REVIEW

Genetics and embryological mechanisms of congenital heart diseases

Génétique et mécanismes embryologiques des cardiopathies congénitales

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Summary Developmental genetics of congenital heart diseases has evolved from analysis of embryo sections towards molecular genetics of cardiac morphogenesis with a dynamic view of cardiac development. Lineage analysis, transgenic animal models and retrospective clonal analysis of the developing heart led to identification of different cardiac lineages and their respective roles. Genetics of congenital heart diseases has also changed from formal genetic analysis of familial recurrences or population based analysis to screening for mutations in candidates genes identified in animal models. Based on these new concepts, genetic counselling in congenital heart diseases is based on the mechanism of a given heart defect rather than on its anatomy. Using this approach, genetic heterogeneity or intrafamilial variability of a molecular anomaly can at least be partially explained. Close cooperation between molecular embryologists, pathologists involved in heart development and paediatric cardiologists is crucial for further increase of knowledge in the field of cardiac morphogenesis and genetics of cardiac defects.

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MOTS CLÉS
Cardiopathies congénitales ;

Résumé La connaissance de l’embryologie des cardiopathies congénitales a évolué depuis l’anatomie segmentaire sur coupes d’embryons. Aujourd’hui, nous disposons de réelles données d’embryologie moléculaire permettant d’avoir une vision dynamique du cœur en développement. L’utilisation de lignées de souris transgéniques, l’analyse clonale du cœur murin et les nouvelles études de lignage cellulaires ont permis l’identification de deux lignages

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cardiocytes contributing to the formation of the heart and to the specification of the resulting structures. This understanding is based on the discovery of genetic mutations and the analysis of familial recurrence. Nowadays, we also know that the development of the heart is a complex process involving the interactions of different cell lineages from the neural crest and the paraxial mesoderm. The use of molecular techniques has revolutionized our understanding of heart development.

**Structure of the primitive cardiac tube**

The cardiac tube, connected to the embryo by the dorsal cardiac mesoderm, has a triangular structure. It is the site of formation of the walls of the heart, the atria and the ventricles. The use of molecular biological techniques has allowed us to understand the mechanisms underlying the formation of the heart chambers.

**Formation of the efferent pathway**

Development of the efferent pathway is a complex phenomenon involving the cells of the neural crest and the paraxial mesoderm. The epithelial-mesenchymal transformation of the endocardium is a critical event that leads to the formation of the heart valves and the cardiac chambers. The use of molecular biology has allowed us to understand the mechanisms underlying this transformation.

**New concepts**

**The origins of the heart**

Data taken from the retrospective clonal mouse analysis shows that there are two cell lineages from the areas known as the cardiogenic and the myocardial lineages. The cardiogenic lineage forms the endocardial cushions, which contribute to the formation of the atria and the ventricles. The myocardial lineage contributes to the formation of the myocardium and the coronary vessels.

**How do these new concepts translate into practice?**

To understand how these new concepts translate into practice, it is important to consider the developmental events that occur at each stage of cardiac development. This understanding is essential for the development of new therapeutic strategies for congenital heart diseases.

**Genetic background and environment**

In the 1980s, the recurrence of congenital heart diseases within the same family and the different anatomical phenotypes in affected individuals led to Nora’s hypothesis of multifactorial inheritance of congenital heart diseases.

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**Table 1**

<table>
<thead>
<tr>
<th>Genetic background</th>
<th>Environmental factors</th>
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<tbody>
<tr>
<td>Genetic mutations</td>
<td>Environmental stress</td>
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<td>Familial recurrence</td>
<td>Chronic illness</td>
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**Conclusion**

The development of the heart is a complex process involving the interactions of different cell lineages. The use of molecular biology has allowed us to understand the mechanisms underlying this process, and has led to the development of new therapeutic strategies for congenital heart diseases.
The recurrence was explained by a risk related to "genetic background" and the environment shared within the same family [7].

### One molecular abnormality—one mechanism—one group of heterogeneous heart diseases

Experiences including the ablation of the neural crest cells in chick embryos, the use of quail-chick chimeric models and then the use of "genetic" ablation models of neural crest cells gave rise to the hypothesis that a disturbed embryonic mechanism in cardiac development could produce anatomically different cardiac phenotypes that were embryological related [8]. The example of heart disease observed in the deletion of chromosome 22q1.1 confirms this concept in humans. Indeed, the children with this cytogenetic abnormality have a heart disease that still involves the efferent pathway or the aortic arches [9]. This concept is expressed in the following way: one molecular abnormality—one mechanism—one group of heart diseases that is potentially heterogeneous anatomically but homogeneous in terms of embryological mechanism.

### Haemodynamic mechanisms of congenital heart diseases

The notion of a phenotype continuum is subtly different from the previous item. The example is that of obstructive heart diseases of the left side heart. Since Abraham Rudolph, it is commonly admitted that the development of heart chambers and resulting vessels is related to the pattern of the combined foetal blood flow that passes through them. Thus, a reduction in flow in the left heart may lead to coarc-tation, at one end of the spectrum, and to hypoplasia of the left heart, at the other end [10]. The idea that these heart diseases belonged to a same embryological group has been perfectly demonstrated through several arguments, namely recurrences of different severity within the same family, prenatal progression of obstructive left heart diseases, and finally identification of the same mutation in NOTCH1 in patients of the same family with a different cardiac phenotype [11]. Recently, a study conducted in zebrafish confirmed the relationship between the quality of the intracardiac blood flow and the future morphology of the heart [12].

### Mechanistic classification of congenital heart diseases

The segmental view of congenital heart diseases, while remaining essential during echocardiography analysis, simplifies the embryological and molecular approach. The use of a mechanistic classification proposed by Clark [13] has clarified things and many attitudes are today based on this: indication for screening of 22q1.1 the deletion in congenital heart diseases of the left side heart. Since Abraham Rudolph, it is commonly admitted that the development of heart chambers and resulting vessels is related to the pattern of the combined foetal blood flow that passes through them. Thus, a reduction in flow in the left heart may lead to coarc-tation, at one end of the spectrum, and to hypoplasia of the left heart, at the other end [10]. The idea that these heart diseases belonged to a same embryological group has been perfectly demonstrated through several arguments, namely recurrences of different severity within the same family, prenatal progression of obstructive left heart diseases, and finally identification of the same mutation in NOTCH1 in patients of the same family with a different cardiac phenotype [11]. Recently, a study conducted in zebrafish confirmed the relationship between the quality of the intracardiac blood flow and the future morphology of the heart [12].

### One heart disease—several genes

A great heterogeneity observed in each congenital heart disease group has made the situation more complex, but it has also enabled the analysis of phenotype and genotype relationships for these malformations. Again, the concept is still reflected in daily practice: differential phenotype of atrioventricular canals in relation to the karyotype or their anatomy thereby offering a quick indication of syndrome [14], complexity of the anatomy of pulmonary revascularisation in pulmonary atresia with interventricular communication in relation to their association with deletion

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**Table 1** Conceptual evolution of the genetics of congenital heart diseases.

<table>
<thead>
<tr>
<th>Concepts</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multifactorial inheritance</td>
<td>All heart diseases</td>
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<tr>
<td>Major role of the environment</td>
<td>Teratogenic: rubella, thalidomide</td>
</tr>
<tr>
<td>Unique mechanism of anatomically different</td>
<td>Deletion of chromosome 22q1.1 and conotruncal heart diseases</td>
</tr>
<tr>
<td>heart disease: one genetic abnormality—several heart diseases</td>
<td>Interatrial communication, atrioventricular canals, tetralogy of Fallot</td>
</tr>
<tr>
<td>Failure of strategies of partial phenocopy: genetically different syndrome and non-syndrome associated heart diseases</td>
<td>Interatrial communication and Holt-Oram syndrome (TBX5), tetralogy of Fallot and deletion of chromosome 22q1.1, atrioventricular canals and critical cardiac region of trisomy 21</td>
</tr>
<tr>
<td>Variability of intrafamilial expression for a same molecular abnormality</td>
<td>Familial heart diseases of deletion of chromosome 22q1.1</td>
</tr>
<tr>
<td>Genetic heterogeneity of congenital heart diseases: one malformation—several genes</td>
<td>Interatrial communication and mutations in NKX2.5, GATA4, MYH7</td>
</tr>
<tr>
<td>Heterogeneity of mechanisms for a same heart disease</td>
<td>Common arterial trunk: septation disease of the efferent pathway or of myocardium rotation from the base of the efferent pathway</td>
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<tr>
<td>Redefinition of the phenotype in relation to the mechanism</td>
<td>Double outlet right ventricles</td>
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Figure 1. One heart disease—several mechanisms—several genes. A malformation may originate from different embryology mechanisms. A common arterial trunk may result from a participation defect of progenitors from the second cardiac field and/or a migration defect of the neural crest cells and/or a rotation defect of the myocardium and/or a formation abnormality of the endocardial cushions. All these mechanisms are controlled by multiple genes (\textit{Pax3, Pitx2, Tbx1, Fgf8, Bmp, ...}). The result is a concept known as “one heart disease—several mechanisms—several genes”. In addition, impairment of these different mechanisms may generate a broad spectrum of heart diseases affecting the conotruncal region (TOF, IAA, DORV ...). CA T: common arterial trunk; DORV: double outlet right ventricle; EM: epithelio-mesenchymal; IAA: interrupted aortic arch; TGA: transposition of the great arteries; TOF: tetralogy of Fallot; TOF&P A: tetralogy of Fallot with pulmonary atresia; VSD: sub-arterial ventricular septal defect.

One heart disease—several mechanisms—several genes

Continuing with these new developments, the identification of a second cardiac field and the use of transgenic mice have helped to demonstrate that the transposition of the great vessels is a heart disease located in the conotruncal region, but not belonging to this group in the strict sense. Indeed, murine models and the identification in humans of laterality gene mutations in this heart disease are proof that there may be a segmental defect in the left—right laterality [6,17–19]. This would explain why this heart disease is not associated with 22q1.1 deletion, which is common in other types of conotruncal heart diseases. If we develop this concept further, we can see that other heart diseases involving the efferent pathway such as the double outlet right ventricles or even the common arterial trunk are observed in these animal models with laterality abnormalities. We may therefore conclude that these malformations may originate from different embryological mechanisms, namely a septation defect of the conotruncal region related to a neural crest abnormality, or a rotation and alignment defect of the efferent pathway on the ventricles corresponding to a segmental defect of laterality [6]. These observations lead to the concept of one heart disease—several mechanisms—several genes (Fig. 1). They explain the genetic heterogeneity of certain malformative heart diseases, not by chance but by the heterogeneity of mechanisms.

The “clinical translation” of this cognitive progress is significant. It can be summarised in several points. The \textit{description of the cardiac phenotype} must be anatomically accurate. It must use the segmental classification, while indicating every anatomical detail that would offer guidance on the mechanism of the heart disease. It is only at this price that a suitable genetic advice may be given.
Certain cardiac malformations are development sequences or algorithms with a highly complex anatomical outcome (cardiac isomerisms), but they are actually simple since all elements of the heart disease derive from a same morphogenetic defect. The role of the clinician is to recognise these sequences so as to describe each step. Certain heart diseases fall within a gravity spectrum such as coarctation of the aorta and hypoplastic left heart syndrome. Knowing how to look for staggered abnormalities of the left track in this group and understanding the progressive nature of these heart diseases that are dependent at least in part upon foetal cardiac flow is essential for screening prenatal and postnatal worsening conditions. Certain heart diseases may be considered as "lures" on the embryological front since they correspond to the anatomical expression of another abnormality. We can cite here the example of the coarctation associated with the persistent left upper vena cava which disturbs the mitral flow during the foetal life. The coarctation here is only the translation of a congenital abnormality to the systemic venous return and not an actual disease of the aorta.

Conclusion

We deliberately chose not to list the many genes known in congenital heart diseases. This type of information was recently published [20,21]. Far from being esoteric, knowledge of normal cardiac development and the mechanisms of congenital heart diseases are essential to daily practice, as much for the daily examination of heart diseases as for genetic counselling before birth or in the case of familial forms.

References