Building the Right Ventricle

Robert G. Kelly

Abnormal development of the arterial pole of the heart underlies a significant fraction of congenital heart defects. Critical steps in arterial pole development are formation of the myocardial outflow tract (or conotruncal region) and its subsequent division into separate left and right ventricular outlets. Division of the cylindrical outflow tract is a complex morphogenetic process driven by cardiac neural crest cell influx and associated with rotation of the myocardial wall and cell death, ensuring alignment of the ascending aorta and pulmonary trunk with the left and right ventricles.1–3 The transient nature of the embryonic outflow tract raises existential but also clinically relevant questions as to the origin of this structure and its fate. In an article in this issue, Rana et al have addressed the latter in the developing right ventricle.4

Using scanning confocal microscopy, Rana et al monitored the rise and fall of the myocardial outflow tract. After a 4-fold increase in length to reach a maximum extension the myocardial outflow tract shortens 5-fold. At the same time a nonmyocardial component appears, giving rise to the ascending aorta and pulmonary trunk. Rana et al focused on the retraction phase by following the fate of clusters of DiI labeled cells in ovo at 2 developmental timepoints and concluded that the proximal outflow tract gives rise to a large part of the right ventricular free wall. Although the concept of ventricularisation of the proximal outflow tract (or conal absorption) to form the right ventricular outlet is not new,5–7 the extent to which myocardium initially in the outflow tract contributes to the trabeculated part of the free ventricular wall was unexpected. Concomitant processes, essential for outflow tract division, including broadening of the outflow tract, cell death and outflow tract rotation, were also monitored by Rana et al but are proposed to play less of a role in outflow tract shortening than incorporation into the right ventricular wall. These observations led Rana et al directly from issues of outflow tract fate to the question of how the right ventricle is built.

Classical experiments performed in mouse embryos by Viragh and Challice and in chick embryos by Maria Victoria De la Cruz and colleagues demonstrated that the rapidly elongating heart tube grows by recruitment of cells at the poles.6,8 Recent vital dye labeling and molecular analyses have revealed that myocardium at the poles accrues from a population of progenitor cells in pharyngeal mesoderm termed the second heart field which also give rise to smooth muscle at the base of the great arteries.9,10 Second heart field cells originate medially to cells of the cardiac crescent, or first heart field, from which the linear heart tube arises. The first and second heart fields thus correspond to different regions of a cellular continuum and a defining feature of the second heart field is differentiation delay. A number of genetic markers of the second heart field have been identified: the LIM homeodomain transcription factor Isll is required for heart tube extension and the fibroblast growth factor encoding genes Fgf10 and Fgf8 are expressed in cells of the second heart field contributing to the arterial pole of the heart; autocrine Fgf8 signaling is required for formation of the right ventricle and outflow tract.11–14 The component of the second heart field contributing to the arterial pole of the heart has been termed the anterior heart field and that subset giving rise to the distal outflow tract and contiguous arterial smooth muscle the secondary heart field.9,10

The right ventricle of the mouse heart is a second heart field derivative. This was initially suggested by the expression profile of an Fgf10 enhancer trap transgene in the second heart field, outflow tract and right ventricle.12 Subsequently, DiI labeling experiments in cultured mouse embryos showed that the linear heart tube gives rise to the left ventricle and that the right ventricle and outflow tract are progressively added to the arterial pole as the heart tube elongates and loops; analysis of the regional myocardial fate of second heart field explants supports this result.15 Lineage analyses using a retrovesporic marker to study the distribution of clonally related cardiomyocytes and Cre lineage tracing experiments using regulatory elements of second heart field genes Isl1, Tbx1, and Mef2c have further confirmed a second heart field origin of the right ventricle.11,16–18 Indeed the Mef2c experiments suggest that the entire ventricular septum is a second heart field derivative, at least as defined by expression of the regulatory element used.18 The left and right facing walls of the ventricular septum, however, share the gene expression profiles of the respective free ventricular walls.18,19 Mouse genetics has identified a cascade of transcription factors required for expansion and differentiation of right ventricular precursor cells. Isl1, together with Gata factors, Foxh1 and Nkx2.5, drives Mef2c expression in the second...
heart field, which activates BOP, encoding a histone methyltransferase, in turn activating expression of Hand2, encoding a basic helix-loop-helix factor; Tbx5 and Nkx2.5 regulation of Hand1 are required for development of the left ventricle (see review20). Coupling this molecular cascade with cell lineage studies and identifying the downstream targets that actually effect ventricular outgrowth are major challenges for the field.

The chick embryo provides a powerful experimental system to investigate the mechanisms underlying heart development. The work of De la Cruz and colleagues in the 1970s demonstrated the importance of in vivo manipulation to understand the dynamic nature of heart formation.6 The fact that Rana et al have revisited these issues underlines the continuing relevance of such approaches. De la Cruz and colleagues established that the definitive ventricles do not correspond to modules of the embryonic heart but rather are composite structures.6-21 The right and left ventricles are composed of embryologically distinct inflow, apical and outflow regions. In vivo labeling experiments using iron oxide particles suggested that, whereas conal absorption gives rise to the outlet of the right ventricle, the apical region of the right ventricle, distinguished by myocardial trabeculations, is derived from the anterior region of the linear heart tube. On face value this appears to be different to the situation in the mouse where the linear heart tube is thought to have a left ventricular fate. An important caveat is the short-lived nature of the linear heart tube in the mouse, suggesting differences in the relative timing of heart tube elongation and looping in the two species. Nevertheless, could different progenitor cell populations have been used to build the right ventricle during evolution of birds and mammals? Intriguingly, transcription of Hand1 and Hand2 and initial expression of Tbx5 are observed in both embryonic ventricles of the avian heart, though restricted to one ventricle in the mouse.22,23

The experimental data of Rana et al, however, suggest that the free wall of the avian right ventricle is constructed from cells in the proximal part of the embryonic outflow tract. Given that these proximal outflow tract cells are added to the elongating heart tube subsequent to the linear heart tube stage, the inference is that the right ventricular free wall of the chick heart is, as is the case in the mouse, a second heart field derivative. Supporting evidence comes from the work of Yelbuz et al who observed that impaired second heart field development in cardiac neural crest ablated embryos leads to right ventricular thinning.24 Compared with the data of De la Cruz and colleagues Rana et al reveal that there is a much more extensive contribution to the right ventricle from cells outside the linear heart tube. One possible explanation for this discrepancy lies in technical differences between iron oxide particle and Dil labeling, a hypothesis that can be tested by comparative cell labeling experiments. The new findings are a step toward integrating avian and mammalian data. Nevertheless, defining exactly how similar mouse and chick right ventricular formation are will require earlier labeling experiments in the chick and evaluation of the degree to which the murine right ventricular wall is derived from absorption of the proximal outflow tract rather than from a distinct right ventricular primordium. Finally, now that the extent of ventricularisation is apparent, the underlying cellular and molecular mechanisms can be investigated.

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None.

References


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