Understanding Conduction System Development
A Hop, Skip and Jump Away?

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In the late 1800s, W.H. Gaskell demonstrated that impulse propagation from the atrium to the ventricle of the tortoise heart reflected conduction along myocardial tissue rather than nerve tissue. A decade later, Stanley Kent proposed, incorrectly as it turns out, that multiple muscular connections normally link the atria and ventricles of mammals, but it was not until the remarkably detailed report almost 100 years ago by Sunao Tawara, working in the laboratory of Ludwig Aschoff in Germany, that the histological identification and characterization of the atrioventricular node, the penetrating bundle of His, the left and right bundle branches and Purkinje fiber network was established. The notion that aberrant conduction between atria and ventricles might account for rhythm disturbances was first proposed in 1930, when the renowned American cardiologist Paul Dudley White and the English physicians John Parkinson and Louis Wolff reported on a series of patients with a short PR interval and apparent bundle branch block who were prone to paroxysmal tachycardia.

During the past decade, there has been growing realization of the importance of diseases involving the cardiac conduction system (CCS), maladies that are now known to reflect diverse pathologic mechanisms including not only post-operative complications following surgical repair of congenital heart defects, but also immunological and metabolic disorders, degenerative processes and most recently - transcriptional dysregulation. For example, homozygous mice harboring inactivating mutations of the Nkx2–5 gene demonstrate defects in looping morphogenesis and embryonic lethality at 9 to 10 days post-coitum; yet not until human genetic studies implicated Nkx2–5 mutations in conduction system disease did more detailed experimentation reveal transient preferential expression of Nkx2–5 in the atrioventricular conduction system, as well as its specific requirement in the recruitment and/or survival of this subset of cells. Similarly, mutations in the Tbx-5 gene were identified as the cause of Holt-Oram syndrome eight years ago and initial studies of its expression pattern within the developing heart was reported soon thereafter. Yet only very recently was the preferential expression of Tbx-5 within the central conduction system appreciated and its role in the maturation of the AV node and patterning of the bundle branches clarified.

In this issue of Circulation Research, yet another transcription factor with an apparent dual role in heart formation and function has been characterized. Hop (homeodomain only protein) is an unusual protein that contains a homeodomain similar to Hox transcription factors but fails to directly bind DNA. Hop functions downstream of Nkx2–5 and appears to play a pivotal role in the regulation of myocyte growth and proliferation through antagonism of serum response factor activity, in a process involving recruitment of histone deacetylase activity. The Hop transcript is strongly expressed throughout the developing myocardium prior to 11.5 days post-coitum in the mouse heart and subsequently becomes restricted to the trabecular zone. Targeted deletion leads to an incompletely penetrant phenotype, with approximately half of Hop-deficient embryos developing myocardial wall thinning, heart failure and death between 9.5 and 10.5 months.
days post-coitum, whereas others survive embryogenesis but go on to develop a hypercellular phenotype.\textsuperscript{34,35}

Using a knock-in strategy to place a lacZ reporter gene under the transcriptional control of the Hop locus, Ismat and colleagues now report that in the adult heart expression of Hop is restricted to the AV node, His bundle and bundle branches, as well as more broadly within the atria.\textsuperscript{36} Although Hop functions downstream of Nkx2–5, unlike the case with Nkx2–5-deficiency, the AV node and His bundle do not appear atrophic in surviving homozygous Hop mutant mice, suggesting a primary role in the maintenance of CCS function, rather than in CCS specification or patterning. The putative role of Hop as a regulator of the balance between proliferation and differentiation is intriguing, inasmuch as Tbx-5, now also known to be preferentially expressed in the CCS, is thought to negatively regulate proliferation\textsuperscript{37} and cells of the CCS appear to have diminished proliferative activity during embryonic and fetal stages compared with working cardiomyocytes.\textsuperscript{25,38}

Ismat et al also examined the functional consequences of Hop deficiency in surviving adult mice.\textsuperscript{39} Programmed electrical stimulation revealed several functional abnormalities including increased P-wave duration, minor prolongation of the AH interval, prolonged atrial refractoriness, widening of the QRS complex and prolongation of the HV interval. These electrophysiological findings are similar, but not identical to those found in connexin40-deficient mice\textsuperscript{40–42} and indeed expression of this gap junction protein, which is a well-characterized transcriptional target of Nkx2–5 as well as Tbx-5,\textsuperscript{43} was markedly reduced in the atria, AV node, His bundle and bundle branches of Hop mutant mice. A growing number of transcription factors with potential roles in conduction system formation and function have been identified, including additional T-box family members such as Tbx-3 and Tbx-2,\textsuperscript{19,44–47} the vertebrate muscle segment related homeobox factor Msx-2,\textsuperscript{44} and the SP1-related factor HF-1.\textsuperscript{48} Moreover, increasingly sophisticated strategies to unambiguously identify cells of the conduction system and determine their unique patterns of gene expression and function continue to evolve.\textsuperscript{49–51} Ismat et al add to our growing understanding of conduction system development, but unraveling this complex process is still not a hop, skip and jump away.

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References

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