Cardiac Hypertrophy and the Wnt/Frizzled Pathway

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The heart responds to sustained pressure overload with hypertrophy. Although at first glance this seems to be an adaptive mechanism by which the heart battles against increased workload, there is evidence that these “compensatory changes,” even early in the game, are different from the benign, truly adaptive response that occurs, for example, in athletes. In this group, hypertrophy is characterized by “physiological” myocyte growth and usually does not carry a poor prognosis. On the other hand, in hypertrophy associated with cardiovascular diseases, such as hypertension or aortic stenosis, increased expression of noncontractile proteins, such as collagen, as well as fetal isoforms of contractile proteins, take place, resulting in fibrosis, diastolic dysfunction, and, subsequently, heart failure. Therefore, differentiating the adaptive or “good” hypertrophy from the maladaptive or “bad” hypertrophy and their different pathways seems to be appropriate. Over the past decades, scientists have been studying left ventricular hypertrophy and its many intracellular mechanisms, trying to better understand the cellular changes that lead to pressure-activated hypertrophy and subsequent heart failure. It appears that some of these changes might be compensatory and some others, detrimental.

The Wnt signaling pathways play key roles in the differentiation, proliferation, death, and function of cells and, as a result, are involved in critical developmental, growth, and homeostatic processes. The Wnts are a family of genes/proteins. They have been linked to Alzheimer’s disease, aortic valve calcification, cancer, and diseases affecting bone. Control of the Wnt pathways is modulated by a number of proteins that either interact with the Wnt ligands directly or with the low-density lipoprotein-receptor related proteins 5 and 6 that, along with 1 of the different Frizzled proteins, take place, resulting in fibrosis, diastolic dysfunction, and, subsequently, heart failure. Therefore, differentiating the adaptive or “good” hypertrophy from the maladaptive or “bad” hypertrophy and their different pathways seems to be appropriate. Over the past decades, scientists have been studying left ventricular hypertrophy and its many intracellular mechanisms, trying to better understand the cellular changes that lead to pressure-activated hypertrophy and subsequent heart failure. It appears that some of these changes might be compensatory and some others, detrimental.

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Nusse and Varmus first described the int-1 gene, a proto-oncogene that induced tumors when the mouse mammary tumor virus was integrated into that locus. Subsequently it was shown that the Drosophila homologue of int-1 was the segment polarity gene wingless, and the name “Wnt” was created as a contraction of wingless and int.2,5

Currently in vertebrates there are ≈19 known Wnt genes. At the time this commentary is being written, there are 4 currently known Wnt signaling pathways: the canonical or Wnt/β-catenin pathway, the Wnt/Ca +2 pathway involving protein kinase A, the planar cell polarity pathway, and a pathway involving protein kinase C.2 The Wnt/β-catenin is the best studied of these pathways: association of Wnt-1 and members of the Frizzled protein family leads to activation of the disheveled (Dvl) protein. Activated Dvl inhibits glycogen synthase kinase-3β (GSK-3β), increasing cytosolic β-catenin levels as a consequence of decreased GSK-3β-mediated degradation. β-Catenin then interacts with members of the lymphoid enhancer factor/T-cell factor family of transcription factors in the nucleus, as well as other transcriptional factors involved in cell growth.3

In this issue of Hypertension, van de Schans et al3 explored the effect of interruption of the Wnt/Frizzled pathway on the onset of cardiac hypertrophy. By subjecting mice lacking the Dvl-1 protein gene (Dvl+/−) to thoracic aortic coarctation (TAC), they were able to attenuate the development of cardiac hypertrophy when compared with their wild-type littermates (Dvl+/+), which were also subjected to TAC.

Dsv functions upstream of GSK-3β, inhibiting it, so the final result in Dsv−/− mice was increased GSK-3β-mediated degradation of β-catenin, with the subsequent inhibition of hypertrophy signaling. The authors showed attenuation of cardiac mass index and myocyte cross-sectional area and decreased mRNA of hypertrophy biomarkers, such as ANP and BNP. Interestingly, they not only found a reduction in β-catenin levels after knocking out Dsv but also reduced amount of phosphorylated Akt, which is known to be downstream to Dsv but upstream of GSK-3β. Akt might also be involved in left ventricular hypertrophy activation through mechanisms that act independently from GSK-3β.6

β-Catenin is known to regulate the proto-oncogenes c-myc, c-fos, c-jun, and cyclin D1. Of note, there was no difference in the expression of these genes between TAC Dsv−/− and TAC Dsv+/+. Although this can be explained by the late timing in which the gene expressions were determined (7 days rather than few hours after banding), the authors also hypothesize that there could be another β-catenin–independent mechanism(s), through which GSK-3β exerts its antihypertrophic effect. One interesting aspect of the present work is the fact that, in the absence of an insult (in this case, aortic banding), Dsv does not seem to play an important role in left ventricular hypertrophy, but it certainly does so when the heart is challenged with increased pressure workload.

Some aspects still remain unanswered in the work under discussion. Although there was a significant attenuation of cardiac mass in the TAC Dvl−/− mice, and a tendency toward diminished cardiac interstitial fibrosis in this group, the latter was not significant. This deserves further research. Increased fibrosis seems to be key in differentiating between adaptive and maladaptive hypertrophy and the transition to diastolic and/or systolic heart failure.7,8 Because the authors have not
provided us with functional data to assess how the intervention affected cardiac performance, it is difficult to conclude, analyzing the present results, which type of hypertrophy attenuation (adaptive versus maladaptive) might Wnt interruption be responsible for.

In the last few years, the dogma that cardiac myocytes are terminally differentiated has been challenged by data showing that new, stem cell–derived cardiac cells are present in hearts after myocardial infarction or aortic stenosis. Because Wnts are involved in the morphological arrangement of cardiac myocytes in neonatal hearts, the hypothesis that Wnt/Frizzled activation might be necessary for new myocyte development for the heart to adapt to a new insult cannot be entirely ruled out. Furthermore, recent work suggests that Wnt/β-catenin signaling suppression might be involved in an animal model of right ventricular arrhythmogenic cardiomyopathy.

Cross-talking between the different Wnt pathways is another aspect that deserves further analysis. It has been suggested that Dsv might also be involved in calcium handling, protein kinase C and calcium-calmodulin kinase II, opening a wide spectrum of possibilities through which the hypertrophic program might be activated.

The work by van de Schans et al offers new insight, showing that it is possible to attenuate pressure overload-induced hypertrophy by interruption of the Wnt/Frizzled pathway through mechanisms involving GSK-3β and Akt. This opens multiple avenues that deserve further investigation to better understand the cellular machinery that leads to left ventricular hypertrophy and heart failure.

Disclosures

None.

References

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