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Invited Review

New developments in the second heart field

Stéphane Zaffran [a,b], Robert G. Kelly [a,c,*]

[a] Aix Marseille University, Marseille, France
[b] Inserm UMRS910, Faculté de Médecine de la Timone, 27 Boulevard Jean Moulin, 13005 Marseille, France
[c] CNRS UMR7288, Developmental Biology Institute of Marseilles-Luminy, Aix Marseille University, Campus de Luminy Case 907, 13288 Marseille Cedex 9, France

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ABSTRACT

During cardiac looping the heart tube elongates by addition of progenitor cells from adjacent pharyngeal mesoderm to the arterial and venous poles. This cell population, termed the second heart field, was first identified ten years ago and many studies in the intervening decade have refined our understanding of how heart tube elongation takes place and identified signaling pathways that regulate proliferation and differentiation during progressive contribution of second heart field cells to the embryonic heart. It has also become apparent that defective second heart field development results in common congenital heart anomalies affecting both the conotruncal region and venous pole of the heart, including atrial and atrioventricular septal defects. In this review we focus on a series of recent papers that have identified new regulators of second heart field development, in particular the retinoic acid signaling pathway and HOX, SIX and EYA transcription factors. We also discuss new findings concerning the regulation of fibroblast growth factor signaling during second heart field deployment and studies that have implicated FGF10 and FGF3 in outflow tract development in addition to FGF8. Second heart field derived parts of the heart share common progenitor cells in pharyngeal mesoderm with craniofacial skeletal muscles and recent findings from xenopus, zebrafish and the protochordate Ciona intestinalis provide insights into the evolution of the second heart field during vertebrate radiation.

Contents

1. Introduction

The second heart field is a population of cardiac progenitor cells located in pharyngeal mesoderm that contributes to growth of the embryonic heart tube by addition of cells at the arterial and venous poles during looping morphogenesis. These cells ultimately contribute to the cardiac outflow tract, right ventricle and a major part of atrial myocardium, while the linear heart tube gives rise predominantly to the left ventricle (Buckingham et al., 2005; Dyer and Kirby, 2009). Impaired second heart field development has been shown in animal models to result in a spectrum of defects in cardiac morphogenesis. In the absence of second heart field addition, heart tube elongation and looping fails, resulting in early embryonic lethality (Cai et al., 2003; Park et al., 2006; Prall et al., 2007). Less severe perturbation of second

* Corresponding author at: CNRS UMR7288, Developmental Biology Institute of Marseilles-Luminy, Aix Marseille University, Campus de Luminy Case 907, 13288 Marseille Cedex 9, France. Tel.: +33 4 91269732; fax: +33 4 91269726.
E-mail address: Robert.Kelly@univ-amu.fr (R.G. Kelly).

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heart field development through conditional mutagenesis in the mouse, or ablation of subpopulations of progenitor cells in the chick, results in incomplete extension of the heart tube and alignment defects during cardiac septation. These include failure of the left ventricle to obtain an independent connection with the ascending aorta, critical for the separation of systemic and pulmonary circulation at birth (Park et al., 2006; Ward et al., 2005). Such defects correspond to common congenital heart defects seen in man, including conotruncal anomalies such as overriding aorta, tetralogy of Fallot and double outlet right ventricle (Moon, 2008). Venous pole anomalies, such as atrial and atrioventricular septal defects, have also been shown to result from defects in second heart field development (Goddeeris et al., 2008; Hoffmann et al., 2009). A detailed understanding of second heart field development is therefore an important objective in deciphering the etiology of congenital heart defects.

The relevance of the second heart field in congenital defects has spurred research into the mechanisms regulating the process of heart tube elongation. Second heart field cells are characterized by the defining properties of elevated proliferation and differentiation delay relative to cells that give rise to the linear heart tube (Dyer and Kirby, 2009; Rochais et al., 2009). A complex network of signaling inputs and transcriptional regulators has been uncovered that controls these properties during progressive heart tube elongation, including pro-proliferative Wnt, Hedgehog and FGF signals and pro-differentiation BMP and non-canonical Wnt signals. Collectively these signals define the dynamic niche of second heart field progenitor cells in the pharyngeal region, involving interactions with pharyngeal epithelia, neural crest derived mesenchyme and pharyngeal mesoderm itself (Rochais et al., 2009). In addition, transcription factors operative in pharyngeal mesoderm such as ISL1 and TBX1, encoded by the major candidate gene for DiGeorge syndrome, have been shown to play critical roles in integrating different signaling inputs during second heart field development (Cai et al., 2003; Chen et al., 2009; Laugwitz et al., 2008; Parisot et al., 2011). Signaling pathway regulation and transcriptional control of second heart field development have been extensively reviewed (Black, 2007; Buckingham et al., 2005; Dyer and Kirby, 2009; Evans et al., 2010; Rochais et al., 2009; Vincent and Buckingham, 2010). Our objective here is to give an update on a number of recently identified players that provide new insights into the control of second heart field development, of relevance for understanding the etiology of congenital heart defects. In particular we will focus on the retinoic acid signaling pathway and HOX, SIX and EYA transcription factors, together with new findings on the regulation of FGF signaling during heart tube extension. This will follow a brief review of the location of second heart field cells in pharyngeal mesoderm in the early embryo. In addition, we discuss new findings from comparative embryology that provide clues as to the origin of the second heart field during vertebrate evolution.

2. The second heart field is pharyngeal mesoderm

Retrospective clonal analysis has revealed that the second heart field and cells giving rise to the linear heart tube correspond to two distinct lineages of progenitor cells that separate from a pool of common progenitors at or prior to the time of gastrulation (Meilhac et al., 2004). As cardiac differentiation initiates in anterior lateral splanchnic mesoderm to generate the cardiac crescent, second heart field cells are situated in contiguous medial splanchnic mesoderm (Kelly et al., 2001; Abu-Issa and Kirby, 2008). Second heart field cells maintain this medial position as the linear heart tube forms in the ventral region of the embryo, forming the dorsal wall of the pericardial cavity where they are characterized by continued proliferation and differentiation delay relative to cells in the early heart tube. Breakdown of the dorsal mesocardium to create the transverse pericardial sinus isolates second heart field cells in the dorsal pericardial wall from the future left ventricular region, contiguity with the tube being now restricted to the arterial and venous poles (Fig. 1; Kelly and Buckingham, 2002). Subsequent addition of second heart field cells to the poles accompanies rightward looping and heart tube elongation. During this process, second heart field cells in the dorsal pericardial wall and underlying mesenchyme are closely apposed to cardiac neural crest cells in the pharyngeal region, prior to the addition of both cell populations to the heart tube.

Differences in gene expression between arterial and venous pole progenitor cells reveal that the second heart field is prepatterned (Galli et al., 2008; Snarr et al., 2007; Vincent and Buckingham, 2010). Indeed, the subset of progenitor cells contributing to the arterial pole identified ten years ago was termed the anterior heart field; however it rapidly became apparent that these cells were part of a larger population of ISL1 positive cardiac progenitor cells (Cai et al., 2003; Kelly et al., 2001; Mjaatvedt et al., 2001; Waldo et al., 2001). The prepattern can be broadly summarized as anterior medial splanchnic mesoderm contributing to the arterial pole of the heart tube and posterior medial splanchnic mesoderm to the venous pole. In this review we will focus on the component of the second heart field contributing to the arterial pole; venous pole contributions will be discussed elsewhere in this issue (Briggs et al., 2012). Further subdivisions have been documented in the anterior second heart field, reflecting spatial and temporal differences in the progenitor cell population. These subdivisions appear to define distinct progenitor cell populations giving rise to specific subregions of the definitive

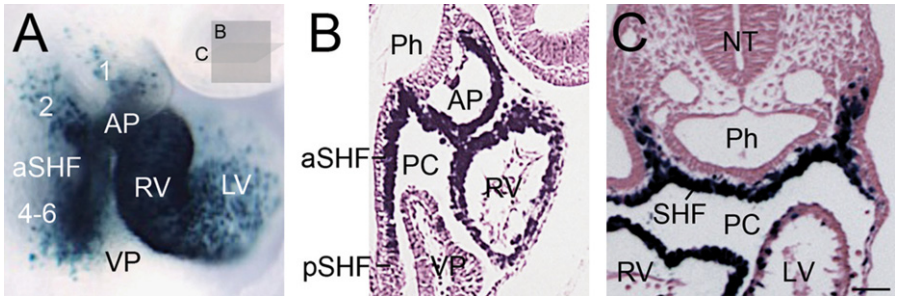

Fig. 1. The second heart field. Expression pattern of an *Fgf10* enhancer trap transgene in the anterior component of the murine second heart field at embryonic day 8.5 showing β-galactosidase expression in the right ventricle and arterial pole and contiguous pharyngeal mesoderm in a right lateral view (A) and in mid-sagittal (B) and transverse (C) sections. 1–6, branchial arches 1–6; AP, arterial pole; VP, venous pole; aSHF, anterior component of the second heart field; pSHF, posterior component of the second heart field; RV, right ventricle; LV, left ventricle; PC, pericardial cavity; Ph, pharynx; NT, neural tube. Scale bar: 50 μm.