Shorty after birth the cardiac muscle cells exit the cell cycle and lose their ability to replicate. Hence, growth of the postnatal heart occurs by hypertrophic rather than hyperplasic processes.1 This basic biological fact has profound clinical implications because the functional loss of cardiac myocytes by apoptosis or necrosis after injury triggers the adjacent myocardium to hypertrophy as means to off-set the increased wall stress. However, in some individuals, for reasons unknown, this adaptive process of compensatory cardiac hypertrophy fails ultimately resulting in overt heart failure. For this reason, there has been tremendous interest during the past 2 decades of heart research focused at deciphering the signaling pathways and molecular effectors that underlie cardiac hypertrophy and heart failure.

In this regard, early studies in fruit flies and worms led to the discovery of the Wnt signaling pathway as a central regulator of embryonic development and cell growth.2 Importantly, the Wnt receptor Frizzled and cytoplasmic scaffold protein Dishevelled (Dvl) together with β-catenin have been linked to embryo cardiogenesis as well as cellular processes involved in physiological hypertrophy of the postnatal adult heart.3 However, a growing body of experimental evidence suggests involvement of both canonical and noncanonical Wnt signaling pathways in the development of pathological cardiac hypertrophy.3,4 Classically, activation of the canonical Wnt signaling involves the stabilization and nuclear targeting of the Wnt protein β-catenin.4 Nuclear-associated β-catenin ostensibly interacts with transcriptional coactivators T-cell factor/lymphoid enhancer factor as well as Yes-associated protein to activate Wnt target gene transcription and cardiac growth. A noncanonical Wnt pathway involving Dvl but not β-catenin has also been reported but this pathway is typically associated with cellular polarization and less with cell growth.4 Despite both canonical and noncanonical Wnt pathways being viewed as separate entities, signaling effectors such as Dvl are common to both pathways.

For example, Dvl was reportedly increased in the hypertrophied heart with transgenic overexpression of Dvl resulting in progressive cardiomyopathy.5 Conversely, genetic ablation of Dvl suppressed pathological cardiac growth after aortic banding in mice.6 Collectively, these studies support a causal relationship between Dvl and cardiac hypertrophy; however, a genetic link bridging Dvl signaling and cardiac growth remains to be elucidated. Notably, the calcium-calmodulin–dependent protein kinase II (CAMKII)–histone deacetylase (HDAC) signaling axis, which is well established as a key nodal point in regulation of cardiac hypertrophy, has been identified recently as a critical downstream target of Dvl.7 The relationship between Dvl and CAMKII signaling for induction cardiac hypertrophy had not been investigated previously.

In this issue, Zhang et al8 provide new compelling evidence for a functional link between the Wnt protein Dvl and CAMKII for the induction of pathological cardiac growth. Moreover, the authors further demonstrate that Dvl-induced cardiomyopathy influences HDAC4-dependent regulation of the muscle transcription factor myosin enhancer factor 2, thereby providing a direct mechanistic link between Wnt signaling and the activation of genes associated with cardiac hypertrophy (Figure). The work presented is novel because it highlights for the first time a previously undescribed relationship between Dvl and CAMKII to explain pathological cardiac growth. In fact, Dvl-induced cardiac apoptosis, fibrosis, and cardiac dysfunction were completely normalized after genetic ablation of both the CAMKIIγ and CAMKIIγ isoforms. Interestingly, neither isoform in the absence of the other was sufficient to suppress Dvl-induced cardiomyopathy and dysfunction, yet ablation of both CAMKIIδ and γ isoforms completely suppressed Dvl-induced cardiac dysfunction. This suggests nonoverlapping roles for these CAMKII isoforms in the Dvl signaling pathway. Whether CAMKIIδ and γ isoforms are universally conserved for other aspects of Wnt signaling or restricted to cardiomyopathy induced by Dvl is unknown and remains to be tested. It is also unclear whether Dvl overexpression affects other CAMKII isoforms or whether these play a compensatory for regulation of HDACs for induction of cardiac gene transcription in the CAMKIIδγ knockout mice. Another interesting aspect of this work was the finding that Wnt-β-catenin was not appreciably influenced by transgenic overexpression of Dvl, leading the authors to conclude that Dvl signals at least in this context, through the noncanonical Wnt pathway, are independent of

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From the Department of Physiology and Pathophysiology, Faculty of Health Sciences, College of Medicine, The Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre, University of Manitoba, Winnipeg, Manitoba, Canada.

Correspondence to Lorrie A. Kirshenbaum, Institute of Cardiovascular Sciences, St Boniface Hospital Research Centre Room 3016, 351 Taché Ave, Winnipeg, Manitoba, Canada, R2H 2A6. E-mail Lorrie@sbrc.ca

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Junjun Lin, Lorrie A. Kirshenbaum

Wnt-1 Dishevelled Signaling Functionally Links Calcium-Calmodulin–Dependent Protein Kinase II and Cardiac Dysfunction

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Calcium-Calmodulin–Dependent Protein Kinase II
β-catenin. This conclusion must be interpreted with caution because classical regulators of β-catenin such as glycogen synthase kinase 3 or phosphatidylinositol-4,5-bisphosphate/protein kinase B were not studied and could be indirectly influenced by Dvl, resulting in activation of genes associated with pathological cardiac growth. Furthermore, a recent report by Heallen et al\(^8\) demonstrated a novel paradigm involving the Hippo kinase signaling pathway as a negative regulator cardiac growth through its inhibitory effects on Wnt-β-catenin pathway. Activation of Hippo blocks cardiac growth by phosphorylating and inactivating Yes-associated protein–β-catenin transcriptional complexes required for β-catenin signaling and cardiac growth. Hence, despite that ablation of CAMKIIδ and γ isoforms in the presence of transgenic Dvl overexpression had no apparent effect on β-catenin, the effects of Dvl on Hippo–Yes-associated protein–β-catenin transcriptional complexes required for β-catenin signaling and cardiac growth cannot be ruled out. Another point of consideration is the impact of Dvl-CAMKII on other HDACs, such as HDAC5, HDAC9, and HDAC8, which have also been implicated as negative epigenetic regulators of cardiac hypertrophy or for that matter the combined effects of Dvl-CAMKII signaling on other histone-modifying proteins such as histone acetylases, such as p300/CBP on cardiac gene expression.

Nevertheless, under the conditions tested the current study provides compelling new evidence for the existence of a novel signaling pathway that operationally links pathological cardiac growth to the Wnt signaling pathway via Dvl. This is the first report to demonstrate a critical role for the CaMKII signaling axis in association with cardiomyopathy induced by Wnt signaling components. Whether Dvl-CAMKII signaling is part of a general cardiac growth paradigm for normal physiological hypertrophy or restricted to pathological cardiac hypertrophy will require further study. It will also be of interest to determine whether agents that selectively target Dvl or CAMKIIδ and γ isoforms will prove beneficial in mitigating aberrant ventricular remodeling and heart failure after myocardial infarction.

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**Disclosures**

None.

**References**


**Figure.** Model for the regulation of cardiac hypertrophy by Dishevelled (Dvl)–calcium-calmodulin–dependent protein kinase II (CAMKII) signaling pathway. Dvl activates CAMKII, which phosphorylates histone decetylase 4 (HDAC4) resulting in its nuclear export, which activates myosin enhancer factor 2 (MEF2), cardiac gene transcription, and cardiac hypertrophy.
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