Wnt Signaling Molecules in Left Ventricular Remodeling
Focus on Dishevelled 1

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Under acute or chronic stresses, the adult heart undergoes a remodeling process that involves cardiomyocyte hypertrophy accompanied by apoptosis, necrosis, and fibrosis that lead to impaired cardiac contractility. The role of endogenous regeneration in this process is currently under investigation. Sustained deleterious stimuli will lead to a compensated form of hypertrophy often culminating in heart failure.1 This form of hypertrophy is often referred to as “maladaptive.” When dealing with hypertrophy, it appears important to distinguish between the term being used on the cellular and molecular level (enlargement of individual cardiomyocytes and re-expression of fetal/embryonic genes) and the organ level (increased heart weight, left ventricular wall thickness, and functional diastolic and systolic impairment). In our view, these processes are certainly linked but not identical. Hypertrophy on the organ levels summarizes several independent cellular and molecular processes (see below), where cardiomyocyte growth is not necessarily the most important.

Independent of its origin, cardiac hypertrophy is associated with alterations in cardiac geometry, mass, architecture, and function controlled by a complex network of interconnected and abundant signal-transduction pathways.2 New signaling molecules are emerging as possible targets to specifically attenuate maladaptive hypertrophy. Pathological, stress-induced growth of cardiomyocytes was shown to depend on Wnt/β-catenin nuclear signaling rather than its adhesive function in cell adhesion. However, the specificity of the cell type and the molecular mechanisms governing the Wnt signaling—dependent changes are currently unknown.3

In this issue of the Hypertension, the study by Malekar et al4 provides new evidences concerning the role of Dishevelled-1 (Dvl-1) as a cross-talk molecule between the canonical and noncanonical Wnt pathways in cardiac hypertrophy. The activation of the canonical Wnt pathway leads to cytoplasmic stabilization of β-catenin via activation of receptors of the Frizzled family and the coreceptor low-density lipoprotein receptor-related protein 5/6. Next, translocation of β-catenin into the nucleus and regulation of gene expression through interaction with transcription factors of

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the T cell factor/lymphoid enhancer factors family occur. In contrast, the noncanonical Wnt signaling pathways acts independent of β-catenin and involves a G-protein and/or Wnt-mediated intracellular calcium influx, activation of protein kinase C, calcium/calmodulin-dependent kinase II, or calcineurin, as well as GTPases of the rho family and jun N-terminal kinase (JNK; see the Figure). The cytoplasmic protein Dvl-1 is a critical component for all of the Wnt signaling branches.5

In line with the increased expression of Dvl-1 after aortic banding in rats, gene expression profiling analysis after myocardial infarct showed activated Wnt signaling indicating an important role for Wnt signaling in pathological, stress-induced left ventricular remodeling.6 Moreover, Haq et al7 showed that the kinase activity of glycogen synthase kinase 3β, which destabilizes β-catenin, was inhibited by hypertrophic stimuli. This observation is consistent with an initial phosphorylation of glycogen synthase kinase 3β during aortic constriction that later returns to baseline levels. Although these studies focused on signaling pathways, it remained unclear what physiological effect β-catenin regulation in the heart exerts. We consistently found mice with genetic β-catenin inhibition to be resistant to pathological stimuli like aortic constriction or infarct, whereas mice with heart-specific β-catenin stabilization demonstrated rapid functional deterioration and increased mortality.8,9 Similarly, in this study by Malekar et al,4 mice with increased levels of Dvl-1 resulting in activated β-catenin signaling showed reduced ejection fraction, increased left ventricular diameters, and increased mortality. After these studies, it therefore appears clear that β-catenin inhibition possibly by inhibiting signaling molecules upstream like Dvl-1 is required for adaptive cardiac remodeling. If this pathway is blocked by either stabilization of β-catenin or forced expression of Dvl-1, heart function deteriorates.

The findings are also consistent with previous studies where mice lacking Dvl-1 subjected to aortic constriction resulted in attenuated cardiac hypertrophy when compared with the wild-type mice.10 van de Schans et al10 demonstrated that Dvl-1 knockout mice have reduced β-catenin levels, as well as Akt phosphorylation, which suggest Akt activation independent from glycogen synthase kinase 3β to participate in left ventricular hypertrophy. In turn, Malekar et al4 showed now that mice overexpressing Dvl-1 upregulated not only β-catenin but also its target genes cyclin D1 and c-Myc, indicating β-catenin transcriptional activation to be stimulated. Moreover, activation of noncanonical Wnt-signaling components involving JNK, protein kinase C, and CAMKII was also shown, clearly indicating that Dvl-1 serves as a cross-talking molecule between both Wnt branches during the process of hypertrophy. Because the authors have not provided us with the analysis of other known target
genes, such as T cell factor/lymphoid enhancer factors family members or axin 2, it is difficult to conclude which pathway is responsible for the activation of cyclin D1 and c-Myc.

Transcription factors essential for embryonic cardiogenesis are activated during adult cardiac remodeling.11 It was shown that the protein diversin and dvl function together and are critical for controlling cardiogenesis both in cell culture and in zebrafish embryos. Moreover, they were shown to be mutually dependent players of noncanonical Wnt signaling. Diversin acts downstream of Wnt11 and Wnt5a noncanonical Wnt signaling activating JNK.5 Malekar et al4 provide very clear evidence concerning the activation of noncanonical Wnt signaling involving JNK, protein kinase C, and CAMKII during the hypertrophy response. These data confirm once again the hypothesis of re-employment of early embryonic cardiac pathways during adult cardiac remodeling to possibly activate mechanisms identical to early cardiac formation.

Mechanistically, Malekar et al4 analyzed the cellular mechanisms leading to ventricular remodeling. They showed increased cardiac mass measured by an increase in cardiomyocyte size, increased fibrosis, and increased apoptosis. Dvl-1 plays an important role in several cellular and molecular aspects of ventricular remodeling and probably interconnecting >1 pathway leading to cardiac fibrosis and cardiomyocyte growth and death. However, recent evidence also suggests endogenous regeneration to be affected by modulation of β-catenin in the adult heart. Similar to the role of β-catenin in cardiac development of the left ventricle from first heart field progenitors, we found β-catenin downregulation to enhance cardiac progenitor cell differentiation toward TropT+ early cardiomyocytes.9 From the data displayed here, it cannot be excluded that this cellular mechanism is also involved in the observed phenotype of Dvl-1 overexpression (see Figure).

Given the consistent effect across several studies concerning the WNT/β-catenin pathway including Dvl-1 in cardiac remodeling, these and other studies have important implications for therapeutic strategies that may be based on modulating Dvl-1 or other components of the WNT/β-catenin pathway to finally specifically target gene activation, leading to functionally deleterious, maladaptive cardiac remodeling.

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Figure. Schematic summary of canonical and noncanonical Wnt signaling pathways linked to cardiac hypertrophy and remodeling. The secreted Wnt activates the transmembrane Frizzled receptor (Frz) leading to activation of the cytoplasmatic protein dishevelled (Dvl). Dvl triggers the activation of the WNT-dependent β-catenin canonical pathway that leads to activation of target genes contributing to cardiomyocyte hypertrophy, fibrosis, apoptosis/necrosis and cell differentiation. Activation of the non-canonical Wnt signaling via Ca2+/calmodulin-dependent protein kinase II (CaMK II) and Rho GTPase (Rho, Rac) leads to activation of protein kinase C (PKC) and c-Jun NH2-terminal kinase (JNK), respectively, that finally contributes to activation of anti-apoptotic and hypertrophic target genes during cardiac hypertrophy.2,12,13


