In 1906, Tawara published his treatise, recently translated from German to English, on the anatomy of the cardiac conduction system, which he elucidated through painstaking dissection and histological examination. In the following decades, the conduction system was generally understood and studied in anatomic and physiological terms. Most molecular biology focused on the genes and proteins that generate or propagate the cardiac action potential. Unlike other tissues and organs, including the heart, little was known about its embryonic development, even though the anatomic form of the conduction system is clearly relevant to its function. Until recently, developmental biology was hampered by the lack of a working model of how the conduction system forms, reagents, and methods. This situation has changed significantly since Gourdie and Mikawa reported their seminal observations in 1995. In an elegant series of chick embryo experiments, their laboratories proved that a developing node or fiber in the central and peripheral conduction systems forms by recruitment of adjacent multipotent myocytes. The murine conduction system develops by the same process of accretion. Soon afterward, Berul et al., Morley et al., and Baker et al. described their applications of intracardiac electrophysiology and optical mapping to study normal and abnormal conduction in the mouse, thus opening the door for experimental genetics and developmental biology.

The inductive patterning of tissues is a central theme in development. In the chick embryo, endothelin-1 is secreted by the coronary arterioles to induce adjacent ventricular myocytes to become Purkinje cells. This particular pathway probably does not operate in the mouse. Some in vitro evidence suggests that neuregulin-1 plays a similar role, but no in vivo signaling pathway has been demonstrated to regulate the development of the mammalian central conduction system until now. Thus, the demonstration of a role for bone morphogenetic protein (BMP) signaling in the development of the atrioventricular (AV) conduction system by Stroud and colleagues is an important step forward. BMPs, so named because they were originally discovered for their ability to induce bone formation, have far-reaching roles in the development of perhaps every organ and tissue in the body. BMP2 and BMP4 are expressed circumferentially around the embryonic AV canal myocardium and have well-described functions in patterning chamber septation and valve formation. Stroud et al. show that conditional deletion of the cognate receptor Bmpr1a in the AV canal myocardium leads to pleiotropic conduction phenotypes that range from ventricular preexcitation to first-degree AV block. These physiological abnormalities were correlated with histopathological evidence for accessory AV pathways and morphologically abnormal AV nodes.

The authors classified the conduction defects that the conditional Bmpr1a knockout animals had into 4 groups: (1) normal, (2) intermittent preexcitation with normal AV node function, (3) predominant bypass conduction with AV node dysfunction, and (4) severe AV node dysfunction without an accessory pathway. It seems paradoxical that deletion of 1 gene could lead to a short, normal, or long PR interval, but contrasting phenotypes have likewise been described in the developing limb bud. BMP signaling regulates the number of digits formed. Mutations in the BMP pathway can result in extra or no digits, depending on the level of BMP signaling, developmental stage, or context within a prepatterned field.

BMP2 and BMP4 probably also pattern the myocardium in ways that depend on the local milieu. In the early embryonic heart tube, the atrium and ventricle are in electrical continuity around the entire circumference of the AV canal. Electrical coupling between all the myocytes in the canal must ultimately be disrupted, except at the future His bundle. The annulus fibrosus simultaneously forms to insulate the atrial from the ventricular myocardium. In addition, some myocytes at the inner curvature of the looping heart tube are specified to become the AV node. One can reasonably hypothesize that BMP signaling regulates each of these processes in combination with other developmental inputs. As the phenotypes observed in the Bmpr1a mutant animals suggest, derangement of BMP signaling could lead to the persistence of accessory AV pathways, discontinuity of the His bundle, exuberant fibrosus that disrupts the architecture of the central conduction system, or abnormal patterning of the AV node. The identification of the other cues that are integrated with BMP signaling is of obvious interest.

In this regard, several transcription factors are known to be expressed preferentially in the conduction system, and mutations of some of them cause conduction defects. For example, the cardiac transcription factor Nkx2-5 is more highly expressed in the developing conduction system than surrounding contractile myocytes, and Nkx2-5 mutations are associated with AV node dysfunction. A null mutation of Nkx2-5 causes the AV node not to form. Haploinsufficiency causes hypocellularity of the central and peripheral conduction systems and absence of the proximal subdomain of the AV node. In another example, a heterozygous knockout of
Tbx5, the transcription factor mutated in Holt-Oram syndrome, causes PR prolongation and patterning defects of the left and right bundle branches.\textsuperscript{22} Nkx2-5 and Tbx5 in concert with another transcription factor, Id2, coordinate the development of the Purkinje system.\textsuperscript{23} As in the limb bud, the cellular context on which BMP signaling acts may direct a myocyte to become a slow nodal cell, a fast-conducting His cell, or entirely uncoupled from its neighbor.

Interestingly, the parallel with the limb bud may extend to other genes besides BMPs and Tbx5. Tbx3 and Msx2, both transcription factors whose expression is regulated by BMP signaling in the limb bud, are respectively expressed in the conduction system and AV canal myocardium.\textsuperscript{24,25} Atrial expression of Tbx3 causes ectopic pacemaker activity consistent with its role in sinus node development; a loss-of-function phenotype has not been reported yet.\textsuperscript{26} Msx2 knockout mice do not appear to have a conduction phenotype or accessory AV pathways,\textsuperscript{27} but a low incidence of 1 of the classes of conduction defects described for the conditional Bmpr1a knockout could have escaped detection.

The demonstration of a role for BMP signaling in conduction system development provides an important foothold to elucidate the genetic basis of wiring the heart. Several transcription factors have been implicated in the development of the AV conduction system, and future investigation that builds on a wealth of knowledge about BMP signaling will undoubtedly help to draw the whole picture. Much effort in recent years has focused on turning stem or other pluripotent cells into contractile myocardium, but significant technical challenges remain. In contrast, one can envision a more modest goal. Armed with a genetic wiring diagram, a future interventional molecular cardiologist could manipulate a stem cell into a cardiac myocyte that expresses the entire repertoire of repolarization and refractoriness in transgenic mouse hearts using optical mapping. J Cardiovasc Electrophysiol. 1999;10:1361–1375.


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Genetic Wiring Diagram of the Cardiac Conduction System
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