



Crosstalk between PKR1 and miR-124 is crucial for EMT regulation of tc21+epicardial mesothelial cells during cardiac development and repair process

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JOURNAL ARTICLE

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Abstract

Background

The epicardial-mesothelial cells (EMCs) are essential regulators of cardiac growth and repairment process. The epicardial-to-mesenchymal transition (EMT) of epicardial fate determination are controlled by both cell autonomous and cardiomyocyte-originated mechanisms. Here, by using an in vitro and in vivo model of epicardial EMT, we investigated the role of miRNAs as regulators of these process and their potential targets.

Methods

EMT was induced in mice embryonic tcf21+EMCs through an angiogenic cytokine, prokineticin treatments. Cre-dependent tracing of TCF21-tm-iCRE-EMCs was utilized to abrogate prokineticin receptor-1 (PKR1) in mice epicardium. Human tcf21+ cardiac fibroblast (mainly originated from epicardial origin also utilized to study for their repairment signaling.

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exhibited $13 \pm 4\%$ embryonic lethality due to a disconnection of epicardial cells from compact layer, failed expansion of the sub-epicardial space, and disruption of heterotypic cell interaction between epicardium and myocardium. EMT-RT profiler and enrichment analysis revealed an impaired EMT in TCF21-tm-iCREPKR1-/- hearts. Ingenuity Pathway Analysis on the EMT molecular network (e.g., Snai1, Snai2, B-catenin, N-cadherin, vimentin), specific to cardiac development and defects revealed MiR-124 as a part of this network that was inversely associated and down-stream of PKR1 in cultured Tcf21+ cells. Furthermore, protein expression of SNAIL2 was significantly downregulated in TCF21-tm-iCREPKR1-/- hearts and cultured Tcf21+ cells upon treatment with mir124 mimic. The luciferase reporter assay showed that miR124 directly targeted the 3'-untranslated region of SNAIL2 in EMCs. In a counter experiment, PKR1 gene replacement or mir124 inhibitor was able to rescue the impaired EMT-genes, and an increase in apoptosis and impaired proliferation in epicardium of embryonic TCF21-tm-iCREPKR1-/- hearts. Importantly, miRNA mimic in cultured tcf21 cells maintained epithelial features in EMCs, and increased EMT-associated transcripts and traits, such as apoptosis. In contrast, MiR124 is involved in wound healing process in tcf21+human CFs and EMCs.

Conclusion

This study shows the importance of a crosstalk between PKR1 and miR-124 with respect to EMT regulation during cardiac development and repair. Controlling fibroblast-committed EMT and pathological fibrotic remodeling is of increasing interest within the field of regenerative tissue engineering and development of interventional strategies after cardiac injury.

Issue Section: [Cardiac Diseases](#)

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