Characterisation of the human epicardium in the developing heart

The vertebrate heart is composed of three cell layers: an inner layer lining the heart chambers (atria and ventricles), the endocardium; an intermediate muscle layer, the myocardium; and an outer layer that envelops the myocardium, the epicardium. During pregnancy (embryogenesis), the epicardium contributes to different cardiovascular cell types and structures including coronary blood vessels, which provide vital oxygen and nourishment to the cardiac muscle (myocardium), via a process termed epithelial-to-mesenchymal transition (EMT). Specifically, epicardium-derived cells (EPDCs) respond to activating signals from the developing myocardium and change from a cobblestone-like morphology (epithelial) to a spindle-like morphology (mesenchymal), migrate into the underlying muscle and differentiate into coronary smooth muscle and endothelial cells; fibroblasts, which act as the scaffold of the heart; or cardiac muscle cells (cardiomyocytes). Towards the end of gestation, once the heart is fully formed, EPDCs progressively loose the capacity to undergo EMT and the epicardium becomes dormant, functioning mainly as a protective layer covering the myocardium.

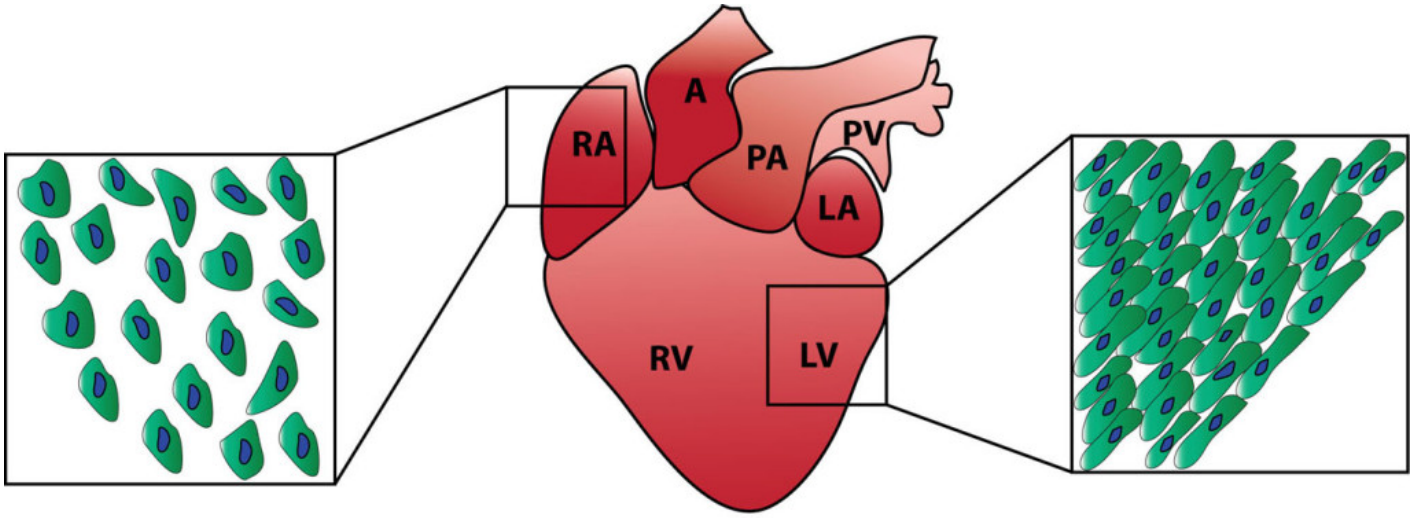

Fig. 1. Schematic representation of the differences in cell-cell alignment in the human developing atrial and ventricular epicardium. A, aorta; LA, left atrium; LA, left ventricle; PA, pulmonary artery; PV, pulmonary veins; RA, right atrium; RV, right ventricle.

In recent years, the notion of a dormant adult epicardium has been challenged by the observation that it can re-acquire embryonic properties after heart injury and may contribute to tissue repair and regeneration. This has elevated the status of the adult epicardium to a resident source of regenerative cells with potential to restore cardiac structure and function after a heart “attack” (or

myocardial infarction) and thus impact on the growing global problem of progression to heart failure following ischaemic heart disease. However, a major bottleneck preventing the development of epicardium-based therapies is the current lack of knowledge about epicardial development and function in the human heart. To-date, most of our understanding of epicardial EMT and its role in adult heart repair, is derived from studies using animal models, such as chicken, fish and mouse, and it is not clear whether these processes are conserved in humans.

Our study, therefore, aimed to validate and extend prior animal studies, by characterising the human epicardium during heart development from 4 to 11 weeks of pregnancy. Two important findings emerged; the first was that, similar to as described in mouse, the human epicardium is complex in structure, comprising more than a simple epithelial cell layer and secondly that the overlying epicardial structure and differentiation potential of EPDCs was distinct between the different cardiac chambers. In contrast to what has been observed in model organisms, the human ventricular epicardium exhibited a more organised and differentiated morphology (spindle-like) with polarised cell-cell alignment, whereas the atrial epicardium retained an embryonic-like morphology (cobblestone) and a more random cellular distribution. This was supported by different expression of protein markers between epicardium overlaying the ventricles versus the atria. Follow up studies will need to investigate whether these chamber-specific differences reflect different functions for the epicardium, dependent upon location in the developing heart, and whether the adult ventricular epicardium in particular has a distinct regenerative capacity given that heart attack predominantly targets the muscle of the left ventricle.

Publication

Characterisation of the human embryonic and foetal epicardium during heart development.
Risebro CA, Vieira JM, Klotz L, Riley PR
Development. 2015 Sep 22