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REVIEW

An overview of cardiac morphogenesis

Une anthologie du développement cardiaque normal

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Summary Accurate knowledge of normal cardiac development is essential for properly understanding the morphogenesis of congenital cardiac malformations that represent the most common congenital anomaly in newborns. The heart is the first organ to function during embryonic development and is fully formed at 8 weeks of gestation. Recent studies stemming from molecular genetics have allowed specification of the role of cellular precursors in the field of heart development. In this article we review the different steps of heart development, focusing on the processes of alignment and septation. We also show, as often as possible, the links between abnormalities of cardiac development and the main congenital heart defects. The development of animal models has permitted the unraveling of many mechanisms that potentially lead to cardiac malformations. A next step towards a better knowledge of cardiac development could be multiscale cardiac modelling.

Abbreviations: AV, Atrioventricular; FHF, First heart field; OT, Outflow tract; SHF, Second heart field; VSD, Ventricular septal defect; WG, Week(s) of gestation.

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MOTS CLÉS
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Résumé La connaissance du développement normal du cœur est essentielle pour la compréhension de la genèse des malformations cardiaques congénitales, lesquelles représentent l'anomalie congénitale la plus fréquente chez le nouveau-né. Le cœur est le premier organe à se former durant le développement de l'embryon et sa formation se termine vers la huitième semaine de grossesse. Les études récentes provenant de la génétique moléculaire ont permis de spécifier le rôle des précurseurs cellulaires dans le champ du développement cardiaque. Dans cet article, nous décrivons les différentes étapes du développement cardiaque en insistant sur les processus d'alignement et de septation. Nous montrons aussi souvent que possible les liens entre les anomalies du développement cardiaque et les principales malformations cardiaques congénitales. Le développement des modèles animaux a permis de révéler de nombreux mécanismes à l'origine des malformations cardiaques. La prochaine étape pour une meilleure compréhension du développement cardiaque pourrait être la modélisation cardiaque multi-niveaux.

Background

The first functioning organ in the embryo is the heart. It begins to beat from 2 weeks of gestation (WG) onwards (4 weeks of amenorrhea) and is fully formed at 8 WG. The development of the heart is highly conserved through evolution and follows the same general pattern in all vertebrates. Fusion of the primary heart tubes is followed by a rightward looping of the newly formed linear heart tube, differentiation of the chambers and valves, and development of the conduction system and coronary circulation.

Congenital heart defects represent the most common congenital anomaly in newborns, with a prevalence of 8—10 per 1000 births [1]. Delineating the normal sequence of heart development is essential for understanding the morphogenesis of congenital cardiac malformations. However, studying cardiac embryology is no easy task because it involves intricate structures and functions that evolve in space and time, and are closely interrelated. Moreover, understanding the developing heart requires a three-dimensional conceptualization that remains very complex for a human mind. In this article, the major processes involved in all stages of normal heart development are reviewed. Particular focus is given to those processes essential to the correct alignment and septation of cardiac structures. This provides a narrative through which congenital heart defects may be investigated, as sequential disruption of normal development.

The beginnings: formation of the primitive heart tube (days 15—21)

The heart starts to form at the beginning of the third WG. By the end of the second WG (day 15), the embryo is a flat disc made of two cell layers: the epiblast and the hypoblast. The primitive streak, which establishes the longitudinal axis of the embryo, appears at the median and caudal parts of the embryonic disc. At day 16, the epiblastic cells migrate towards the primitive streak and invaginate (gastrulation), leading to the differentiation of the embryo into three layers: ectoderm, mesoderm and endoderm.

The heart derives from the anterior mesoderm. At this stage, the mesodermal cells are still precardiac cells. However, the different axes of the embryo are already predetermined, particularly the left-right axis. Mesodermal cells differentiate into cardiac cells in response to induction signals from the endoderm, such as bone morphogenetic protein [2]. In the mesoderm, there are five transcription factors that are considered to be the primordial genes involved in cardiac development and these are highly conserved through the evolution of animal species: NKX2.5, Mef2, GATA, Tbx and Hand [3]. This ancestral genetic network controls the fate of the cardiac cells, the expression of protein-coding genes and cardiac morphogenesis. These genes regulate themselves and control their expression [3]. Precardiac cells are multipotent and differentiate into myocardial, endothelial and smooth muscle cells by a phenomenon called progressive lineage restriction [4]. Myocardial cells thus differentiate into chamber-specific myocytes (atrial and ventricular) and conduction cells [5].

Mesodermal precardiac cells migrate towards the cephalic pole of the embryo to form the cardiogenic crescent or first heart field (FHF). With cephalic then lateral inflexion of the embryo, the crescent migrates anteriorly and its two parts fuse on the midline to form the primitive linear heart tube (Fig. 1). This tube consists of an inner endothelial layer and an external myocardial layer, separated by cardiac jelly.

Tissue origins: the cardiac fields

The heart does not develop solely from cells of the primary linear heart tube. Very early in cardiac development, a second population of cardiac cells is present at the medial and ventral parts of the FHF [6]. This group of cells, called the second heart field (SHF), migrates medially and into the pharyngeal regions when the primary heart tube forms. SHF cells express the transcription factor islet-1 and differentiate into cardiac myocytes, smooth muscle cells and endothelial cells [7].

After the loop, the SHF is located within the pharyngeal mesoderm, at the inner curvature, between the outflow and inflow tracts. The role of the SHF is of major importance