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 signaling to FAK in rat neonatal cardiomyocytes. In a series of elegant molecular studies, they demonstrate that Shp2 associates with, dephosphorylates, and inhibits FAK in nonstretched myocytes and that stretch relieves this inhibition, which subsequently activates the mTORC1 (mammalian target of rapamycin complex 1) pathway (Figure, left). mTORC1 activation appears to be the main effector driving the stretch-induced hypertrophy in this model, because the mTORC1 inhibitor rapamycin markedly attenuates the hypertrophy. Activation of the Akt/mTOR pathway has been implicated primarily in physiological hypertrophy, but chronic hyperactivation of this pathway also appears to contribute to pathological hypertrophy.11 In this in vitro stretch model, the hypertrophy appears to be “pathological,” because the β-myosin heavy chain (MHC) isoform is also induced.12 FAK is known to regulate the hypertrophic program of fetal gene expression.8,13 Protein synthesis and cell size regulation are well-known functions of mTORC1,14 but it would be of interest to determine whether the β-MHC transcriptional induction by stretch or Shp2 depletion is mTORC1-dependent. FAK also promoted extracellular signal-regulated kinase (ERK)1/2 activation, an mTORC1-independent signal also known to mediate hypertrophic responses.

The study by Marin et al additionally demonstrates that downregulation of Shp2 itself is sufficient to induce cardiomyocyte hypertrophy in the absence of applied stretch. They noted a dose-dependent induction of hypertrophy in response to Shp2 inhibition with small interfering RNA. Shp2 inhibition was sufficient to activate FAK, Src, and the Akt/mTORC1 pathway in the absence of stretch, and the consequent hypertrophy was sensitive to inhibitors of FAK/Src and to rapamycin.7 Notably, this suggests that in the absence of excessive stretch, Shp2 limits cell growth by maintaining low basal activity of FAK and mTORC1.

mTORC1 has been clearly implicated in cardiac and skeletal muscle hypertrophy in response to mechanical forces,14 but very little is known about how these forces regulate mTORC1 at the molecular level. Marin et al also provide novel insights into mechanotransduction to mTORC1, implicating FAK and Src in transduction of the stretch signal. The mechanisms by which these tyrosine kinases promote the activation of Akt and the subsequent inhibition of tuberous sclerosis complex (TSC) 2 that activate mTORC1 in this context are still unknown.7 How might stretch regulate Shp2 and FAK? Mechanical stress induces a subcellular redistribution of FAK and disrupts the association of FAK with the C-terminal region of MHC.15 RhoA and ROCK have also been implicated upstream of FAK in stretch-induced hypertrophic signaling, and FAK and RhoA dissociate after stretching cardiomyocytes.16

**Shp Shape**

**FAKs About Hypertrophy**

Kathleen A. Martin, John Hwa

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Shp2 is necessary for pressure overload–induced cardiac hypertrophy in the in vitro stretch model and being required for pressure overload–induced cardiac hypertrophy in the mouse model. 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). 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. The gp130 cytokine receptor provides 1 example of the complexity of hypertrophic phenotypes that can emanate from a single receptor. 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, whereas gp130 activation primarily of STAT3 promotes concentric hypertrophy. 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. Finally, in human genetic syndromes, Shp2 phenotypes differ from the mouse model. The study by Kontaridis et al would predict that Shp2 gain of function would induce hypertrophy, but such Ptpn11 mutations in Noonan’s Syndrome rarely exhibit hypertrophy. Conversely, in patients with LEOPARD syndrome with Shp2 loss-of-function mutations, cardiac hypertrophy is common. 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. 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 heterogeneous 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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