Three embryonic cell lineages related with the epicardium show distinct developmental fates

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The embryonic epicardium generates a population of mesenchymal cells that contribute to the coronary vessels and the connective tissue of the adult heart. We have used murine cell-tracing models to compare the developmental fate of three different lineages related with the epicardium. Mice bearing R26R-EYFP reporters were crossed with mice expressing Cre-recombinase under control of the promoters of the cardiac troponin gene (cTnT), the Wilms tumor suppressor gene (Wt1), and the G2 enhancer of the GATA4 gene. Thus, we could trace, using confocal microscopy and flow cytometry, the lineage of the cardiac cells expressing Wt1, cTnT and GATA4 under control of the G2 enhancer, from midgestation to adults. Additionally we have studied a knockin Wt1-GFP reporter model to detect cells with Wt1 expression in the developing and adult heart.

During development, Wt1 is expressed in a major part of the proepicardium and epicardium, and also in some epicardial-derived mesenchymal cells, in part of the mesenchymal and coronary endothelial cells and also in a fraction of the cardiomyocytes. GATA4 expression is activated by the enhancer G2 in lateral mesoderm and pro/epicardium, but not in epicardial-derived cells, although most of these cells as well as some cardiomyocytes originate from a G2-GATA4 expressing lineage. cTnT is expressed in all the cardiomyocytes, but a part of the epicardial cells also derives from a cTnTCre-EYFP positive cell lineage.

The developmental fate of these linages reveals interesting differences, according to our preliminary results. For example, the G2-GATA4 cell linage contributes more than the Wt1 cell lineage to the coronary endothelium during development. However, both lineages are highly represented in the adult cardiac endothelium, suggesting postnatal expression of Wt1 in the coronary endothelium and incorporation of endothelial progenitor cells from bone marrow (where the G2-GATA4 reporter is active in 20% of hematopoietic stem cells). We have also observed a high contribution of both lineages to adult myocardium and we suggest some explanations for this observation.

Our results are revealing a substantial heterogeneity of the embryonic epicardial cells concerning to their potential of differentiation, and they also recommend caution when using a sole cell tracing model to study the fate of the epicardial-derived cells.