The Plasma Membrane Calcium ATPase (PMCA4) as a regulator of inflammatory gene expression in the aortic endothelium

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Aims. The inflammatory response requires the participation of endothelial cell adhesion molecules to capture circulating leukocytes. The selectin family of adhesion molecules mediate the initial adhesive interactions. Firm adhesion and subsequent transendothelial migration involve immunoglobulin-like adhesion molecules such as VCAM-1. Thus, endothelial cells are recognised contributors to immune cell infiltration that is often involved in the initiation and progression of vascular disease.

Emerging evidence suggests that the PMCA4 calcium transporter regulates pro-inflammatory signal transduction. This work investigates PMCA4 in the endothelial response to inflammatory stress and characterises a role in leukocyte adhesion and trafficking.

Methods and Results: IL-1β downregulates the expression of PMCA4 in Aortic Endothelial Cells (hAoEC). The effect of PMCA4 silencing on endothelial gene expression was assessed by gene array screening and RNA-sequencing. The knockdown of PMCA4 induced the expression of cell adhesion molecules, Selectin P (*SELP*) and *SELL*. The IL-1β-induced expression of the metalloproteinases *ADAMTS-1* and *-4* was also enhanced. Ingenuity pathway analysis (IPA) revealed a role in immune cell trafficking with a propensity to develop aneurysms. Similarly, silencing enhanced the VEGF-induced *ADAMTS-1, VCAM-1* and *SELE* expression which was partially ablated using cyclosporin A. Consistent with the IPA, a significant decrease in PMCA4 mRNA expression was observed in abdominal aortic lesions from angiotensin II infused hypercholesterolaemic ApoE$^{-/-}$ mice.

Conclusion: The downregulation of PMCA4 is associated with a state of endothelial activation, indicated by the induction of cell adhesion molecules. Our findings suggest that the Ca^{2+} transporter is involved in the process of leukocyte adhesion and diapedesis.