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A transcriptomic approach to elucidate new functions of Wt1 in the embryonic epicardium development

O. Martinez-Estrada[1]; V. Velecela[2]; A. Torres-Cano[1]; A. Garcia-Melero[1]; C. Muller[1]; M. Reina[1]; FX. Soriano[1]; N. Hastie[2]; FO. Martinez[3]
[1]University of Barcelona, Department of Cell Biology, Physiology and Immunology, Barcelona, Spain; [2]University of Edinburgh, MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, Edinburgh, United Kingdom; [3]University of Surrey, Department of Biochemical Science, Guildford, United Kingdom

The embryonic epicardium is an important source of cardiovascular precursor cells and paracrine factors required for adequate heart formation. Over the last ten years several studies have revealed different aspects of epicardial biology however virtually nothing is known about the molecular mechanisms that govern epicardial maturation. Wt1 gene expression is one of the main hallmarks of the embryonic epicardial signature. Interestingly it is also expressed de novo following heart damage. Given the enormous interest in this topic we decided to characterise the global expression profiles of Wt1 positive cells during different days of embryonic heart development using Wt1GFPKI mice as a model. We have identified the dynamic gene expression changes that characterise the several successive cellular transitions required for normal epicardial development. The integration of this program with the gene expression profile of epicardial cells isolated from Wt1KO mice has permitted the identification of novel functions for Wt1 in epicardial development. Here we demonstrated that epicardial maturation is characterised by a dynamic expression of BMP4 signalling. We observed that inhibition of this pathway leads to a series of changes in epicardial cells that resemble the phenotype of mature mesothelial cells. In addition we also demonstrated that the BMP4 pathway is tightly regulated by WT1. Understanding the molecular mechanisms that take place during heart morphogenesis could constitute the first step in the generation of therapeutic strategies for the treatment of cardiovascular diseases.

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Neuropilin 1 mediates epicardial activation and revascularisation of the regenerating zebrafish heart

C. Pellet-Many[1]; V. Lowe[2]; J. Sayers[1]; I. Zachary[1]
[1]University College London, Centre for Cardiovascular Biology and Medicine, London, United Kingdom; [2]Queen Mary University of London, William Harvey Research Institute, London, United Kingdom

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Background: Unlike adult mammals, zebrafish are able to naturally regenerate their heart. A key mechanism in zebrafish heart regeneration is the activation of the epicardium, leading to the establishment of a supporting scaffold for newly formed cardiomyocytes, angiogenesis and cytokine secretion. Neuropilins (NRPs) are cell surface co-receptors mediating functional signalling of kinase receptors for cytokines known to play critical roles in zebrafish heart regeneration, including Platelet-derived growth factor (PDGF), Vascular endothelial growth factor (VEGF), and Fibroblast growth factor (FGF).

Methods: and results: Herein, we investigated the role of neuropilin 1 in the response of the zebrafish heart to injury and its subsequent regeneration. Zebrafish have four neuropilin isoforms, nrp 1a, 1b, 2a and 2b. We found that all isoforms were upregulated following cardiac cryoinjury and were strongly expressed by the activated epicardium. A nrp1a mutant, coding for a truncated, non-functional protein, shows a significant delay in heart regeneration in comparison to wild type fish and displays a lasting collagen deposition. Importantly, epicardial cells from nrp1a mutant zebrafish heart explants display an impaired response to activation by cryoinjury and have a lower re-expression of the developmental gene Wilms' tumour 1. Moreover, the revascularisation of the heart is compromised: less new vessels are seen invading the injured region of the mutant hearts in comparison to wild-type.

Conclusion: These results identify a key role for Nrp1 in zebrafish heart regeneration, mediated through epicardial activation and migration and revascularisation of the damaged area of the heart.