no supply of oxygen to the heart due to narrowing of cardiac blood vessels. This may cause the death of cardiomyocytes, fibroblast and endothelial cells and lead to cardiac hypertrophy, and ultimately heart failure. Although current surgical treatments based on mechanical revascularisation like coronary bypass, grafting, or angioplasty exist, the chances of recurrent heart failure is higher in these patients. Emerging studies show that formation of new capillaries and blood vessels in the ischaemic heart is a promising therapeutical approach to circumvent the occluded blood supply. Unfortunately, the promising results obtained in animal pre-clinical models by delivery of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), into the ischaemic heart, have failed to be translated into clinical practice. Therefore, there is an urgent need to refine current approaches of therapeutic angiogenesis in order to improve neovascularization processes in the ischaemic heart. The recent identification from our laboratory of Plasma Membrane Calcium ATPase 4 (PMCA4) as a negative regulator of VEGF-driven angiogenesis has prompted us to hypothesise that targeting PMCA4-regulated pro-angiogenic signalling pathways can be used to increase cardiac revascularisation and restore blood flow to the myocardium at risk.

METHODS: As a first attempt to elucidate the pro-angiogenic signalling pathways regulated by PMCA4, we have evaluated in this work the expression of genes related to Notch signalling in primary endothelial cells lacking PMCA4. Expression of *PMCA4* in HUVEC was silenced by transfection with a siRNA specific for human PMCA4 (or non-target siRNA as control) and stimulated with VEGF. RNA isolated from control or PMCA4-silenced cells was used to screen an array of genes related to Notch signalling. Differences in gene expression were further validated by qPCR using TaqMan gene expression assays.

RESULTS: Our results demonstrate that siRNA-mediated *PMCA4* gene knockdown in primary endothelial cells strongly enhances the VEGF-induced upregulation of *DLL1* and *Hey1* gene expression. Lack of PMCA4 did not alter the expression of other important Notch ligands involved in angiogenesis regulation such as *DLL4*, demonstrating the specificity of our data. These data indicate that PMCA4 acts as a negative regulator of the VEGF-induced expression of *DLL1* and *Hey1*.

CONCLUSION: These results suggest that PMCA4 negatively regulates Notch signaling activation in endothelial cells stimulated by the pro-angiogenic factor VEGF.