Editorial Comment

The Gene Expression Profiling of Concentric and Eccentric Cardiac Hypertrophy

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Cardiac hypertrophy in its initial phase is recognized to be an adaptive response to increased biomechanical stresses such as pressure or volume overload, because Laplace's law dictates that increased wall stress is offset by an increase in wall thickness (*1*). However, recent clinical studies have shown that cardiac hypertrophy is an independent risk factor for sudden death, arrhythmia, and myocardial infarction (*2*), and prolonged exposure to pressure or volume overload leads to heart failure through poorly understood mechanisms (*3*). Therefore, it is important to clarify the precise molecular mechanisms responsible for the development of hypertrophy and its transition to heart failure.

There are two morphologically distinct types of hypertrophic heart growth, concentric hypertrophy (increase in wall thickness and cardiac mass with little change in chamber volume) and eccentric hypertrophy (increase in cardiac mass with increased chamber volume; the relative wall thickness may be either normal, increased, or decreased). Concentric hypertrophy is induced by the pressure overload observed in patients with hypertension or aortic stenosis, whereas eccentric hypertrophy is induced by volume overload due to mitral/aortic regurgitation or anemia. Although a number of studies have implicated a variety of signaling molecules in hypertrophic growth of the heart in general (*4–6*), relatively little is known regarding the signaling pathways that specifically induce the eccentric form of cardiac hypertrophy. At the cellular level, concentric hypertrophy is associated with an increase in myocyte width, whereas eccentric hypertrophy is associated with an increase in myocyte length (*7*). In this respect, it is noteworthy that stimulation with cardiotrophin-1 or leukemia inhibitory factor (LIF) leads to hypertrophy associated with elongation of myocytes due to assembly of sarcomeric units predominantly in series rather than in parallel (*8*), suggesting that gp130-mediated signals contribute to the development of eccentric hypertrophy. In an independent study, it was shown that overexpression of activated MEK5 (a mitogen-activated protein kinase [MAPK] kinase that selectively upregulates extracellular receptor-kinase [ERK]5 MAPK) results in eccentric hypertrophy in transgenic mice, and that LIF-induced elongation of cultured cardiac myocytes is attenuated by the expression of dominant-negative MEK5 (*9*), suggesting that the gp130-MEK5-ERK5 pathway promotes myocyte elongation and eccentric hypertrophy. These findings support a view that activation of a specific signaling pathway(s) mediates the eccentric form of hypertrophic heart growth. However, it should be noted that ERK5 is activated in the heart of spontaneously hypertensive rats, a genetic model of hypertension and pressure overload–induced cardiac hypertrophy (*10*). Furthermore, examination of the kinetics of various signaling pathways in response to pressure or volume overload revealed that pro-hypertrophic signaling pathways are differentially activated between concentric and eccentric cardiac hypertrophy (*11*). For example, pressure overload and volume overload activate ERK1/2 in the early and late phase of hypertrophy, respectively, and pressure overload induces transient Akt activation, whereas volume overload induces sustained Akt activation. These observations suggest another possibility that the different mode of activation of multiple signaling pathways determines whether the resultant hypertrophy is concentric or eccentric. It remains to be elucidated why two different stimuli (pressure and volume overload) lead to differential activation of intracellular signals in the

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heart, and how the different mode of activation of multiple signaling pathways results in morphologically distinct forms of hypertrophy.

Recent technical advances in transcriptome studies have enabled high-throughput analyses of global gene expression patterns in various settings, and several groups have reported the gene expression profiles of pressure overload hypertrophy both in humans and in animals (*12–17*). In this issue of *Hypertension Research*, Miyazaki *et al*. have extended previous studies and compared the gene expression profiles between pressure overload– and volume overload–induced cardiac hypertrophy (*18*). They have shown that 64 genes behaved similarly (33 were upregulated and 31 downregulated both in pressure and volume overload), the expressions of 93 genes were modulated only by pressure overload (52 were upregulated and 41 downregulated), and the expressions of 134 genes were selectively altered by volume overload (88 were upregulated and 46 downregulated). Although it is not always easy to extract meaningful conclusions from these data alone, the authors suggest that the upregulation of genes encoding actin-binding proteins by volume overload may contribute to the formation of eccentric morphology. Among several genes differentially regulated by pressure and volume overload, of particular interest are the genes that respond to these two hypertrophic stimuli in an opposite manner. For example, tropomyosin 4, thymosin β-4, transgelin (SM22α), and vascular endothelial growth factor (VEGF) are upregulated by volume overload and downregulated by pressure overload, whereas pyruvate dehydrogenase kinase-1 is upregulated by pressure overload and downregulated by volume overload. It will be of great interest to identify pressure overload– or volume overload–responsive elements in the promoter/enhancer regions of these genes, and to identify transcription factors that regulate pressure or volume overload–specific transcriptional programs.

The study by Miyazaki *et al*. (*18*) is obviously an important initial step towards the understanding of the molecular mechanisms by which pressure and volume overload induce morphologically distinct patterns of cardiac hypertrophy. Further studies to dissect signaling pathways of hypertrophic heart growth will lead to the development of novel therapeutic strategies to prevent or reverse cardiac hypertrophy and heart failure.

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