

## Editorial

# Model systems for the study of heart development and disease

The heart and its associated vasculature is the first organ system to form during fetal development in mammals. Heart formation involves a precise orchestration of events that culminate in cardiac cell specification, cell migration and interaction, complex morphogenetic movements, and specialized differentiation states. Heart development requires instructive communication between neighboring cells and the activation of transcription factor networks, which in turn regulate gene expression programs needed to produce integral heart-functioning proteins. When all aspects of the heart formation process are successful, a four-chambered beating organ is obtained, capable of circulating oxygenated and deoxygenated blood within systemic and pulmonary vasculature systems. When this vital process is perturbed, congenital heart anomalies can occur that threaten the viability of a fetus or compromise the health of a surviving individual. In fact, congenital heart disease is the most common type of birth defect observed in humans.

Several organisms have been used as experimental systems to decipher genetic and cellular events required for normal heart development. In this issue of *Seminars in Cell & Developmental Biology*, we bring together a collection of reviews on the importance of model systems for the study of heart development and disease. *Tao* and *Schulz* communicate what is known about heart development in *Drosophila*, which possesses a linear contractile organ that resembles the vertebrate heart at its transient linear tube stage. Based on this relatively simple structure and the productive use of genetic approaches, *Drosophila* has served as a powerful system to discover genes and their regulatory networks required for various aspects of heart tube formation. Similarly, the simple tunicate *Ciona intestinalis* has emerged as an important new system for the study of cardiac development. *Ciona* are members of our own phylum, the *Chordata*, and therefore share close evolutionary relationships with humans and all other vertebrates. Unlike vertebrates, however, *Ciona* have a small number of cells and a simple genome that lacks the genetic redundancy that characterizes the entire vertebrate clade. Thus this model organism is ideally suited for studies of gene function and regulatory networks in the absence of extensive redundancy. *Davidson* introduces *Ciona* as a model for the study of heart development and describes how conserved gene regulatory networks have been analyzed in this organism. *Schoenebeck* and *Yelon* discuss how a decade of research with the zebrafish system has resulted in an extensive collection of

mutations and the cloning of mutated genes that are critical regulators of cardiogenesis. They also describe sophisticated imaging techniques that allow for detailed mechanistic analyses of genes controlling cardiac specification, morphogenesis, and function. *Poss* advocates the use of the zebrafish model as a potential means to discover ways to stimulate the regenerative capacity of the human heart. Studies are reviewed on the cellular and molecular mechanisms controlling heart regeneration in zebrafish and how such findings may be of importance to cardiac biology and disease in humans. *Warkman* and *Krieg* elaborate on the frog *Xenopus* as a valuable model for studies on vertebrate heart development. Advantages include methodologies inherent to the *Xenopus* system, genome sequence advancements, and the ability to undertake both forward and reverse genetic approaches in this organism.

This issue continues with a group of reviews that focus on the use of the mouse and chick systems for genetic analyses of specification and chamber formation, as well as specialized cellular migration, differentiation, and signaling events needed to generate a functional four-chambered heart, which is characteristic of the amniotes. *Dunwoodie* provides an overview of heart development in the mouse and describes the origins of cardiac lineages and the signals that induce progenitor cells in the precardiac mesoderm to a cardiac fate. The formation of the working chamber myocardium, which comprises the majority of the adult heart mass, and the signals that control chamber formation, are discussed. The hearts of birds and mammals arise from at least two distinct sources of mesoderm, the classical primary or first heart field, and a newly described second heart field that gives rise to the right ventricle, outflow tract, and ventricle septum. *Black* provides an overview of the first and second heart fields and describes the transcription factor pathways that function in the development of the second heart field. *Xu* and *Baldini* provide an overview of heart development in the mouse with an emphasis on genetic tools available for gene function analyses and other targeted genome manipulations. A summary is presented on a regulatory network controlling secondary heart field cell lineages. *Smith* and *Bader* comment on the importance of intercellular signaling in cardiac development, specifically how signals emanating from both epicardial and endocardial sources are critical. The types of signaling pathways used in heart development, and the cellular consequences thereof, are elaborated. *Mikawa* and *Hurtado* describe the for-

mation of the cardiac conduction system, a specialized network of cells that regulate the rhythmic heartbeat. The cells of the cardiac conduction system arise from the transdifferentiation of myocytes into the highly specialized Purkinje fibers and cells of the sinoatrial and atrioventricular nodes. Importantly, endocardial cells play an essential role in the induction of ventricular myocytes into the Purkinje fiber network. *Hutson* and *Kirby* discuss the role of the cardiac neural crest in cardiac development and in congenital heart defects. Ablation of the cardiac neural crest in the chick results in conotruncal abnormalities and disrupted cardiac function, and the role of this essential cell lineage in reciprocal signaling interactions with other lineages is discussed.

The closing reviews address the analysis of acquired and congenital heart disease, also genome and stem cell technologies for the analysis of heart disease and risk, as well as the possibility of cardiac repair. *Wessells* and *Bodmer* review the performance and physiological changes that occur in the mammalian heart during aging. Incredibly, many of the age-dependent changes in the heart are conserved between mammals and flies, and the use of *Drosophila* as a model for cardiac aging is discussed. *Oka* and colleagues provide a summary of transcriptional regulators that work combinatorially to orchestrate cardiac development. Many of these transcription factors are re-employed in the adult heart during hypertrophic or cardiomyopathic disease conditions. *Ransom* and *Srivastava* provide an overview of congenital heart defects with an emphasis on normal and abnormal cardiac morphogenesis and several important genetic lesions known to result in structural defects in the heart. Importantly, most congenital heart defects occur sporadically, and the prospects for addressing these cases as complex genetic traits are discussed. *Visel* and co-workers discuss recent advances in comparative genomics and the use of bioinformatics to identify novel *cis*-regulatory elements. It is clear mutations in regulatory sequences contribute to human disease, but the extent of these mutations in cardiovascular disease is not yet fully appreciated. The use of comparative genomic technologies should aid our understanding of complex human diseases. Finally, *Evans* and colleagues

review the challenges associated with cardiac repair following myocardial infarction and ischemic injury, and highlight the possible use of cardiac stem cells for heart repair. The recent identification of progenitor cells, which are positive for the second heart field marker *Isl1* present in the adult myocardium, suggests the possibility these cells may serve as a critical source of progenitors for regeneration and repair.

In summary, these contributions provide up-to-date information on the signaling systems and gene regulatory networks required for normal heart development. They also address questions relevant to human health, those being what are the causes of certain cardiac pathologies and how can heart progenitor cells be manipulated to repair or regenerate the diseased organ. It is obvious the use of complementing animal systems has had a prolific effect on advancing knowledge in this field. It is also clear the continued use of such valued models will facilitate further seminal discoveries needed for a comprehensive understanding of the cellular, genetic, and molecular bases of heart development and disease.

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