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New insights into the molecular phenotype of eccentric hypertrophy

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Cardiac hypertrophy is defined as an increase in the size of the heart caused by an increase in the size of the cardiomyocytes therein, which is achieved by an increase in the number of sarcomeres, a basic unit of a muscle's cross-striated myofibril [1-3]. Cardiac hypertrophy is caused by hemodynamic overload, which includes pressure overload (PO) caused by aortic stenosis and high blood pressure, and volume overload (VO) caused by valvular insufficiency, chronic myocardial infarction, arteriovenous shunt, and pregnancy [1,2]. PO and VO induce distinct forms of cardiac hypertrophy with different morphologies, mechanical properties, and gene expression profiles, at least at early phases. PO causes “concentric” hypertrophy, characterized by increased ventricular wall thickness and little chamber dilation, where *parallel* addition of sarcomeres increases the size of cardiomyocytes in both minor and major axes. In contrast, VO results in “eccentric” hypertrophy, characterized by increased ventricular volume with little increase in the wall thickness, where *serial* addition of sarcomeres increases the size of cardiomyocytes primarily by elongation [1-3].

Molecular, biological and functional properties in the heart are differentially regulated between PO- and VO-induced hypertrophy (Table 1). For example, synthesis of contractile proteins is increased during the early phase of PO cardiac hypertrophy [4-8]. In contrast, an increase in LV mass may be at least initially caused by reduced protein degradation, with protein synthesis becoming significant only at a later phase, in VO cardiac hypertrophy [4]. Perhaps one of the most interesting differences between PO and VO hypertrophy in terms of their functional significance and the underlying signaling mechanisms is the expression of fetal sarcomere proteins. Calderone and colleagues have shown that alpha-skeletal actin (αSKA), a fetal isoform of the contractile protein, is up-regulated in myocardium subjected to PO, but not in myocardium under VO in rats [9]. Other studies also demonstrated that αSKA is a marker of concentric, rather than eccentric hypertrophy, both in rodents and humans [10-12]. Since increased expression of αSKA is associated with increased ventricular contractility [13], and its expression decreases when concentric hypertrophy develops into the eccentric phenotype with reduced cardiac function [16], it may be possible that αSKA is essential, especially at the initial phase of PO, for the heart to offset the systolic impedance and maintain cardiac output [14]. The functional significance of the fact that αSKA is not up-regulated during VO hypertrophy remains unknown.

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Two major triggers of intracellular signaling pathways which modulate cardiac hypertrophy include biomechanical signaling and neurohumoral factors [1,2]. Biomechanical stress activates stretch-sensitive molecules in the heart, including ion channels, integrins, G protein-coupled receptors, and other cytoskeletal proteins, which convert mechanical signals to chemical ones and transmit them to sarcomeres, second messengers, and the nucleus [1,2]. In addition, neurohormonal factors, such as angiotensin II, endothelin-1, CT-1 and LIF, are secreted from cardiomyocytes and non-myocytes as autocrine or paracrine factors in response to mechanical forces, thereby causing cardiac hypertrophy, fibrosis, cell death, contractile dysfunction and rhythm disturbances [1,2,15-17].

Interestingly, the heart appears to have an ability to sense distinct forms of mechanical loading and initiate unique signaling mechanisms to induce different forms of hypertrophy. For example, the direction of mechanical stretch is a crucial determinant of growth in cardiomyocytes [18]. A stretch in the same direction as the cardiomyocyte sarcomere axis does not stimulate synthesis and turnover of contractile proteins. On the other hand, a stretch across the short axis of cardiomyocytes, which mimics stretch of cardiomyocytes in the heart under PO, leads to increased contractile protein synthesis and decreased degradation, resulting in protein accumulation [18]. Mechanical load of cardiomyocytes during the systolic phase is associated with increased activation of MEK1/2/ERK1/2 compared to cardiomyocytes subjected to diastolic load in vitro [19]. Increased diastolic stress may promote eccentric hypertrophy through reduced tyrosine phosphorylation of focal adhesion kinase and decreased interaction between focal adhesion kinase and cytoskeletal proteins, such as p130 and paxillin [20]. Systolic loading in vivo is associated with increased JNK activity, whereas increased diastolic stress causes a rapid activation of p38 MAPK [21].

Activation of stimulus-specific signaling molecules, either directly or indirectly through secretion of specific cytokines, mediates either PO- or VO-induced cardiac hypertrophy. Importantly, however, the causative roles of the aforementioned stimulus-specific signaling molecules in mediating VO-induced eccentric hypertrophy remain to be elucidated.

In this issue of the Journal, Nakaoka and colleagues [22] describe a new insight regarding the signaling mechanism mediating eccentric cardiac hypertrophy. Previously, the authors showed that LIF-induced elongation of cardiomyocytes is mediated by activation of SHP2, an SH2 domain-containing tyrosine phosphatase, and its association with Gab1, an adaptor protein [11]. In the present study, the authors demonstrated that LIF-induced activation of SHP2 negatively regulates expression of αSKA through inhibition of RhoA. The work not only confirms the importance of SHP2 activation in mediating the phenotype of eccentric hypertrophy, but also provides a specific explanation as to why eccentric hypertrophy is not accompanied by upregulation of αSKA. Specifically, inhibition of RhoA, together with activation of ERK5, plays an important role in mediating the cardiac phenotype observed in LIF-induced cardiac hypertrophy. RhoA is activated by PO [23] and Gαq-agonists inducing concentric hypertrophy [24], whereas it is inhibited by LIF [22]. Since RhoA regulates transcription mediated through SRF [25], RhoA may play an important role in mediating distinct gene expression profiles between concentric and eccentric hypertrophy. It should be noted that, since suppression of SHP2 allows LIF to induce activation of RhoA and expression of αSKA, LIF should be able to independently activate RhoA, which is negatively regulated by SHP2. It has been shown that activation of MEK5/ERK5 not only promotes elongation of myocytes but also inhibits parallel sarcomere assembly [26]. Thus, the signaling mechanism mediating eccentric hypertrophy appears to have cross-talk with that mediating concentric hypertrophy. It is possible that suppression of SHP2 may convert LIF-induced hypertrophy from eccentric to concentric. Even if this hypothesis is incorrect, the fact that SHP2 co-regulates cell shape and expression of αSKA is intriguing.

Although it is becoming increasingly clear that cytokines activating gp130 and the downstream signaling pathway could induce a cardiac phenotype mimicking eccentric hypertrophy, surprisingly, the involvement of these mechanisms in VO-induced eccentric hypertrophy has not been clearly demonstrated in vivo. For example, whether or not the IL6 family cytokines are selectively upregulated in VO-induced hypertrophy compared to PO-induced hypertrophy, and, if so, whether they are involved in the development of eccentric hypertrophy remain to be elucidated. The involvement of gp130, SHP2 or ERK5 in VO-induced hypertrophy also remains to be shown. Perhaps the most straightforward experiment would have been to test whether the development of eccentric hypertrophy by VO or by LIF can be inhibited in the absence of these molecules. Unfortunately, interpreting these experiments may not actually be straightforward, however, because gp130, SHP2 and ERK5 have multiple cellular functions, most importantly promoting cell survival mechanisms. Hemodynamic overload in the complete absence of these molecules induces cell death, and the consequent LV dysfunction independently affects cardiac hypertrophy and the gene expression profile, which makes interpretation of experimental results difficult. For example, the homozygous deletion of gp130 [27] or SHP2 [28] is sufficient to stimulate cardiac dilation secondary to cardiac dysfunction. The use of heterozygous deletion may partially alleviate this problem.

Since we now know that the gp130/SHP2 pathway induces eccentric hypertrophy in cardiomyocytes, future investigations should clarify the nature of the biomechanical sensors that are selectively activated during VO stress, and their intracellular mediators. In addition, neurohumoral factors that are specifically released in response to VO should be investigated. Eventually, how the biomechanical sensors, cytokines and the gp130/SHP2 pathway are connected to one another should be clarified (Figure 1). Intracellular signaling cascades involved in the promotion of eccentric hypertrophy may positively or negatively regulate cell survival, which is the major determinant of transition from compensated hypertrophy to cardiac failure. Since many of the signaling mechanisms described by Nakaoka are involved in cell survival, they may be involved in the initial (adaptive) phase of eccentric hypertrophy. We speculate that the signaling mechanisms mediating dilation of the heart during transition from compensated (concentric) to uncompensated (eccentric) hypertrophy could be distinct from the gp130/SHP2 pathway described in this work since such a process should be accompanied by cell death and consequent cardiac dysfunction. Elucidating the signaling mechanism mediating the development of eccentric hypertrophy at both adaptive and maladaptive phases may allow us to identify novel strategies to modulate ventricular remodeling and gene expression and delay or even prevent the onset of heart failure in patients with cardiac disease characterized by VO.

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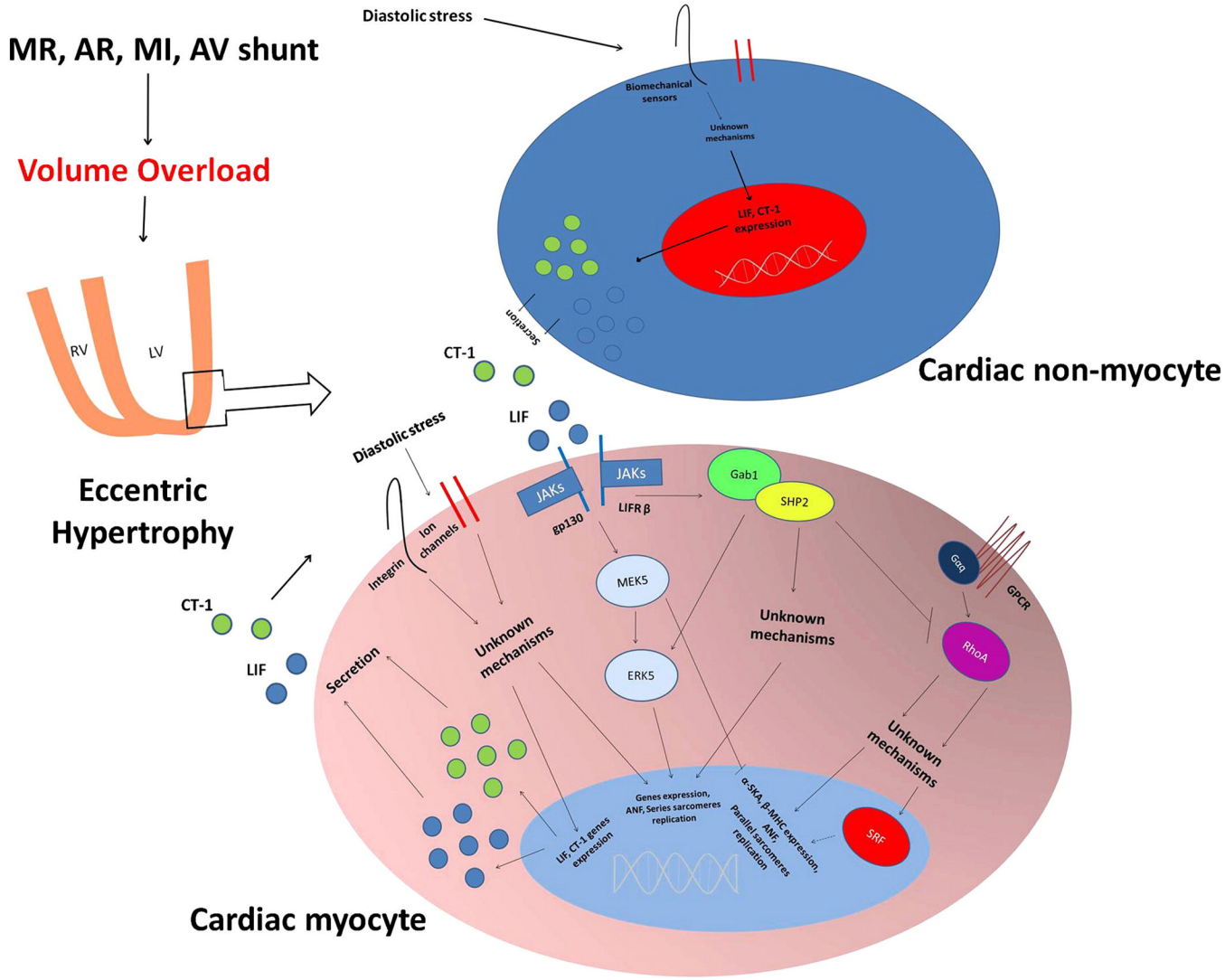

Figure 1.

Proposed mechanisms promoting the development of compensated eccentric hypertrophy following volume overload. An increase in diastolic stress might activate biomechanical sensors which activate intracellular signals that, in turn, modulate gene expression favoring eccentric hypertrophy development, and stimulate LIF and CT-1 transcription, translation and secretion. At the same time, cardiac non-myocytes may secrete LIF and CT-1 in response to VO. Thus, through autocrine and paracrine effects, secreted LIF and CT-1 activate the cardiomyocyte intracellular Gab1-SHP2 complex, by activating gp 130 and LIF receptors. SHP2 promotes cardiomyocyte elongation through ERK5 activation and perhaps also through other unknown mechanisms. At the same time SHP2 also inhibits RhoA, which regulates gene expression through SRF. MR: mitral regurgitation; AR: aortic regurgitation; MI: myocardial infarction; AV: arteriovenous.

Table 1

Morphological and molecular characteristics of concentric and eccentric hypertrophy, and their extra- and intracellular mediators. CM= cardiomyocyte; EM=extracellular matrix, FAK=focal adhesion kinase.

		Pathological hypertrophy	
Morphologic and molecular characteristics		**Concentric**	**Eccentric**
Gravimetric, morphological and structural parameters	**Ventricular mass**	↑↑	↑↑
	Ventricular volume	=/↓	↑↑
	Relative wall thickness	↑↑	=
	Cardiomyocyte growth in width	↑↑↑	=/↑
	Cardiomyocyte growth in length	↑	↑↑↑
	Sarcomere replication	Parallel	Series
CM protein turnover and fetal gene up-regulation [4,6,7,9,29]	**Contractile protein synthesis**	↑↑	=/↑
	Contractile protein degradation	↓↓	↓↓
	Fetal myosin switch	↑↑	=/↑
	Alpha-skeletal actin expression	↑↑	=
	Atrial natriuretic factor	↑↑	↑↑
	Tubulin amount	↑↑	=
EM protein turnover [30]	**EM accumulation**	↑↑	↑
	MMP-9 activity	↑	↑↑↑
	MMP-1/TIMP-1 ratio	↓	=/↓
Biomechanical, neurohumoral and intracellular mediators [1,2,10,11,20,31-36]	**Biomechanical sensors signals**	Melusin, ILK-1, FAK (activation)	FAK, gp130 and paxillin (reduced signaling),
	Neuro-humoral mediators	Angiotensin II, Endothelin-1, norepinephrine	CT-1, LIF, IGF-1
	Receptors	GPCR	gp130, LIF receptor
	Signaling molecules	cAMP, Ca^{2+}, RhoA PI3K/Akt, MEK1/2, ERK1/2, calcineurin, Elf-4E	Ca^{2+}, Gab1 SHP2, MEK5/ERK5, calcineurin, calmodulin kinases II-IV