Developmental anatomy of the heart: a tale of mice and man

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Wessels, Andy, and David Sedmera. Developmental anatomy of the heart: a tale of mice and man. Physiol Genomics 15: 165–176, 2003; 10.1152/physiolgenomics.00033.2003.—Because of the increasing availability of tools for genetic manipulation, the mouse has become the most popular animal model for studying normal and abnormal cardiac development. However, despite the enormous advances in mouse genetics, which have led to the production of numerous mutants with cardiac abnormalities resembling those seen in human congenital heart disease, relatively little comparative work has been published to demonstrate the similarities and differences in the developmental cardiac anatomy in both species. In this review we discuss some aspects of the comparative anatomy, with emphasis on the atrial anatomy, the valvuloseptal complex, and ventricular myocardial development. From the data presented it can be concluded that, apart from the obvious differences in size, the mouse and human heart are anatomically remarkably similar throughout development. The partitioning of the cardiac chambers (septation) follows the same sequence of events, while also the maturation of the cardiac valves and myocardium is quite similar in both species. The major anatomical differences are seen in the venous pole of the heart. We conclude that, taking note of the few anatomical “variations,” the use of the mouse as a model system for the human heart is warranted. Thus the analysis of mouse mutants with impaired septation will provide valuable information on cellular mechanisms involved in valvuloseptal morphogenesis (a process often disrupted in congenital heart disease), while the study of embryonic lethal mouse mutants that present with lack of compaction of ventricular trabeculae will ultimately provide clues on the etiology of this abnormality in humans.

mouse; human; cardiac development; embryo

A fast-increasing number of genetically modified mouse models with structural and functional abnormalities in the cardiovascular system undoubtedly will contribute to an improved understanding of molecular and morphological mechanisms that regulate human heart development in health and disease. It becomes more and more obvious, however, that for proper extrapolation of findings in the murine model systems it is crucial to have detailed knowledge of the specific anatomical/morphological details of developing and adult heart in mice and humans (2, 33, 35).

Before discussing some of the specific anatomical features in both species, it is important to consider the dimensions and properties of the full-grown hearts. The human heart weighs about 250–300 g and beats, on average, 60–70 times per minute. In contrast, the mouse heart weighs only about 0.2 g, and has a heart-beat of around 500–600 times per minute. Apart from their size, the most pronounced difference in external features between the adult mouse and human heart is found in their overall shape. The most important factor determining this shape is the anatomical context of the adult heart within in thoracic cavity. In human, the heart “rests” on the diaphragm. This is reflected in its more pyramidal shape and a flat dorsal (or inferior) surface. In comparison, the mouse heart, which in the four-legged mouse does not rest on the diaphragm and has more room to move freely within the pericardial cavity, has a more ellipsoidal (“rugby ball” shape). Another difference in external features is that in the human heart the atria are very prominent structures, whereas in the mouse heart the atrial chambers and their appendages are relatively small.

Developmentally, it is interesting to note that the gestational window during which the heart develops is quite different in the mouse and human. In the human...
it takes about 2 mo (from conception) for the heart to complete septation, followed by another 7 mo to further mature until the baby is born and the pulmonary circulation kicks in. In the mouse, however, it takes only 2 wk from the time of conception for cardiac septation to complete. After that, the mouse fetus has less than 1 wk of prenatal life before birth. Without going into any detail, it suffices to say that some of the developmental events that in the human are more or less completed at birth are still in progress in the neonatal mouse. There are several publications in literature in which the comparative developmental stages in mouse and human are listed (28, 39). These tables are helpful when studying developmental events. It is important to realize, however, that the staging protocol used to determine the developmental stages in mouse and human are listed (28, 39). These stages in mouse and human are listed (28, 39). These tables are helpful when studying developmental events. It is important to realize, however, that the staging protocol used to determine the developmental stage of mouse embryos is not always the same. For instance, when using the “vaginal plug” method, most investigators will mark the morning on which a sperm plug is observed as embryonic day 0.5 (ED0.5; Ref. 34). Others, however, will consider this ED1.0. This obviously can lead to confusion, and more importantly, misinterpretation of data. Thus, when describing and comparing developmental events, it is very important to be very explicit about the staging process when presenting developmental data. Moreover, when working with tissues generated by others (previously collected materials, existing collections, collaborations) where the exact staging protocol that has been followed is not known, it is equally important to point that out when reporting on data based on these tissues. As more and more clinical imaging techniques are now being adapted for use in studies on mouse models [e.g., MRI, ultrasound (10)], it is imperative to keep the issues mentioned above in mind. Thus, although the murine and human heart are anatomically very similar, it is crucial to be very careful when extrapolating information obtained by studying the mouse into the human context.

In this review we will first discuss some of the anatomical characteristics of the human and murine cardiovascular system. It will be demonstrated that these characteristics do not differ significantly. In the remainder of the review we will, therefore, focus on the general development of the cardiovascular system in both species by providing some insight in the mechanisms that lead to the formation of the functional, fully septated, four-chambered heart. As cardiac development is a very complex process, and it is beyond the scope of this review to discuss all the aspects that relate to this event, we will limit ourselves to the discussion of two topics that relate to congenital malformations frequently seen in humans. First, as many of the congenital heart defects found in the newborn human heart include abnormalities of the valvuloseptal complex, we will discuss some of the developmental events that lead to proper valvuloseptal morphogenesis. We will also, albeit less extensively, describe some of the events that are involved in myocardial differentiation and maturation.

**MATERIAL AND METHODS**

Most of the images of human and murine specimens used in the illustrations of this review were generated in the context of studies published previously (26, 27, 31, 37, 38, 40–43). Some of the scanning electron microscope (SEM) images are from the collection of late Tomas Pexieder. Details regarding tissue collection, preparation, histology, immunohistochemical staining procedures, characterization and properties of antibodies, and the preparation of SEM samples can be found in papers mentioned above and in the remainder of the text. As most of the photographs in the respective histological and SEM collections did not contain scale bars, we could unfortunately not provide scale bars for the figures in this paper.

**THE ANATOMY OF THE POSTNATAL HEART IN MOUSE AND HUMAN**

The basic anatomical features of the postnatal heart in the human and mouse are very similar (Fig. 1). Thus in both species the heart has four chambers; two atria, separated by an interatrial septum (IAS), and two ventricles, separated by an interventricular septum (IVS). In addition, located between the IAS and IVS there is a small “septal segment,” which, as a result of the offset of the atrioventricular (AV) valves, is known as the atrioventricular septum (AVS), as it is basically situated in between the subaortic outlet segment of the left ventricle from the right atrium. In the human, this AVS is a thin fibrous structure, known as the membranous septum. In the mouse this structure is relatively thick and mostly muscular, partly as a result of delayed delamination of the septal leaflet of the tricuspid valve (35), and partly as a result of myocardialization of the mesenchymal tissues (13). In the junction situated between the atria and ventricles, i.e., the AV junction (AVJ), we find two AV valves. The arrangement of the AV valves in mouse and human is comparable (35). In the left AVJ we find a mitral valve, which has two distinct leaflets (a bicuspid valve), whereas in the right AVJ a tricuspid valve is located, which has three distinct leaflets. In the human heart the valves are at their “tips” in continuity with very pronounced papillary muscles via relatively long and numerous tendinous chords (chorda tendininae; Fig. 1A). In the mouse these chordae are far less prominent (Fig. 2, A and C). The inner lining of the ventricles is characterized by the presence of numerous myocardial protrusions better known as trabeculae (trabeculae carneae). In the human, but not so in the mouse, there is a pronounced difference in the morphology of the trabeculae in the right vs. the left ventricle (35). In the left ventricle of the human heart, the trabeculae are relatively thin, whereas the trabeculae in the right ventricle have been described as being coarse. In addition to the trabeculation and the chordae tendineae, we can, within the apical cavity of the ventricles in both species, also discriminate thin, cordlike, structures that resemble the tendinous chords attached to the papillary muscle. Because of their tendonlike appearance, in older anatomy textbooks (e.g., Toldt-Hochstetter, Anatomischer Atlas, 1948) these structures are often
described as trabeculae tendineae. However, despite of this resemblance, these thin structures are not really tendons, but are actually extensions of the subendocardial ventricular network of the cardiac conduction system, and are therefore nowadays generally referred to as “false tendons” (Fig. 2D). As they consist almost exclusively of Purkinje cells (i.e., specialized myocytes of the conduction system) within a fibrous sheet, they can be used to obtain enriched preparations of conduction system related genes (20) or to perform physiological experiments (9). A slight morphological difference in the overall ventricular anatomy between mouse and human is found in the relative size and shape of the muscular ventricular septum and the position of the aortic outlet in relation to the IVS (cf. Figs. 1 and 2). In the human heart the muscular IVS is a massive structure, its thickness approaching or exceeding that of the left ventricular free wall (Fig. 1, A and B). The human muscular IVS has a very broad base just below the AV valve attachments. In the mouse, the IVS is not quite as massive and compact (Fig. 2, A and B), and at the base it gradually tapers toward the AV septum. The difference in the angle of the aortic outlet relative to the axis of the IVS is another remarkable feature (cf. Fig. 1B and Fig. 2A). The most prominent anatomical variations between the cardiovascular systems in mouse and human are probably those found in the venous components of the atria (Fig. 3). All of these variations reflect the species-specific differences in development of the venous tributaries connecting to the inferior atrial wall. Thus, whereas in the human heart the left atrium receives four pulmonary veins (37), in the mouse heart, the pulmonary veins join in a pulmonary confluence behind the left atrium (Fig. 3, G and H), which in turn empties via a single foramen into the dorsal wall of the left atrium (13, 36). Another anatomical difference in the atrial anatomy relates to the venous drainage into the right atrium. During the early stages of cardiac morphogenesis, in both the human and murine embryo, the left and right superior caval veins (LSCV and RSCV) initially drain into the sinus venosus. The sinus venosus itself opens via the sinoatrial foramen into the right atrium (36, 37). As development progresses, in the human heart the left caval vein regresses and the remaining proximal portion (with part of the left sinus horn) becomes the coronary sinus, the remnant of the LSCV becoming the so-called ligament of Marshall and oblique vein (Fig. 3, A–C). In the mouse, however, the LSCV does not regress and persists into postnatal life (Fig. 3H). In the human, persistent LSCV is considered a congenital malformation (incidence <1:100) frequently associated with other congenital malformations. It is likely that these differences in development of the venous tributaries into the atrial chambers are the underlying reasons for the relatively small size of the atrial components in the murine heart.

Valvuloseptal Development

The first step in cardiac development in the vertebrate heart involves the formation of two bilateral heart fields of precardiac mesoderm. These heart fields are situated on opposite sides of the embryonic midline (6, 24) and contain endocardial as well as myocardial precursor cells. As the embryo develops, the heart fields fuse, resulting in the formation of a primary heart tube. This tubular heart consists of a myocardial outer mantle with an endocardial inner lining. Between these two concentric epithelial cell layers, an acellular matrix is found which is generally referred to as the cardiac jelly (Fig. 4A). During cardiac looping, the cardiac jelly basically disappears from the future major chambers of the heart (i.e., atria and ventricles), whereas in the junction between the atria and ventricles, the atrioventricular junction (AVJ), as well as in the developing outflow tract (OFT), the cardiac jelly starts to accumulate. This results in the formation of
Fig. 2. Scanning electron micrographs (SEM) of the postnatal mouse heart. A and B: SEM images of the posterior (A) and anterior (B) half of an adult mouse heart. C: an enlargement of the boxed area in A, showing the relatively small leaflets of the murine mitral valve (cf. Fig. 1A). D: an enlargement of the boxed area in B and demonstrates some of the false tendons in the apical portion of the right ventricle. See legend to Fig. 1 for definitions of abbreviations.

Fig. 3. Development of the venous pole of the heart. A–C: a schematic representation of the development of the venous pole in human heart (modified from Fig. 7-10 in Human Embryology, William J. Larsen, Churchill Livingstone, 1993). D–F: immunohistochemically stained section of human embryos stained for α-MHC at, respectively, 5.5 (D), 7 (E), and 8 wk (F) of development. G: a histological section of a nonperfused neonatal mouse heart. H: a schematic representation of G (color coding according to A–C). A: in early development (~4–5 wk) the left and right horns of the sinus venosus communicate with the developing (unseptated) atrium. The left sinus horn (LSH) receives blood from several vessels including the left superior caval vein (LSCV), and the right sinus horn (RSH) is connected to the right superior caval vein (RSCV). As development progresses, the LSCV regresses (see B), resulting in the formation of the oblique vein (see C), with the remnant of the LSH becoming the coronary sinus (CS) emptying into the right atrium (RA; see C). The cartoon also illustrates how during human cardiac development the confluence of the pulmonary veins (PuV; see A) becomes incorporated into the left atrium (see B and C). D: at 5.5 wk of development the pulmonary veins connect to the LA through a single communication (note that the walls of the pulmonary veins are not myocardial at this point). At 7 wk the walls of the confluence of the pulmonary veins are becoming myocardial (E). The process of incorporation is nearly completed at 8 wk; the walls of the pulmonary veins are now myocardialized up to the pericardial reflection (arrows). The images in G and H demonstrate that in the mouse the pulmonary confluence does not become incorporated into the LA. Instead, the pulmonary veins drain into the LA via a single channel (arrow). G and H also illustrate that, unlike in the human, persisting LSCV is a normal anatomical situation in the postnatal mouse. ICV, inferior caval vein; PA, pulmonary artery; SCV, superior caval vein. See legends of previous figures for other abbreviations.
the endocardial cushion tissues in the AVJ (see Figs. 4, E–H, for examples in the mouse and Figs. 6, E and F for an example in the human) and OFT. An important developmental event in the subsequent maturation of these cushions is the endocardial epithelial-to-mesenchymal transformation (EMT; see Ref. 19). During this EMT, a subset of the endocardial cells delaminate from their epithelial context, transform, thereby assuming a mesenchymal phenotype, and start to migrate into the extracellular matrix of the cushions (Fig. 4B). This process, which is, at least partly, regulated by growth factors that are produced in the underlying myocardium (for a review, see Ref. 7), results in the mesenchymalization of the cushions. The endocardial cushion
tissues are extremely important for cardiac morphogenesis. They are the major “building blocks” of, and provide the “glue” for, virtually all of the septal structures in the heart (38). Dysmorphogenesis of the endocardial cushions and/or failure of proper fusion are generally thought to play a major role in the etiology of congenital heart disease in humans, for instance, in the setting of common AV defects. Gross abnormalities in formation of endocardial cushion tissue is observed in a variety of genetically modified mouse models such as the neurofibromin-1 (16), hyaluronan synthase-2 (Has2) (4), and RXR-α knockout mice (8) and is usually associated with fetal lethality. The spectrum of cushion abnormalities is very broad. In some genetically altered mice, hardly any cushion tissue is formed, whereas others develop hypercellularized and/or enlarged cushions. In many cases this appears to be a result of perturbed endocardial-to-mesenchymal transformation leading to either too many (16) or too few (14) endocardially derived cells in the cushions tissues. Although, in general, mice with cushion abnormalities manifest defects in both the AV as well as the OFT region, sometimes this is not the case and only the OFT cushions are affected (NFAT-C and SOX-4; Ref. 44). As indicated above, endocardial cushions develop in the AVJs as well as in the OFT. There are many similarities in the fate of endocardial cushions in AVJ and OFT. The cushion tissues in the AVJ contribute to the formation of AV septal structures and AV valves, and the cushion tissues in the OFT take part in septation of the OFT and in the formation of the semilunar valves of aorta and pulmonary artery (see, e.g., Ref. 23). In the next section we will discuss some of the aspects of AV development in a little more detail.

The AV junction. As briefly outlined above, the endocardial jelly in the AVJ forms the base material for the AV cushions (21, 38). Initially only two endocardial cushions develop which face each other on opposing sides of the common AV canal. These cushions, which we will refer to as the “major” AV cushions, are known as the inferior (also known as posteroinferior or dorsal) AV cushion and the superior (also known as ventral or anterosuperior) AV cushion (Fig. 4, B and E). The major AV cushions are the most prominent endocardial cushion tissues in the heart, and, as development proceeds, the leading edges of the cushions fuse (Fig. 4, C, F, and G), thereby separating the common AV canal into a left and right AV orifice (Fig. 4, C, D, and F). At this point, another set of, relatively small, endocardial cushions starts to develop in the lateral aspects of the AVJ. These cushions are generally referred to as the lateral cushions (Fig. 4, C and F). Interestingly, although the lateral cushions are very important for valvuloseptal morphogenesis, as they contribute to the formation of anterosuperior leaflet of the tricuspid valve (17) and the mural leaflet of the mitral valve, the mechanisms that are responsible for inducing their development and differentiation have thus far been very poorly studied.

Fate of the AV cushions. After fusion, the (major) AV cushion-derived tissue basically forms a large mesenchymal “bridge” spanning from the posterior wall of the AV canal to the anterior wall of the heart (37). Postero-inferiorly, this mesenchymal component is in continuity with the dorsal mesenchymal protrusion/dorsal mesocardium and the mesenchymal cap (also endocardial cushion material) that covers the leading edge of the forming primary interatrial septum (pIAS) septum (described in detail in Ref. 37). This mesenchymal cap is anterosuperiorly also in continuity with the remnant of the superior AVC cushion. The pIAS at this point has not closed the communication between left and right atrium yet, and as a result the mesenchymal bridge spans the primary atrial foramen (interatrial communication) between the dorsal and ventral aspects of the fused cushions. As development progresses, the mesenchymal cap on the primary septum and the fused cushions merge completely, thereby closing this primary foramen. The remodeling of this mesenchymal “crux of the heart,” which at this point basically consists of the fused major AV cushions and the mesenchymal cap of the pIAS and which is situated between the muscular IVS and the IAS (Fig. 5A), eventually leads to the formation of the membranous AV septum, the septal leaflet of the tricuspid valve (17), and the aortic leaflet of the mitral valve (Fig. 5B). Although the endocardial cushion tissues are important in the formation of the valves, AV valve morphogenesis also involves a number of myocardial remodeling steps (Fig. 6). Below, we have summarized (and simplified) the steps that are involved in the formation of the valves. It is important to realize that not all the leaflets of the AV valves develop exactly the same (see Refs. 17 and 21). However, in the context of this paper it suffices to describe the general principle, focusing on the fate of the lateral cushions. First, it is important to determine the relationship between the cushions and the adjacent tissues. The cushions have an upper (atrial) boundary

Fig. 4. Development of the atrioventricular cushions in the mouse. A–D: schematic of the development of the AV cushions in the mouse/human heart. A: the tubular heart stage. The outer myocardial layer and the inner endocardial cell layer sandwich the cardiac jelly (CJ). B: the stage in which the cardiac jelly has given rise to the formation of the major AV cushions. The cells within the subendocardial space indicate that endocardial-to-mesenchymal transformation has been initiated. C: the mesenchymalized major cushions are fusing, while at the lateral aspects of the AV canal the lateral AV cushions have formed. In D, the fusion has been completed, and a wedge of mesenchyme separates the left from the right AV orifice. The specimen shown in E is representative for the cartoon in B, F shows a specimen that correlates to C, while H demonstrates the fused mesenchymal tissues as depicted in D. G: a higher magnification of the boxed area in F, showing the fusion of the endocardial layers of the two major AV cushions. "cap," mesenchymal cap on leading edge of IAS; endo, endocardium; epi, epicardium; iAVC, inferior AV cushion; lAVC, left lateral AV cushion; OFT, outflow tract; sAVC, superior AV cushion; myo, myocardium; rLAVC, right lateral AV cushion. See legends of previous figures for other abbreviations.
and a lower (ventricular) boundary. The bulk of the cushion tissue is plastered against the AV junctional and ventricular myocardium (Fig. 6, A, E, and F). The first myocardial remodeling event leads to the interruption of the continuity between atrial and myocardial ventricular myocardium (Fig. 6, B and C) and is a result of the fusion between cushion-derived tissues and epicardially derived mesenchyme (38). Specifically, this process takes place at the lower end of the AV canal myocardium resulting in the incorporation of most of the AV canal myocardium into the lower rim of the atrial chambers (Fig. 6C). This process establishes the functional separation, and electrical insulation, between atrial and ventricular working myocardium (for a detailed description of this process see Refs. 18, 38, and 41). There is only one place where this separation does not take place, and that is where the specialized myocardium of the AV conduction axis (AV node and proximal His bundle) develops (38). These components of the AV conduction system (AVCS) relay the cardiac impulse from atria to ventricles. The second myocardial remodeling event that plays an important role in the formation of the freely moveable leaflets of the AV valves is myocardial delamination (17, 21). During this process the lower part of the AV cushions, with associated myocardial layer (Fig. 6, B, C, G, and H), separates from adjacent ventricular myocardium by a hitherto undetermined process. This results in the

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**Fig. 5.** Contributions of the major atrioventricular cushions to valvuloseptal morphogenesis in the human heart. These panels show two serial sections of a human heart at ~6 wk of development stained for the presence of atrial MHC (A) and ventricular MHC (B), as described before (42). A: this is how the mesenchymal tissues of the two major cushions and the mesenchymal cap on the IAS have fused to form the mesenchymal “crux” of the heart. B: this indicates how the structures indicated in A contribute to valvuloseptal morphogenesis in the AV junction (AVJ). epi, epicardially derived mesenchyme. See legends of previous figures for other abbreviations.

**Fig. 6.** Atrioventricular valve development in the embryonic human heart. A–D: schematic representations of AV valves in the developing human heart. E–N: a series of immunohistochemically stained sections of representative stages in this process. Sections shown in E, J, K, L, and N were stained with the “cushion-tissue antigen” antibody 249-9G9 (anti-CTA; Ref. 38), the sections in F, G, and I were stained with anti-ventricular MHC (43), the section in H (sister section to G) with anti-mesenchymal cell antigen (anti-MCA; Ref. 38), and the section in M (sister section to N) was stained with an antibody that recognizes the atrial as well as the ventricular isoform of MHC (38). The sections shown in E and F are from a heart at ~5 wk of development (38). G and H: sister sections from a 9-wk-old heart. I–K: sister sections from a heart at 12–13 wk of development. L–N: sister sections from a heart at 17 wk of development. The panels demonstrate (represented schematically in A–D) how during development the leaflets of the valves delaminate and detach from the myocardial wall. Initially, the leaflets contain a considerable amount of myocardium at their ventricular aspect (best seen in G), but as development progresses this myocardium gradually disappears (cf. G, I, and M). AV myo, atrioventricular myocardium. See legends of previous figures for other abbreviations.
formation of “immature” or “prevalvar” bilayered leaflets, with the inferior (or “ventricular”) layer consisting of myocardium and the superior (“atrial”) layer being cushion derived (Fig. 6, C and G). Toward the ventricular apex, these leaflets are attached to the ventricular walls and/or IVS through the developing papillary muscles (Fig. 6, G and H). The myocardium gradually disappears from the developing leaflets between 10 and 17 wk of development (Fig. 6, I–N). Interestingly, in the right AVJ of the chick heart, the initial development of the lateral AV leaflet resembles that of the mouse and human. However, instead of the regression of muscular tissue, leading to the formation of a fibrous leaflet, the mesenchymal tissue gets replaced by myocardium, resulting in the formation of a characteristic muscular flap valve in the right AVJ of the chick. Immunohistochemical studies indicate that the mechanism that is responsible for this process is myocardialization, i.e., the ingrowth of existing myocardium into flanking mesenchymal tissues. Experimental studies have revealed that this myocardialization process in the avian right AV valve can be disturbed by surgical left atrial ligation (25). This procedure leads to the formation of a (albeit dysmorphic) fibrous leaflet, reminiscent of the situation in mouse and human. In-depth studies of the molecular mechanisms involved in the molecular regulation of this myocardialization process might provide important clues regarding valvuloseptal morphogenesis in general, as myocardial-to-fibrous and fibrous-to-myocardial “transformations” are common steps in normal and perturbed cardiovascular development in the chick, mouse, and human heart (13, 29, 30).

**Myocardial Compaction**

Ventricular trabeculation starts to develop in the apical region of the ventricles soon after looping in both mouse and human. The trabeculation serves primarily as a means to increase myocardial oxygenation in absence of coronary circulation. At its peak prior to completion of ventricular septation, the trabeculae can form as much as 80% of the myocardial mass in the embryonic human heart (3) and provide most of the
ventricular wall thickness between ED11 and ED16 in the mouse. Concomitant with ventricular septation, the trabeculae start to compact at their base adjacent to the outer compact myocardium, adding substantially to its thickness (reviewed in Ref. 26). This process is fairly rapid (in mouse, between ED13 and ED14, in human between 10 and 12 wk; Ref. 26), coinciding with establishment of the coronary circulation. From ED16 in the mouse and the 4th mo of gestation in human, the compact layer forms most of the ventricular myocardium, although its structural complexity continues to develop (12). Noncompaction of the myocardium presents serious functional consequences for the heart. Several mouse null mutants present with a complete lack of compaction [e.g., RXR-α knockout mouse (8); see Fig. 7], which results in lethality around ED14 (reviewed in Ref. 26), emphasizing the importance of the compact myocardium for force generation in later fetal stages. In humans, ventricular noncompaction is usually localized. Although it can occur in isolation, it was found in association with heart failure and sudden cardiac death (32). Even if only a relatively small proportion of ventricular wall is affected, ventricular dynamics is perturbed (11). This condition can now be diagnosed by ultrasound and is classified as a distinct cardiomyopathy. There is a growing body of evidence that the epicardium and the epicardially derived cells play a crucial role in the development of the compact layer of the ventricular myocardial walls. Not only is the “thin-myocardium syndrome” observed in several mouse models with perturbed epicardial development [e.g., α4-integrin (45) and VCAM-1 (15) knockout mice], recent experimental studies in which epicardial development was perturbed in avian embryos also demonstrated inhibition of ventricular compaction (22). The mechanism(s) that are responsible for the regulation of ventricular myocardial differentiation, growth, and compaction are at present poorly understood, but it is to be expected that further analysis of mutant mice with “thin compact myocardium,” such as the RXR-α knockout mouse (5, 14), can provide clues on the cascade of genetically regulated events that lead to trabecular compaction and hence molecular etiology of this condition in humans.

CONCLUSIONS

In this review we have demonstrated that, given the considerable differences in cardiac size and heart rate, the cardiac anatomy in mouse and human is, with the exception of some small variations (mainly in the venous pole), remarkably similar. We have also shown that, at least within the context of the topics discussed, the developmental events that lead to the formation of the four-chambered heart are also very comparable. Consequently, the mouse can serve as a good model with which to study the human heart. The genetic modification of the murine genome is resulting in a growing numbers of mouse models presenting with cardiac malformations that are very reminiscent of the heart anomalies seen in patients with congenital heart disease. We conclude that mouse molecular genetics combined with detailed morphological assessment of generated cardiac malformations in the genetically modified mouse models will lead to important breakthroughs in the identification of a series of (candidate) genes, and the elucidation of pathways, involved in the etiology of human congenital heart disease.

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