Biochimica et Biophysica Acta 1833 (2013) 795–798

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Second heart field cardiac progenitor cells in the early mouse embryo ☆

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ARTICLE INFO

Article history:
Received 18 July 2012
Received in revised form 28 September 2012
Accepted 1 October 2012
Available online 7 October 2012

Keywords:
Heart development
Cardiac progenitor cell
Outflow tract

ABSTRACT

At the end of the first week of mouse gestation, cardiomyocyte differentiation initiates in the cardiac crescent to give rise to the linear heart tube. The heart tube subsequently elongates by addition of cardiac progenitor cells from adjacent pharyngeal mesoderm to the growing arterial and venous poles. These progenitor cells, termed the second heart field, originate in splanchnic mesoderm medial to cells of the cardiac crescent and are patterned into anterior and posterior domains adjacent to the arterial and venous poles of the heart, respectively. Perturbation of second heart field cell deployment results in a spectrum of congenital heart anomalies including conotruncal and atrial septal defects seen in human patients. Here, we briefly review current knowledge of how the properties of second heart field cells are controlled by a network of transcriptional regulators and intercellular signaling pathways. Focus will be on 1) the regulation of cardiac progenitor cell proliferation in pharyngeal mesoderm, 2) the control of progressive progenitor cell differentiation and 3) the patterning of cardiac progenitor cells in the dorsal pericardial wall. Coordination of these three processes in the early embryo drives progressive heart tube elongation during cardiac morphogenesis. This article is part of a Special Issue entitled: Cardiomyocyte Biology: Cardiac Pathways of Differentiation, Metabolism and Contraction.

1. Introduction

Morphogenesis of the embryonic heart occurs progressively between day 7 and day 10 of mouse gestation. During this period, the earliest cardiomyocytes differentiate in lateral anterior splanchnic mesoderm to form the cardiac crescent underlying the head folds [1]. The cardiac crescent gives rise to the linear heart tube, with a posterior venous pole and anterior arterial pole, that rapidly elongates and undergoes rightward looping to generate the embryonic heart tube by mid-gestation. Subsequently, cardiac septation takes place, generating the right and left atrial and ventricular chambers and converting the cylindrical myocardial outflow tract into the ascending aorta, outlet of the left ventricle, and the pulmonary trunk, outlet of the right ventricle. The process of heart tube extension is essential to generate the template for cardiac septation. Thus defects in either the septation process itself, or prior heart tube elongation, lead to failure to separate systemic and pulmonary circulatory systems, resulting in life-threatening congenital heart anomalies [2].

Heart tube elongation is driven by the addition of cardiac progenitor cells to the arterial and venous poles of the heart tube. These progenitor cells are situated in medial splanchnic pharyngeal mesoderm and have been termed the second heart field [3–5]. Here, we briefly discuss how a network of intercellular signals and transcriptional regulators control the properties of second heart field cells, including continued proliferation and delayed differentiation. In addition, we review new insights into how the progenitor cell field is patterned. Integration of these processes drives progressive heart tube elongation during cardiac morphogenesis.

2. The regulation of proliferation in the dorsal pericardial wall

Progressive restriction of mesodermal precursor cells to a myocardial fate initiates with expression of the transcriptional regulator Mesp1 in anterior mesoderm, followed by activation of a combinatorial code of cardiac transcription factor encoding genes including *Nkx2-5*, *Mef2c*, *Gata4* and *Baf60c* and rapid differentiation of the first cardiomyocytes in the cardiac crescent [1]. Cells expressing the transcription factor Isl1 in pharyngeal mesoderm medial to the cardiac crescent continue to proliferate and contribute to growth of the myocardium [6]. Initially, these cells contribute throughout the length of the forming heart tube, across the dorsal mesocardium. After breakdown of this structure and closure of the dorsal side of the heart

☆ This article is part of a Special Issue entitled: Cardiomyocyte Biology: Cardiac Pathways of Differentiation, Metabolism and Contraction.

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http://dx.doi.org/10.1016/j.bbamcr.2012.10.003

tube, cardiac progenitor cells in pharyngeal mesoderm are isolated in the dorsal pericardial wall and contribute to the growing heart tube by addition at the poles (Fig. 1). Studies from the Moorman group in the chick embryo and recently in the mouse have revealed extremely high rates of proliferation in the dorsal pericardial wall during heart tube extension [7,8]. In the chick embryo, the proliferative center is positioned caudally and cells have been estimated to move from this proliferative center towards the poles of the heart tube at a rate of 70 μm/h [7]. Upon differentiation, cell division rates dramatically drop, to be resumed during the process of cardiac chamber formation. In the mouse, the entire dorsal pericardial wall has been found to proliferate at a high rate, with cell division rates decreasing as cells differentiate at the poles of the heart tube [8].

Proliferation of cardiac progenitor cells in the dorsal pericardial wall appears to be driven by fibroblast growth factor (FGF) signaling (Fig. 2). FGF ligands implicated in second heart field development include Fgf3, Fgf8 and Fgf10 [9–12]. FGF ligands are expressed in pharyngeal mesoderm and adjacent pharyngeal epithelia including ventral pharyngeal endoderm and lateral ectoderm. Fgf8, within pharyngeal mesoderm, appears to be the major driver of heart tube extension, with compound mutant analysis revealing roles for Fgf3 and Fgf10. FGF ligand expression in the pharyngeal region is regulated by Wnt/β-catenin and Notch signaling [13–15]. Conditional loss-of-function analysis of these signaling pathways in the second heart field results in shortening of the cardiac outflow tract leading to subsequent arterial pole septation defects [9,14–16]. In addition, influx of neural crest cells into the caudal pharyngeal regions modulates local FGF signaling and leads to decreased proliferation in the second heart field, potentially acting as a proliferative brake during the terminal stages of heart tube elongation [17]. Wnt/β-catenin signaling has recently been shown to operate downstream of Notch in the regulation of progenitor cell differentiation and outflow tract morphogenesis [15]. Proximity to the underlying ventral pharyngeal endoderm is likely to be an essential factor in maintaining progenitor cell properties of second heart field cells in the dorsal pericardial wall. Ventral endoderm is a source of Hedgehog (Hh) signaling that also positively regulates proliferation in the dorsal pericardial wall of avian embryos and is required for second heart field deployment in the mouse [18,19]. Hh signaling has been shown to regulate progenitor cell proliferation in the posterior SHF in part through the transcription factor Tbx5, in a pathway essential for atrial septation [20].

Signal emission and reception during this process are regulated by a number of key transcription factors, including the LIM-homeodomain protein Isl1, that controls Wnt and FGF ligand gene expression, and the T-box transcription factor Tbx1, that regulates FGF ligand expression as well as FGF signal response [6,21,22]. *TBX1* is the major candidate gene for DiGeorge syndrome in man, associated with craniofacial and cardiovascular anomalies including conotruncal congenital heart

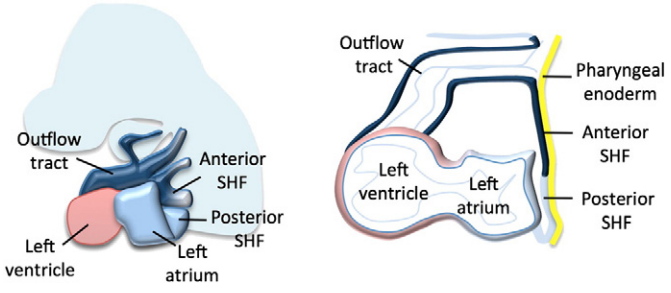

Fig. 1. Second heart field cardiac progenitor cells are situated in the dorsal wall of the pericardial cavity during heart tube extension. Cartoons showing a left lateral view (left) and mid-sagittal section (right) of the pharyngeal region of a mouse embryo at embryonic day 9.5. Note the localization of the anterior and posterior domains of the second heart field in the dorsal pericardial wall.
Adapted from [5].

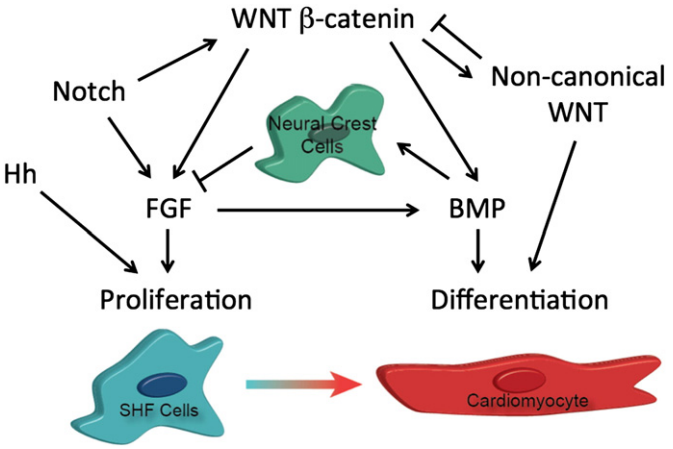

Fig. 2. Cartoon showing the major signaling pathways known to control proliferation and progressive differentiation of second heart field cardiac progenitor cells in the early embryo. See text for details.

defects [23]. In mouse embryos lacking Tbx1, the dorsal pericardial wall is hypoplastic due to decreased proliferation in pharyngeal mesoderm at day 8.5 of development [24]. The reduction in cardiac progenitor cells associated with decreased proliferation results in a short narrow outflow tract at midgestation [24,25,26]. The transcription factors Six1 and Eya1 appear to play an intermediate role in the activation of *Fgf8* downstream of Tbx1 [27]. *Hes1*, a target gene of the Notch signaling pathway, is expressed in the dorsal pericardial wall and is required for maximal progenitor cell proliferation [28]. Elevated expression of the CDK inhibitor p27Kip1 in *Hes1* null embryos suggests that Hes1 prevents precocious differentiation in the dorsal pericardial wall. Besides proliferation, cell survival is an important regulatory step in SHF development and the bHLH transcription factor Hand2 has been implicated in this process [29].

3. The control of progressive differentiation during heart tube elongation

As cells in the dorsal pericardial wall contribute to the poles of the heart tube, decreased proliferation coincides with the onset of myocardial differentiation. There appears to be a sharp transition between undifferentiated progenitor cells in the dorsal pericardial wall and differentiated cardiomyocytes in the outflow tract. At the arterial pole of the heart, differentiation is driven by BMP signaling from the distal outflow tract. BMP signaling promotes differentiation in part by antagonizing pro-proliferative FGF signals, potentially via activating BMP target genes such as *Msx1* in neural crest-derived cells (Fig. 2) [30,31]. BMP signaling also activates transcription of microRNAs that specifically target progenitor cell transcripts such as those encoding Isl1 and Tbx1 [32]. Proximal to the heart tube, cardiac progenitor cells initiate expression of genes encoding key cardiac transcription factors including Nkx2-5, Tbx20, Mef2c, Gata4 and Hand2, combinatorially required to activate the cardiomyogenic genetic program [33]. Loss of function of Nkx2-5 leads to overspecification of cardiac progenitor cells in pharyngeal mesoderm through upregulation of the chromatin regulator Jarid2 and BMP ligand gene expression [34,35]. Elevated BMP signaling in *Nkx2-5* null embryos, in turn, causes decreased proliferation in the second heart field. BMP signaling in the distal outflow tract region is downregulated in embryos lacking the T-box transcription factors Tbx2 and Tbx3, resulting in elevated FGF signaling proximal to the outflow tract [36]. These T-box factors, together with Tbx1, constitute a regulatory network upstream of the signaling axis controlling proliferation and differentiation of cardiac progenitor cells during heart tube extension. Loss of function of any two of these three genes results in severely altered BMP and FGF signaling, pharyngeal

hypoplasia and heart tube elongation defects [36]. Tbx1 itself plays an important role in regulating cardiac progenitor cell differentiation. In *Tbx1* mutant embryos, abnormal activation of differentiation markers is observed in the dorsal pericardial wall, while gain of Tbx1 function causes reduction of differentiation markers in the outflow tract [37]. Tbx1 has been shown to prevent progenitor cell differentiation by diverse molecular mechanisms, including 1) direct interaction with Smad1 causing inhibition of BMP target gene activation, 2) direct interaction with SRF, a transcription factor involved in cardiomyocyte differentiation that appears to be targeted for degradation in the presence of Tbx1, and 3) transcriptional repression of Mef2c, required to initiate myogenic differentiation [38,37,39]. Tbx1 thus occupies a nodal position in the positive regulation of proliferation and negative regulation of differentiation in the second heart field (Fig. 2). In contrast to Tbx1, Isl1 appears to be maintained in the distal outflow tract and to contribute to the differentiation program through activation of *Mef2c* [40]. Consistent with this finding, misexpression of Isl1 in differentiated cardiomyocytes does not block differentiation [41]. Isl1 expression is negatively regulated by continued Wnt/β-catenin signaling, that is in turn inhibited by pro-differentiation non-canonical Wnt ligands Wnt5a and Wnt11 [42]. *Wnt5a* has recently been identified as a Tbx1 target gene, dependent on interactions between Tbx1 and components of a chromatin remodeling complex, and loss of Tbx1 and Wnt5a causes severe hypoplasia of second heart field derived regions of the heart [43]. In addition to the above signaling pathways, continued activation of *Mef2c* in cardiac progenitor cells requires retinoic acid signaling, potentially mediated via Gata4 [44]. Retinoic acid signaling may therefore play a role in the maintenance of progenitor cell populations in the dorsal pericardial wall [44].

4. Patterning of cardiac progenitor cells in the dorsal pericardial wall

Cardiac progenitor cells in the dorsal pericardial wall are thus regulated by a complex interplay of intercellular signals and transcription factors, the integrated action of which promotes proliferation and controls progressive differentiation (Fig. 2). In addition, cardiac progenitor cells in the dorsal pericardial wall become patterned such that two populations of cells can be distinguished: the anterior second heart field adjacent to the arterial pole and the posterior second heart field adjacent to the venous pole (Fig. 1). Ultimately, descendants of these progenitor cell subpopulations give rise to right ventricular and outflow tract myocytes and atrial (including atrial septum) myocytes. Different genetic markers have been identified that distinguish these populations of progenitor cells and thus provide a read-out of anterior–posterior patterning in pharyngeal mesoderm. These include *Fgf10* and a *Mef2c* enhancer transgene expressed in the anterior second heart field, and *Tbx5* and *Osr1* expressed in the posterior second heart field (reviewed in [5]). Cre lineage analysis using the *Mef2c* enhancer suggests that cells at the border between the anterior and posterior domains contribute to both poles of the heart [45]. This is supported by analysis of the contribution of progenitor cells expressing anterior *Hox* genes to the developing heart [46]. *Hox* genes are important regulators of anterior–posterior positional information in the developing embryo; *Hoxb1-Cre* lineage labeled cells contribute to atrial myocardium and also to the inferior wall of the outflow tract, and ultimately to myocardium at the base of the outlet of the right ventricle, or sub-pulmonary myocardium [46]. Consistent with these observations, recent dil labeling experiments in the mouse have identified a contribution of posterior SHF cells to the arterial pole of the heart and retrospective clonal analysis has shown that venous pole and subpulmonary myocytes are clonally related [47,48]. Future subpulmonary myocardium appears to be particularly dependent on Tbx1 function, consistent with analysis of *Tbx1-Cre* lineage contributions to the inferior wall of the developing outflow tract [49,50]. Interestingly, failure of subpulmonary myocardial development in *Tbx1* null embryos is associated with abnormal expression of an *Fgf10* transgene in myocardium at the venous pole of the heart [25]. This observation suggests that Tbx1 plays a role not only in coordinating proliferation and differentiation delay, but also in patterning of cardiac progenitor cells in the dorsal pericardial wall.

5. Conclusions

A complex network of signals and transcription factors regulates the properties of cardiac progenitor cells in the early mouse embryo during heart tube elongation, an essential step in morphogenesis of the definitive heart. These events are integrated with patterning of cardiac progenitor cells along different axes: the medial–lateral axis, more medial pharyngeal mesodermal cells contributing to later growth of the heart tube, and the anterior–posterior axis, anterior progenitor cells contributing to the arterial pole and posterior progenitor cells to the venous pole and subpulmonary myocardium. Our understanding of how addition of progenitor cells to the heart tube is regulated remains nevertheless rudimentary and the mechanisms by which proliferation, differentiation and patterning are coordinated is the subject of extensive ongoing research. In addition, how cardiac progenitor cells behave during the dynamic process of heart tube elongation is unknown. Finally, the study of the maintenance and progressive differentiation of cardiac progenitor cells in the early embryo may provide insights into promoting myocardial repair of the damaged heart.

Acknowledgments

Supported by the Fondation pour la Récherche Médicale, the EU FP7 Collaborative Project CardioGeNet (Health-2007-B-223463) and the Netherlands Organization for Scientific Research (Mosaic grant 017.004.040).

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