Heart failure affects more than 5 million people a year in the United States, and the underlying molecular causes are still poorly understood. Many studies have reported that pathways important for cardiac development are also important for adult cardiac homeostasis and response to injury and stress. In this issue of Circulation Research, Kim et al report the identification of a new Notch ligand, weary (wry), using an elegant genetic screen in Drosophila. wry is expressed in the Drosophila dorsal tube, the analog of the mammalian heart, and loss of wry results in dilated cardiomyopathy. The protein structure of wry suggests high similarity to known Notch ligands; however, it lacks the highly conserved Delta–Serrate–Lag domain found in other Notch ligands, suggesting divergence in both structure and function. Despite this difference, the authors show that wry can regulate Notch-mediated transcription in flies. These studies identify a new Notch ligand and show that this critical developmental pathway may be an important new target for future therapies directed toward adult cardiomyopathy.

The adaptive response of the adult mammalian heart to various stressors and environmental insults is limited by its lack of regenerative potential. The result is often extensive cardiomyocyte hypertrophy, eventually followed by cardiomyocyte death, dilated myopathy, and heart failure. Although certain therapies can alleviate symptoms, there are no cures for heart failure outside of transplantation. Thus, new mechanistic insights into this important disease, as well as novel therapeutic targets, are essential for progress to occur.

One of the standing paradigms in cardiac biology is that signaling and transcription pathways important for cardiac development are often reactivated in the hypertrophic response and subsequent heart failure. Much of the support for this argument comes from findings showing that embryonic isoforms of cardiac specific genes including myosin heavy chain are reexpressed during heart failure, whereas the adult isoforms are downregulated. Several important signaling pathways have been shown to regulate cardiac development including bone morphogenetic protein, Wnt, and Notch. Of these, Notch signaling plays a critical role in a variety of cellular processes including cell fate changes, proliferation, and differentiation. Notch signaling involves cell–cell interactions between Notch ligands (Notch1–4) and the Delta1–4 and Jagged1–2 families of Notch receptors. Ligand receptor interactions result in the cleaving of the Notch intracellular domain (NICD) and its translocation to the nucleus, where it interacts with a transcriptional complex including the CSL and Mastermind proteins. Notch signaling activates a host of target genes including members of the Hes, Hey, and HRT transcription factor families. This is just an outline of a highly complex signaling network that can crosstalk with other pathways. Recent reviews provide a more thorough description of the subject.

Notch signaling has been shown to be important for several aspects of cardiac development including regulation of chamber formation and proper septation of the cardiac outflow tract. Notch signaling also plays a key role in early cardiac differentiation from pluripotent stem cells where it can either inhibit or promote cardiac mesoderm fate. The contradicting data that have been gathered could be a result of the tightly controlled temporal requirement of Notch. Based on the present data, it is reasonable to conclude that Notch signaling promotes cardiac fate from multipotent mesoderm, whereas earlier activation inhibits cardiac fate specification. Such a temporal-specific control of cardiac fate specification is also found in the Wnt pathway, which often works collaboratively with Notch.

In this issue of Circulation Research, Kim et al devised an elegant method of phenotyping cardiac dysfunction in Drosophila using optical coherence tomography (OCT). This method allows the accurate assessment of cardiac function in flies and enhances the use of simple model organisms such as Drosophila to screen for new genes and pathways important for cardiac function in humans. The Drosophila dorsal tube is the fly analog of the mammalian heart and studies of dorsal tube development have uncovered many important factors and pathways that regulate cardiac development including the transcription factor Nkx2.5, also known as tinman in flies. The authors used OCT to screen genomic deficiencies in a cardiac cDNA in flies and discovered a deletion mutant that exhibited several attributes of heart failure including increased end systolic dimension and impaired fractional shortening. Through methods now standard in the fly field, the authors narrowed the possible gene involved to a locus called CG31665, which they subsequently named weary or wry and showed that RNAi mediated knock-down of this gene resulted in a dilated cardiomyopathy. Kim et al also showed that re-expression of the wry cDNA in a cardiac specific fashion rescued the weary deletion discovered in the genetic screen. Using the power of Drosophila genetics, the authors used temperature-sensitive RNAi methods to knock-
down wry in the adult heart to ask whether the cardiac dysfunction observed in wry mutants is attributable to a developmental role for this gene or to its role in adult cardiac homeostasis. The data showed that inhibition of wry in the adult fly resulted in a similar phenotype as that observed in the straight wry mutants. Thus, wry is required in the postdevelopmental period for proper cardiac function.

Analysis of the wry coding sequence showed that its structure was similar to that of other Notch ligands and includes EGF repeats and a putative transmembrane domain. However, wry does not contain a Delta-Serrate-Lag like domain, suggesting it resembles noncanonical Notch ligands such as DNER and contactin.\(^{13,14}\) This led the authors to look more closely at Notch signaling in the *Drosophila* heart and they found that many Notch signaling components were expressed during cardiac development in the fly. To further investigate whether Notch signaling played an important role in adult cardiac function in flies, Kim et al examined other Notch pathway components using OCT and found that mutations in other genes, including additional Notch ligands, resulted in abnormal cardiac function. The authors then went a step further and generated RNAi knockdown models for other Notch ligands, again showing that this resulted in defective cardiac function in adult flies. Moreover, cardiomyocyte differentiation from pluripotent stem cells early and then promote their differentiation later. Notch is important for outflow tract development, chamber-specific cardiomyocyte differentiation, and adult cardiomyocyte homeostasis.

Cardiomyocytes are quiescent in adult mammals but respond to proliferative signals via a hypertrophic response. Because physiological hypertrophy is thought to be an important and necessary response to stress and injury, Notch may be critical for this process in adults. Loss of Notch would lead to an aberrant hypertrophic response, cardiomyocyte drop-out, and eventual heart failure. Whether a wry ortholog or other Notch components plays a central role in this process in humans remains to be shown. Notch signaling, like many important signaling pathways, is an active target for the development of new therapies in the drug development field. Although inhibition of such a critical pathway in adult mammals is fraught with its effects on other tissues and processes (eg, hematopoiesis), the results from Kim et al should provide further impetus to look more closely at this pathway in the context of heart failure.

Finally, the findings of Kim et al once again prove the value of basic developmental studies such as genetic screens in simple, tractable model organisms for functional identification of important factors and pathways relevant to human heart disease. Coupled with new imaging techniques such as OCT, additional screens are likely to identify novel factors and pathways which will expand the list of potential therapeutic targets for adult heart disease in humans.

**Sources of Funding**

Supported by NIH grant HL100405 and the American Heart Association Jon DeHaan Foundation Myogenesis Center Grant.

**Disclosures**

None.

**References**


KEY WORDS: cardiac development | cardiac transcription factors | cardiogenesis | cardiomyopathy | signal transduction
Weary of the Stress: Time to Put Another Notch In Cardiomyopathy
Edward E. Morrisey

Circ Res. 2010;106:1187-1189
doi: 10.1161/CIRCRESAHA.110.218974
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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