Shp Shape
FAKs About Hypertrophy
Kathleen A. Martin, John Hwa

Despite recent advances in cardiovascular disease prevention and treatment, heart failure remains a major cause of morbidity and mortality in Western countries. Cardiac hypertrophy, an increase in heart weight relative to body weight, can be a beneficial adaptive response, as in the heart of the athlete (“physiological hypertrophy”), but it is clear that distinct forms of pathological hypertrophy (induced by pressure or volume overload) can progress to cardiac failure.1,2 Cardiac hypertrophy, even in the absence of overt failure, has prognostic significance. Hypertensive patients with echocardiographically determined increases in left ventricular mass and geometry have a higher risk of cardiovascular death.3 This finding has led to intensive investigations into drugs that reduce hypertrophy.4 Angiotensin-converting enzyme inhibitors have been shown to reduce hypertrophy,4 influence remodeling,5 and improve survival.6 In recent years, we have progressed in dissecting the molecular signaling mechanisms underlying distinct hypertrophic phenotypes (including physiological, concentric, or eccentric), but it appears that our present understanding reflects only the tip of the iceberg of the complex regulation of remodeling in the heart. A major question that remains is how mechanical (and neurohormonal) stimuli are transduced into molecular signals that drive hypertrophy.

Several recent studies reveal that the tyrosine phosphatase Shp2 (Src homology 2 domain–containing protein tyrosine phosphatase), encoded by the Ptpn11 gene, may be a key player in transducing mechanical signals into the molecular and pathophysiological manifestations of cardiac hypertrophy. In this issue of Circulation Research, Marin et al implicate Shp2 as a critical mediator of stretch-induced cardiomyocyte hypertrophy.7 Integrins link the extracellular matrix with the intracellular cytoskeleton, and proteins such as the tyrosine kinases focal adhesion kinase (FAK) and Src are involved in transducing motility-associated signals. FAK had been implicated in the hypertrophic response to cyclic stretch.8 In vivo studies also point to a requirement for FAK in pressure overload–induced cardiac hypertrophy.9,10 The present study now reveals that Shp2 mediates stretch signal-

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Figure. Left, In unstretched myocytes, Shp2 associates with and dephosphorylates FAK, inhibiting FAK activity. In response to a pathological degree of cyclic stretch (15% above initial length), Shp2 dissociates from FAK, relieving this repression. Activated phosphorylated FAK then phosphorylates and activates the tyrosine kinase Src, and the activity of FAK and Src are necessary for the phosphorylation of Akt and TSC2. Akt phosphorylation of TSC2 relieves repression of the mTORC1 pathway, promoting protein synthesis and cell growth. Right, Muscle-specific genetic deletion of Shp2 results in hyperactivation of RhoA/ROCK and impaired ERK1/2 activation and cardiac hypertrophy in response to pressure overload. ERK1/2 promotes and RhoA/ROCK inhibits cardiomyocyte hypertrophy. (Note that arrows in the figure do not necessarily indicate a direct interaction between proteins.)

Although FAK and Shp2 associate in nonstretched cardiomyocytes, it remains to be determined whether all of these FAK-associated proteins might exist in a common complex, and how this may lead to transduction of the stretch signal to various downstream effectors of the hypertrophic response, including ERK1/2 and mTORC1.

Whereas Marin et al7 report that Shp2 inhibition mediates stretch-induced hypertrophy, another recent study reports that Shp2 is necessary for pressure overload–induced cardiac hypertrophy. Kontaridis et al17 demonstrate that skeletal and cardiac muscle–specific genetic deletion of Shp2 (MCK-Shp2–null mice) results in spontaneous dilated cardiomyopathy without hypertrophy. Despite impaired cardiac function, the mice survive for up to 12 months with no evidence of cardiac failure. Consistent with a defect in the hypertrophic response, MHC isoform levels did not change, and there was no increase in heart weight nor in the size or number of individual myocytes. However, the shape of the myocytes differed. Isolated myocytes were longer and thinner than those from control animals, suggesting that this cellular morphology contributes to the dilatation at the organ level. Importantly, when these mice are subjected to pressure overload, Shp2 deletion also prevents the hypertrophic response (Figure, right). Pressure overload normally results in concentric hypertrophy, in which sarcomeres are added in parallel to increase myocardite width, but this was absent in the Shp2-null mice.

Shp2 is required for ERK1/2 activation by many stimuli, and Kontaridis et al confirm that ERK1/2 activation is impaired in the MCK-Shp2–null mice in response to multiple agonists or pressure overload. These mice also exhibit hyperactivity of RhoA in the basal state. The aberrant ERK1/2 and RhoA/ROCK signaling is thought to contribute to the phenotype in vivo, because modulation of these pathways leads to distinct cell shape changes that parallel those seen in the MCK-Shp2 nulls. ERK1/2 inhibition in cardiomyocytes from control mice was sufficient to induce the elongated, narrow cellular morphology characteristic of the Shp2-null cells, whereas inhibition of the RhoA effector ROCK in cardiomyocytes from control mice promoted a morphology with increased cell width but shortened length, opposite to that exhibited by the null cells. Notably, previous work places both RhoA/ROCK16 and Shp217 upstream of FAK. This new work suggests that Shp2 also influences RhoA/ROCK activity,17 suggesting a potential point of convergence.

How can we reconcile the apparent paradox of Shp2 inhibiting cardiomyocyte hypertrophy in the in vitro stretch model7 and being required for pressure overload–induced cardiac hypertrophy in the mouse model17? One obvious potential explanation is the difference in the models. Because the in vitro cyclic stretch model lacks the context of a cardiac cycle (systole and diastole), it is difficult to determine whether this is modeling pressure or volume overload, each of which results in a distinct hypertrophic response (concentric or eccentric, respectively).1 Shp2 may transduce different signals in response to distinct mechanical stimuli. Furthermore, paracrine and neurohormonal inputs may modulate responses in vivo. It is also likely that signal strength, duration, localization, and the context in which the signal occurs, and not the mere presence or absence of the signal itself, determines the ultimate downstream consequences of Shp2 activation.18 The gp130 cytokine receptor provides 1 example of the complexity of hypertrophic phenotypes that can emanate from a single receptor.19 Shp2 can associate with this receptor in complex with either Grb2 or Gab1, activating the ERK1/2 or Akt pathways, respectively. Depending on the activating ligand and hetero- or homodimerization of the receptor, differential signaling can occur. Leukaemia inhibitory factor activation of gp130 activates ERK5 via a Gab1/Shp2 complex and specifically induces an eccentric hypertrophic phenotype,20 whereas gp130 activation primarily of STAT3 promotes concentric hypertrophy.19 Finally, the repressor SOCS3 can directly compete with Shp2 for gp130 binding, preventing activation of STAT3, ERKs, and Akt. The nature of the signaling complexes assembled at this receptor can dictate the type of hypertrophy induced, and an imbalance in activation of downstream signaling effectors may potentially drive the transition from adaptive to maladaptive.19 Finally, in human genetic syndromes, Shp2 phenotypes differ from the mouse model. The study by Kontaridis et al17 would predict that Shp2 gain of function would induce hypertrophy, but such Ptpn11 mutations in Noonan’s Syndrome rarely exhibit hypertrophy.21 Conversely, in patients with LEOPARD syndrome with Shp2 loss-of-function mutations, cardiac hypertrophy is common.21 The differences between the human syndromes and the mouse MCK-Shp2–null model may arise from differences in species, differences between embryonic mutation (human) and adult onset genetic deletion (mouse model), and deletion versus expression of a mutant Shp2 protein.17 The human syndrome phenotypes,
notably, are consistent with the role for Shp2 suggested by Marin et al.7

We suggest that the multiple and sometimes opposing roles in cardiomyocyte hypertrophy ascribed to Shp2 in the described studies may be analogous to the classic example of the blind men examining an elephant, where each describes only a component of the whole (trunk, tail, ear, etc.). The complexity and variability of the hypertrophic response is such that it is not easily characterized in a reductionist approach. Furthermore, it is likely that hypertrophy is a heterogenous group of responses rather than the simplistic physiological, concentric, and eccentric classifications. Although those of us who study signal transduction often attempt such linear characterizations of biological processes, it is becoming increasing clear that hypertrophy is more than the sum of its parts or individual pathways.

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