Genetic and Cellular Interaction During Cardiovascular Development Implicated in Congenital Heart Diseases

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Congenital heart disease (CHD) is the most common life-threatening congenital anomaly. CHD occurs due to defects in cardiovascular development, and the majority of CHDs are caused by a multifactorial inheritance mechanism, which refers to the interaction between genetic and environmental factors. During embryogenesis, the cardiovascular system is derived from at least four distinct cell lineages: the first heart field, second heart field, cardiac neural crest, and proepicardial organ. Understanding the genes involved in each lineage is essential to uncover the genomic architecture of CHD.

Therefore, we provide an overview of recent research progress using animal models and mutation analyses to better understand the molecular mechanisms and pathways linking cardiovascular development and CHD. For example, we highlight our recent work on genes encoding three isoforms of inositol 1,4,5-trisphosphate receptors (IP$_3$R1, 2, and 3) that regulate various vital and developmental processes, which have genetic redundancy during cardiovascular development. Specifically, IP$_3$R1 and 2 have redundant roles in the atrioventricular cushion derived from the first heart field lineage, whereas IP$_3$R1 and 3 exhibit redundancy in the right ventricle and the outflow tract derived from the second heart field lineage, respectively. Moreover, 22q11.2 deletion syndrome (22q11DS) is highly associated with CHD involving the outflow tract, characterized by defects of the cardiac neural crest lineage. However, our studies have shown that $\text{TBX1}$, a major genetic determinant of 22q11DS, was not expressed in the cardiac neural crest but rather in the second heart field, suggesting the importance of the cellular interaction between the cardiac neural crest and the second heart field. Comprehensive genetic analysis using the Japanese genome bank of CHD and mouse models revealed that a molecular regulatory network involving GATA6, FOXC1/2, TBX1, SEMA3C, and FGF8 was essential for reciprocal signaling between the cardiac neural crest and the second heart field during cardiovascular development. Elucidation of the genomic architecture of CHD using induced pluripotent stem cells and next-generation sequencing technology, in addition to genetically modified animal models and human mutation analyses, would facilitate the development of regenerative medicine and/or preventive medicine for CHD in the near future.

Keywords: heart field, neural crest, outflow tract, inositol trisphosphate receptor, $\text{TBX1}$, 22q11.2 deletion
INTRODUCTION

Congenital heart disease (CHD) is the most common life-threatening congenital anomaly that occurs in ~1% of live births. With advances in pediatric cardiology and cardiac surgery, most patients with CHD survive to adulthood; therefore, understanding the inheritance of CHD has become an increasingly critical clinical issue. Although insight gleaned from molecular genetics combined with developmental biology approaches has helped to uncover the detailed mechanisms of cardiovascular development, the genomic architecture of CHD remains largely unknown. We provide an overview of the progress that research has made till date in understanding the molecular mechanisms contributing to cardiovascular development, which in turn can provide new directions for research to uncover the inheritance of CHD and key susceptibility genes. We first provide general background into the etiology of CHD and the nature of cardiac development, highlighting our work on the role of inositol 1,4,5-trisphosphate receptors (IP$_3$Rs) in this process. In addition, we focus on recent research demonstrating a mechanistic link of the T-box-containing transcription factor (TBX1) with CHD in the context of 22q11.2 deletion syndrome (22q11DS). Finally, we highlight progress to date in understanding the general genetic architecture associated with CHD and the underlying regulatory mechanisms.

ETIOLOGY OF CHD

CHD is considered to occur due to defects in cardiovascular development during the first 6 weeks of gestation. At this stage, the heart and vessels develop from a simple primitive tube structure into a four-chambered heart with two great vessels. Genetic factors, including chromosomal abnormalities, are estimated to account for approximately 8% of CHD cases, with single-gene mutations accounting for about 5% of cases, and environmental factors, including maternal infections, systemic diseases, and administration of drugs, accounting for about 2% of CHD cases. However, the etiology of the remaining ~85% of CHDs is generally unknown, and is therefore attributed to so-called “multifactorial inheritance,” which refers to the interaction between certain genetic and environmental factors (1, 2). Recently, more genetic factors associated with CHD have been reported, including chromosomal abnormalities for 12% of cases, de novo copy number variants such as chromosomal microdeletion accounting for 15% of cases and de novo gene mutation affecting protein function in 10% of cases, and inherited gene mutations in 1.3% of cases (Tables 1, 2) (3–5). As shown in Tables 1, 2, candidate monogenic factors include many transcription factors and signal molecules that are essential for development of the heart and are responsible for multiple types of CHD. Genetic alterations of these factors are considered to disrupt the spatiotemporal regulation of complex three-dimensional heart structure. However, the interaction of multiple genetic and environmental factors is still considered as the primary etiology of the remaining majority of CHDs.

DEVELOPMENTAL ORIGINS OF THE CARDIOVASCULAR SYSTEM

Current knowledge in molecular embryology suggests that the cardiovascular system is derived from at least four distinct cell lineages, namely, the first heart field (FHF), second heart field (SHF), cardiac neural crest (CNC), and proepicardial organ (PEO) (Figure 1) (6–9). The FHF stands for the crescent shaped heart primordium that is derived from the anterior lateral plate mesoderm. The SHF cells (shown in red in Figure 1) form a primitive straight heart tube, consisting of an interior endocardial layer and an anterior myocardial layer along with cardiac jelly (extracellular matrix) layer in between. In addition to the FHF, the SHF (shown in blue in Figure 1) develops medially to the cardiac crescent from the splanchnic mesoderm and lies along the pharyngeal region dorsal to the primitive heart tube derived from the FHF (10–12). Eventually, the heart tube provides a scaffold and cardiac progenitor cells derived from the SHF migrate into both anterior and posterior ends of it. The heart tube proceeds looping rightward, the cells originally from the FHF finally form exclusively the left ventricle and part of the atria, whereas cells from the SHF migrated into the anterior portions of the heart tube form a large portion of the outflow tract of and the right ventricle. In addition, cells from the SHF cross the pharyngeal mesoderm into the posterior end of the heart tube contribute to a part of the atria. Meanwhile, CNC cells (shown in yellow in Figure 1), specifically developed in the dorsal region of the neural tube between the mid-otic placode and the third somite, migrate to the outflow tract where they give rise to the outflow tract septum to separate the truncus arteriosus into the aorta and pulmonary artery (13–15). CNC cells also migrate to pharyngeal arch arteries 3, 4, and 6, where they differentiate into smooth muscle cells of the great vessels. The neural crest cells from the preotic region of the neural tube contribute to the development of coronary arteries (16). The PEO (shown in green in Figure 1) is derived from the coelomic mesothelium that overlays the liver bud and gives rise to the epicardial layer over the heart (12). Some epicardial cells invade the subepicardial space through a process of epithelial–mesenchymal transformation, and contribute to the development of the coronary vessels and connective tissues (17, 18). To further uncover the genetic architecture of CHD, it is essential to adopt an approach for identifying the specific genes involved in each of these progenitor cell lineages, and to determine how their interaction regulates cardiovascular development.

IP$_3$Rs IN CARDIOVASCULAR DEVELOPMENT

We have investigated the roles of three isoforms of IP$_3$R (IP$_3$R1, 2, and 3) in cardiovascular development, demonstrating their genetic redundancy (Figure 2). In particular, IP$_3$R1 and 2 have redundant roles in the FHF-derived lineage, whereas IP$_3$R1 and 3 exhibit redundancy in SHF-derived lineages. IP$_3$Rs are intracellular Ca$^{2+}$-release channels, which are opened by...
### TABLE 1 | Genetic causes of non-syndromic congenital heart diseases.

| Gene          | Cardiovascular malformation                                      | Gene MIM  |
|---------------|------------------------------------------------------------------|-----------|
| **Transcription factors** |                                                                  |           |
| CITED2        | ASD, VSD, AS, PS, SIT, Dextrocardia, TGA, TOF, RVOTO, TAPVR      | 602937    |
| GATA4         | Dextrocardia, AVSD, DORV, TOF, BAV, CoA, AR, PAPVR, PDA, PS, ASD, VSD | 600576    |
| GATA5         | AVSD, DORV, LVNC, BAV, CoA                                       | 611496    |
| GATA6         | AVSD, TOF, PDA, PTA, PS, ASD, VSD                                 | 601656    |
| MED13L        | TGA                                                              | 608771    |
| NR2F2         | AVSD, AS, CoA, VSD, HLHS, TOF, DORV                              | 107773    |
| NKX2–5        | AS, AVSD, BAV, CoA, Dextrocardia, DORV, Ebstein’s anomaly, HTX, HLHS, IAA, LVNC, Mitral valve anomalies, PA, PAPVR, PDA, PS, SVAS, TA, TAPVR, TGA, TOF, PTA, VSD | 600584    |
| NKX2–6        | PTA                                                              | 611770    |
| TBX1          | DORV, TOF, IAA, PTA, VSD,                                          | 602054    |
| TBX2          | ASD, VSD, RVOTO                                                   | 600747    |
| TBX5          | AVSD, TOF, BAV, CoA, ASD, VSD                                    | 601620    |
| TBX20         | AVSD, VSD, MS, DCM, LVNC                                         | 606061    |
| MEF2C         | DORV                                                             | 606020    |
| ZFPM2/FOG2    | AVSD, DORV, TOF, VSD                                             | 603693    |
| FOXH1         | TOF, TGA, HTX, VSD                                               | 603621    |
| FOXO1         | TOF                                                              | 136533    |
| FOXP1         | AVSD, HLHS                                                       | 605515    |
| HAND1         | AVSD, DORV, HLHS, HLH, HRV, ASD, VSD                             | 602406    |
| HAND2         | TOF, LVNC, VSD                                                   | 602407    |
| MSX1          | BAV, CoA                                                         | 142983    |
| NIFATC1       | TOF, LVNC, BAV, CoA, TA, VSD                                     | 600489    |
| ETS1          | DORV, HLHS, ASD, VSD                                             | 164720    |
| JARID2        | Left-sided lesions                                               | 601594    |
| NR1D2         | AVSD                                                             | 602304    |
| RBPJ          | ILHS                                                             | 147183    |
| RX3           | PTA                                                              | 601337    |
| **Cell signaling and adhesion proteins** |                                                                  |           |
| ACVR1/ALK2    | HTX, AVSD, DORV, TGA, Left-sided lesions, ASD                    | 102576    |
| ACVR2B        | HTX, Dextrocardia, AVSD, DORV, TGA, HLHS, PS, Venous anomaly      | 602730    |
| BMPR1A        | AVSD                                                             | 601299    |
| BMPR2         | AVSD, PDA, PAPVR, AS, VSD                                        | 600799    |
| GDF1          | HTX, AVSD, DORV, TOG                                             | 602880    |
| SMAD6         | HLHS, AS, BAV, CoA                                               | 602931    |
| CRELD1        | ASD, AVSD                                                        | 607170    |
| GJA1          | HLHS, VSD, PA                                                    | 121014    |
| JAG1          | Aortic dextroposition, TOF, BAV, CoA, PS, VSD                    | 601920    |
| NOTCH1        | HTX, AVSD, TOF, HLNS, LVNC, BAV, CoA, AS, MS, VSD                | 190198    |
| NOTCH2        | AVSD, TOF, BAV, CoA, AS, VSD                                     | 600275    |
| PDGFRα        | TAPVR                                                            | 173490    |
| TAB2          | BAV, AS, TOF                                                     | 605101    |
| ADAM17        | AVSD                                                             | 603639    |
| HES1          | TGA                                                              | 139605    |
| HEY2          | AVSD                                                             | 604674    |
| APC           | BAV, CoA                                                         | 611731    |
| DCHS1         | LVNC, MVP                                                        | 603057    |
| DVL1          | LVNC, PDA                                                        | 601365    |
| EDN1          | TOF                                                              | 131240    |
| PCDHA9        | ILHS                                                             | 606315    |
| VEGFA         | TOF, PDA, PTA, AS, BAV, CoA, IAA, VSD                            | 192240    |
| **Structural proteins** |                                                                  |           |
| ACTC1         | ASD, HCM, DCM, LVNC                                              | 102540    |
| DCHS1         | MVP                                                              | 603057    |

(Continued)
TABLE 1 | Continued

| Gene | Cardiovascular malformation | Gene MIM |
|------|------------------------------|----------|
| ELN  | SVAS                         | 130160   |
| MYH6 | ASD, HCM, DCM                | 160710   |
| MYH7 | Ebstein’s anomaly, LVNC, HCM, DCM | 160760 |
| MYH11| PDA, TAA                     | 160745   |

IP3 binding to regulate various vital processes for diverse cell functions (19). As the modifications distinguishing the isoforms vary, such as phosphorylation sites, splicing sites, and associated molecules, each IP3R may play a distinct role as a signaling hub offering different trajectories of cell signaling (20). In cardiovascular development, expression of IP3R1 was detectably higher in the atrial than in the ventricular myocardium, IP3R2 was mainly expressed in the trabecular layer of the ventricular myocardium, and IP3R3 was uniformly expressed in the atrial and ventricular myocardia from embryonic day 9.5. These dynamic and complementary expression patterns of each subtype of IP3R suggest their specific and/or redundant functions during the development of the heart. Although single subtype-knockout mice showed no developmental disorders and could survive after birth, IP3R1-IP3R2 double-knockout mice died in utero with developmental defects of the ventricular myocardium and atrioventricular canal of the heart, along with impaired Ca2+-dependent calcineurin/NFATc signaling by embryonic day 11.5 (21). Moreover, IP3R1-IP3R3 double-knockout embryos showed hypoplasia of the outflow tract and the right ventricle,

TABLE 2 | CNVs associated with CHD.

| Locus         | Size (kb) | Mode              | CNV                     | Copy number | Candidate genes for CHD | Type of CHD |
|---------------|-----------|-------------------|-------------------------|-------------|-------------------------|-------------|
| 1q21.1        | 418-3,981 | de novo, inherited | Gain, Loss             | 3–45        | PRKAB2, FM05, CHD1L, BCL9, ACP6, GJA5, CD160, PDZK1, NBPF11, JM05, GJA8 | TOF, AS, COA, PA, VSD |
| 3p25.1        | 175-12,380| de novo, inherited | Gain                    | 2           | RAF1, TMEM40             | TOF         |
| 3q22.1-3q26.1 | 680-32,134| de novo, inherited | Gain, Loss              | 0–300       | FOXL2, NPHP3, FAM62C, CEP70, FAIM, PK3CB, FOXL2, BPESC1 | DORV, TAPVR, AVSD |
| 4q22.1        | 45        | de novo           | Gain                    | 1           | PPM1K                   | TOF         |
| 5q14.1-14.3   | 4937-5454 | Inherited, de novo | Gain                    | 41,103      | EDIL3, VCAN, SSBP2, TMEM167A | TOF         |
| 5q11.1        | 0.6       | de novo           | Gain                    | 1           | ISL1                     | TOF         |
| 5q35.3        | 264-1777  | de novo, n/a      | Gain                    | 19–38       | CNOT6, GFTP2, FLT4, ZNF879, ZNF345C, ADAMTS2, NSD1 | TOF         |
| 7q11.23       | 330-348   | n/a               | Gain                    | 5–8         | FKBP6                    | HLHS, Ebstein |
| 8p23.1        | 67-12,000 | n/a               | Gain, Loss              | 4           | GATA4, NEIL2, FDF1, CSTB, SOX7 | AVSD, VSD, TOF, ASD, BAV |
| 9q34.3        | 190-263   | de novo           | Loss                    | 2–9         | NOTCH1, EHMT1            | TOF, COA, HLHS |
| 9q34.3        | 1.7       | de novo           | Gain                    | 1           | NOTCH1                   | TOF         |
| 11p15.5       | 256-271   | n/a               | Gain                    | 13          | HPAS                     | SV, AS      |
| 13q14.11      | 55-1430   | n/a, de novo      | Gain                    | 7           | TNFSF11                  | TOF, TAPVR, VSD, BAV |
| 15q11.2       | 238-2,285 | n/a               | Loss                    | 4           | TUBGCP5, CYFIP1, NIPA2, NIPA1 | COA, ASD, VSD, TAPVR |
| 16p13.11      | 1414-2903 | n/a               | Gain                    | 11–14       | MYH11                    | HLHS        |
| 18q11.1-2     | 306-6118  | n/a               | Gain                    | 1–28        | GATA6                    | VSD         |
| 19p13.3       | 52-805    | n/a, de novo      | Gain, Loss              | 1–34        | MIER2, CNN2, FSTL3, PTBP1, WDR18, GNA11, STPR4 | TOF         |
| 22q11.21      | 0.7-13    | de novo           | Gain                    | 1           | PRODH                    | TOF         |
| Xp22.2        | 509-615   | n/a               | Gain                    | 2–4         | MID1                     | TOF, AVSD   |

CNV, copy number variation; CHD, congenital heart disease; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; TOF, tetralogy of Fallot; COA, coarctation of the aorta; TAPVR, total anomalous pulmonary venous return; AVSD, atrioventricular septal defect; PA, pulmonary atresia; DORV, double outlet right ventricle; BAV, bicuspid aortic valve; HLHS, hypoplastic left heart syndrome; AS, aortic stenosis; SV, single ventricle.
reduced expression of specific molecular markers, and enhanced apoptosis of mesodermal cells in the SHF with reduced activity of the Mef2C-Smyd1 pathway, a transcriptional cascade essential for the SHF (22). In addition, IP₃R1 and IP₃R3 were found to be required for extra-embryonic vascularization in the placenta, allantois, and yolk sac at the embryonic-maternal interface (23).

**GENOMIC ARCHITECTURE OF CHD IMPLICATED WITH 22Q11.2 DELETION SYNDROME**

22q11DS is the most common chromosomal microdeletion syndrome and is also known as DiGeorge syndrome or Takao syndrome (24, 25). 22q11DS is highly associated with...
CHD, involving the outflow tract, including persistent truncus arteriosus (PTA) and tetralogy of Fallot (TOF). Based on observations from experimental ablation of the CNC in chicken embryos, the outflow tract defects implicated in 22q11DS were thought to be the primary defect of the CNC development that leads to the outflow tract septum of the heart. At the beginning of the twenty-first century, the transcription factor TBX1 was identified to be the major etiology of outflow tract defects in this syndrome using new genetic engineering methods to model 22q11DS in mice (26–28). Mice with null or hypomorphic mutations for Tbx1 demonstrate PTA (28, 29). Delineation of the expression pattern of TBX1 shed further light on the molecular and cellular basis of normal and abnormal development of the outflow tract. We and other groups surprisingly revealed that TBX1 was not expressed in the CNC, but was robustly expressed in the core region of pharyngeal mesoderm in the pharyngeal arch as well as in the SHF, pharyngeal endoderm, and head mesenchyme (30–32). Moreover, we showed that TBX1-expressing descendants that represent a subset of cells originated from the SHF, predominantly contribute to the right ventricular
outflow tract and pulmonary trunk (33). These findings are very intriguing because they suggest that deletion of TBX1 in 22q11DS may result in defects of CNC-derived tissues in a non-cell-autonomous fashion through the cellular interaction between CNC and the SHF. It is believed that TOF results from malalignment of the outflow tract septum, leading to an overriding aorta with malformed ventricular septal defect (34, 35). The developmental defects of CNC is considered to cause malalignment of outflow tract septum, thus leading to TOF. Alternatively, developmental defects of the SHF may cause hypoplasia of the right ventricular outflow tract that may also result in pulmonary stenosis and malalignment of the outflow tract septum with overriding aorta (34, 35). Our data about TBX1 in the SHF provides a new insight into the developmental mechanisms underlying TOF where cellular and molecular interaction of CNC and SHF are essential (33). As for PTA in 22q11DS or TBX1 deletion, it is considered that the TBX1-expressing descendants are severely decreased in number, affecting the development and/or migration of CNC cells, thus result in complete absence of the outflow tract septum. Indeed, we recently showed that PTA in mice hypomorphic for Tbx1 might result from agenesis of the pulmonary trunk using IP3R2-LacZ mice, in which a LacZ gene was genetically inserted in-frame at the translation initiation site of IP3R2 locus on the mouse genome as a molecular marker (36). This developmental model is consistent of the observation that the outflow tract defects ranging from TOF to PTA are highly associated with 22q11DS (Figure 3).
EXPLORING THE GENOMIC ARCHITECTURE OF CHD AND THE REGULATORY MECHANISM UNDERLYING THE INTERACTION OF CARDIAC PROGENITOR LINEAGES

To further elucidate the genomic architecture of CHD, we performed mutation analysis using the genome bank of Japanese patients with non-syndromic CHD, and identified GATA6 as the genetic cause of PTA (37). Mutations in GATA6 disturb the transcriptional regulation of downstream target genes that play an essential role in cardiac development, including semaphorin 3C (SEMA3C) and plexin A2 (PLXNA2). SEMA3C is a neurovascular guiding molecule that functions as a ligand for PLXNA2 and an attractant for CNC cells (38). Mutation of GATA6 eliminates activation of SEMA3C and PLXNA2. Mutation of the GATA sites on the enhancer elements of SEMA3C and PLXNA2 abolished these transactivation activities in the outflow tract myocardium and the CNC derivatives in the outflow tract. Further analysis of the regulatory mechanism of SEMA3C revealed that a molecular network involving GATA6, FOXC1/2, TBX1, SEMA3C, and FGF8 plays an important role in the interaction between SHF and CNC cells (39). Moreover, we found that TBX1 restricts the expression of SEMA3C to the SHF in the pharyngeal arch region by inhibiting ectopic SEMA3C expression in CNC cells during migration via FGF8 signaling, whereas GATA6, FOXC1, and FOXC2 activate the expression of SEMA3C in the SHF in the outflow tract myocardium at the same time. A recent report also showed the positive regulation of SEMA3C expression in the proximal outflow tract by TBX1 (40). This spatial and temporal regulation of SEMA3C expression is essential for proper homing of CNC cells from the pharyngeal region to the outflow tract. With loss of TBX1, downregulation of TBX1-FGF8 signaling in the pharyngeal region may lead to misexpression of SEMA3C in the migrating CNC cells, resulting in the failure of their migration with ectopic aggregation, ultimately causing outflow tract defects (Figure 4) (39). Although many other genes are also associated with the regulation of CNC cell migration, our results regarding the SEMA3C regulatory mechanism provide important evidence of interactions between CNC and the SHF for the developmental basis of CHD.

CONCLUDING REMARKS

In recent decades, detailed molecular biological analyses using genetically modified animals and accumulation of solid evidence from human mutation studies have dramatically advanced the understanding of cardiovascular development. In addition, with the recent development of stem cell science, including induced pluripotent stem cells and comprehensive expression analysis procedures using next-generation sequencing, elucidating the more detailed temporal and spatial gene regulatory mechanisms underlying cardiovascular development has become possible with evaluations at the single-cell level (9, 41–43). As a future direction for clinical application, detailed elucidation of the genomic architecture of CHD implicated in the mechanism regulating interactions between cells of multiple different origins would facilitate the development of regenerative medicine and/or preventive medicine for complex heart diseases such as CHD.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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