Contemporary cardiogenesis: new insights into heart development

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Cardiac development is a dynamic process during which progressive specification and differentiation of cardiovascular progenitor cells are intrinsically linked to complex morphogenetic events conferring function to the forming heart.1,2 Cardiogenesis initiates in the mesoderm of the anterior lateral region of the early embryo in response to inductive signals from surrounding tissues. Differentiation of the first cardiomyocytes surrounding an endocardial tube is rapidly followed by formation of a linear heart tube that subsequently elongates, loops to the right and undergoes ballooning morphogenesis to generate distinct atrial and ventricular chambers. Cardiac valve development, septation, and establishment of the coronary vasculature and conduction system follow as the heart acquires its definitive form. Defects in these processes result in a wide range of congenital heart anomalies, including major life-threatening defects such as cardiac arrhythmias and failure to separate systemic and pulmonary circulatory systems. Furthermore, the onset of certain cardiac pathologies in the adult is associated with activation of embryonic transcriptional programmes. Thus, understanding cardiac development, in particular through the study of model organisms, is crucial for both basic and translational research. This is an exciting period in the field of heart development as new molecular, genetic, and cellular approaches accelerate our understanding of the origins and diversification of different cardiac cell lineages as well as the molecular mechanisms and cellular interactions underlying normal and pathological heart development. The collection of reviews in this spotlight issue of Cardiovascular Research aims to provide a broad introduction to aspects of heart development of clinical relevance in addition to highlighting the most recent achievements, as well as the current potential and challenges, in the field of cardiac development.

The first step in heart development is the specification of mesodermal progenitor cells to the cardiogenic lineage. Many reports have documented the critical roles of intercellular signalling pathways, including fibroblast growth factor, bone morphogenetic protein, Wnt, and Hedgehog pathways in specification into the cardiovascular lineage. However, how the output of multiple signalling pathways is integrated remains unclear. The review of Lopez-Sanchez and Garcia-Martinez3 provides a detailed update of the early events of cardiovascular specification, emphasizing the sequential changes in gene expression patterns and cellular interactions during formation of the linear heart tube. Better understanding of these early signalling events may contribute to efforts to stimulate repair of adult hearts by driving new cardiomyocyte differentiation after damage. Subsequent extension of the heart tube during cardiac looping occurs by progressive addition of progenitor cells at the cardiac poles from a population of progenitor cells termed the second heart field.4,5 While the linear heart tube contributes predominantly to the left ventricle, the second heart field contributes to the outflow tract and right ventricle at the arterial pole of the heart and to the right and left atrial chambers at the venous pole. Refinement of the second heart field model in the decade since the discovery of this cell population has led to important insights into early heart tube morphogenesis, cardiac evolution, and the aetiology of congenital heart defects. Here, Tzahor and Evans6 document recent evidence that second heart field progenitors arise in the pharyngeal mesoderm that also gives rise to craniofacial skeletal muscles, and they discuss the lineage, evolutionary, and clinical implications of this cardiocraniofacial developmental field.

Transcriptional regulation plays a central role in heart development including the control of cardiac patterning, regional differentiation and signal response, and mutations in cardiac transcription factors, such as NKX2.5, TBX5, TBX20, and GATA4, cause congenital heart defects.7 Three reviews in this issue deal with this topic. Transcriptional control of spatiotemporal patterns of gene expression involves the intersection of transcription factor activity with the regulation of chromatin structure. Takeuchi and colleagues8 provide a useful and comprehensive review of the importance of this intersection and the epigenetic control of gene expression in the developing heart. A better understanding of the epigenetic regulation of cardiac gene expression will contribute to optimizing reprogramming efforts in the generation of induced pluripotent stem cells and cardiomyocytes. Defects in members of the T-box family of transcription factors underlie major syndromes associated with cardiac defects such as DiGeorge and Holt-Oram syndromes. Greulich et al.9 review the multiple roles of this clinically important gene family and illustrate how T-box genes function in networks to positively and negatively regulate transcription and proliferation during patterning of the embryonic heart. The
homeodomain transcription factor Pitx2 plays a major role in establishing cardiac laterality and, through regulation of atrial identity, in defining the position of the sinoatrial node.10 Franco et al.11 discuss the dynamic expression of regulators of cardiac rhythm and action potential in the developing heart in the context of Pitx2. They review recent studies implicating this gene in the aetiology of atrial fibrillation and arrhythmias, based on genome-wide association studies identifying genetic risk variants in the vicinity of the PITX2 locus in patients with atrial fibrillation.12 Molecular advances in understanding the development and pathology of the conduction system of the heart are an important feature of this review collection. Miquerol et al.13 discuss embryological studies in different models that have defined the cellular lineages and regulatory events controlling establishment of the ventricular conduction system, including the network of fast conducting Purkinje fibres that coordinate ventricular contraction. The developmental origins of arrhythmias and the transcriptional circuitry underlying development of the central conduction system are reviewed by Postma et al.14 In addition, these authors discuss recent human genetic studies identifying common variation at regulatory loci modulating adult cardiac electrophysiology associated with susceptibility to arrhythmias.

The heart is functional from the earliest stages of cardiac tube formation, and the link between form and physiological function, both from developmental and evolutionary perspectives, is reviewed by Sedmera,15 who describes how feed-forward circuitry between morphogenesis and function drives conduction system and trabecular development. The maintenance of functional output of the heart as development proceeds is critically dependent on establishment of the coronary vasculature. Riley and Smart16 review recent controversial findings concerning the cellular origins of the different cell types that constitute coronary vessels, including the epicardium, sinus venosus, and endocardium, as well as studies addressing the maintenance, remodelling, and repair of coronary vasculature in the adult. Advances in this area are essential for understanding and treating coronary disease.

The present issue thus aims to provide a comprehensive overview of heart development from the early embryo to the fully functional pumping heart. Importantly, multiple interacting mechanisms are involved in discrete pathways during heart development, and therefore new, integrative, avenues should be explored. In this context, Sperling17 provides a thorough introduction to systems biology approaches to analyse the developing heart, discussing both experimental design and recent findings on transcriptional networks and system-wide approaches to the study of congenital heart disease. The interface between basic research in animal models and clinical studies has led to seminal papers identifying mutations associated with cardiac diseases such as cardiac hypertrophy and/or dilatation. To date, more than 400 point mutations have been reported,18 although, in most cases, functional consequences remain unexplored. Therefore, the development of experimental models that can accelerate dissection of genotype–phenotype relationships is fundamental. Bakkers19 highlights the suitability of the zebrafish model for studies of cardiovascular development and illustrates the pioneering work done using this simple and fast-developing experimental model to assess candidate genetic substrates linked to congenital heart disease.

In summary, the state-of-the-art reviews in this spotlight issue of Cardiovascular Research inform on pivotal aspects of cardiac development and their implications in cardiac disease. New questions and controversial issues are highlighted, for example those dealing with cardiac cell lineages, coronary vasculogenesis, or the notion that frequent cardiac pathophysiological conditions such as arrhythmias are ultimately coded by genetic embryonic defects and are thus congenital anomalies. Importantly, this issue illustrates the current excitement in this dynamic research field as well as the translational opportunities that will inevitably follow from a better understanding of how the heart develops.

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**References**