Investigating SDF-1alpha signalling via CXCR7 receptor in the endothelium

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Topic(s):
Ischemia, Infarction, Cardioprotection

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S120

Funding Acknowledgements:
British Heart Foundation

Background: SDF-1a (Stromal-derived factor-1a) is a chemoattractant cytokine that can deliver both acute and chronic cardioprotective benefits to the heart(1). Although CXCR4 has been viewed as a main receptor for SDF-1a, a secondary receptor, CXCR7, has emerged as an important mediator of SDF-1a signaling. Despite being a G-protein coupled receptor it signals independently of G proteins, through an alternative, β-arrestin-mediated signalling pathway. CXCR7 is known to be expressed in the developing and adult heart. Interestingly, endothelial CXCR7 has been found to promote regeneration and ameliorate fibrosis in various tissues and organs. In addition, CXCR7 is deemed to be upregulated under hypoxic conditions; however, its exact role in ischaemic disease has yet to be determined. Therefore, we sought to examine the expression and function of CXCR7 in cardiovascular tissues, focusing on its potential as a novel cardioprotective strategy.

Methods: RNAscope in situ hybridization, RT-qPCR and flow cytometry were used to investigate expression and function of CXCR7 on endothelial cell lines, isolated mouse endothelial cells, and in the whole mouse heart. We examined CXCR7 expression in endothelial cell lines and downstream signaling pathways under basal and hypoxic conditions. Moreover, we also generated an inducible, endothelial-specific, CXCR7 knock-out mouse model to investigate the role of endothelial CXCR7 in the adult mouse.

Results: CXCR7 is expressed in the adult mouse heart and primary mouse cardiac endothelial cells. However, most of the CXCR7 protein in the endothelial cells investigated (MCEC and HUVEC), was found to be intracellular, with <30% cells exhibiting plasma-membrane labelling under basal conditions. In line with this expression profile, exposure to CXCR7 agonists failed to activate cardioprotective protein kinases ERK1/2 or PI3K/Akt. Deletion of CXCR7 in the endothelium of adult mice had no immediate phenotypic effects. These mice are currently being studied in order to investigate whether endothelial CXCR7 plays a role during myocardial infarction or in acute cardioprotection via SDF-1a.

Conclusions: CXCR7 is expressed in the vascular endothelium of the adult mouse, but its role in activating cardioprotective signalling pathways is unclear. Further experiments are needed to elucidate the role of CXCR7 in cardiac function and its potential as an effective cardioprotective strategy.