Hypertension induces cardiac myocytes in the left ventricle to activate a hypertrophic response that involves the upregulation of contractile proteins and the re-expression of fetal genes.1 Transcriptional induction is an important component of this response, and the zinc finger–containing transcription factors GATA4 and GATA6 have been shown to directly stimulate cardiac hypertrophy.2 LIM domain proteins (named after the first 3 LIM proteins identified: Lin11, Isl-1, and Mec-3) interact with transcriptional regulators, kinases, and structural proteins. Because of these protein-protein interactions, LIM domain proteins have been assigned roles in cell growth, differentiation, and cytoskeletal remodeling.3 Several LIM proteins have been identified by proteomic and functional screens of left ventricles subjected to pressure overload.4,5

LIM and cysteine-rich domains 1 (Lmcd1) protein has 2 LIM domains in the C-terminus and a cysteine-rich domain in the N-terminus. Because it contains ≥1 LIM domain in the C-terminus, Lmcd1 is classified as a group 3 LIM protein, and most of the previously identified group 3 LIM proteins have been shown to localize to the cytoplasm. Lmcd1 is expressed in most tissues and is particularly highly expressed in cardiac and skeletal muscle.6 Beyond a few initial identification studies, little is known about the roles that Lmcd1 plays in the heart, particularly after pathological stimulation. In this issue, Bian et al7 demonstrate in primary cardiac myocytes and cardiac-specific Lmcd1 transgenic mice (driven by the α-myosin heavy chain promoter) after transverse aortic constriction that increased Lmcd1 augmented the hypertrophic response, increases in atrial natriuretic peptide and B-type natriuretic peptide levels, the fibrotic response, and increases in calcineurin/nuclear factor of activated T cells activation. In the absence of a hypertrophic stimulus, overexpression alone did not induce cardiac hypertrophy in mice at this age. Together, these results place Lmcd1 at a critical juncture in the hypertrophy signaling pathway.

Although these data are exciting and suggest novel therapeutic possibilities, there are several questions that will need to be answered next. For one, the fact that only cardiac myocytes are targeted means that the potential role of Lmcd1 in other pressure overload–relevant cell types, including endothelial cells, vascular smooth muscle cells, and fibroblasts, will need to be explored. Will inhibiting Lmcd1 in all cell types produce an equally beneficial effect or will there be a divergence of functions? Another issue is that, whereas Lmcd1 coimmunoprecipitated with calcineurin to indicate a cytosolic localization, whether Lmcd1 is only cytosolic or has nuclear functions as well needs to be explored. Lmcd1 proteins have been found in both the cytoplasm and nucleus, and Rath et al8 demonstrated that Lmcd1 downregulates GATA6 signaling on cardiac tissue promoters by directly binding GATA6 and preventing its DNA binding. Additional confirmation that Lmcd1 directly binds to calcineurin, using a yeast 2-hybrid strategy, for instance, is warranted. The current study provides evidence that Lmcd1 can directly bind to calcineurin, but whether there are additional mechanisms has not been evaluated.

In this study by Bian et al,7 cyclosporin A was used to block calcineurin and to prevent the development of cardiac hypertrophy. Cyclosporin A was given using a pretreatment experimental design, but whether Lmcd1 inhibition also has reversal potential was not addressed. Starting treatment after the induction of hypertrophy, either using pharmacological agents or conditional Lmcd1 null mice, will help to address this issue. Although multiple cardiac hypertrophy and fibrosis makers were evaluated, including A-type and B-type natriuretic peptides, β-myosin heavy chain, connective tissue growth factor, collagen I, and collagen IV, and were shown to be altered by Lmcd1 overexpression or inhibition, more mechanistic insight is needed. The fact that Lmcd1 overexpression in cardiac myocytes induces fibrosis means that downstream cardiac fibroblasts are activated by Lmcd1 stimulation, because fibroblasts are the major source of extracellular matrix (particularly collagen I). Lmcd1 overexpression in cardiac myocytes upregulated connective tissue growth factor and transforming growth factor-β1 expression in vivo, indicating that cardiac fibroblast activation may be occurring through these mediators. The fact that small hairpin RNA Lmcd1 in vitro had the same effect in reducing myocyte hypertrophy as cyclosporin A in vivo suggests that Lmcd1 may be a downstream target of cyclosporin A or that the pathways regulated by these 2 factors merge.

In this study, only male mice were evaluated. In the clinical setting, however, hypertension occurs at least in equal rates in men and postmenopausal women. Therefore, future studies will need to determine whether Lmcd1 functions similarly in both sexes. Another issue that will need to be worked out is how Lmcd1 coordinates functions with other transcription factors, such as the Forkhead box transcription factors O1 subfamily, which also blunt the hypertrophic response by inhibiting calcineurin.8 It will be interesting to see how
Lmcd1 interacts with the phosphatidylinositol 3-kinase/Akt pathway, as well as other pathways activated by hypertrophic agonists. Where Lmcd1 conceptually fits into the big picture of cardiac hypertrophy is illustrated in the Figure. In summary, Bian et al provide us with the first evidence of Lmcd1 involvement in cardiac hypertrophy. Using an overexpression strategy, they demonstrate that increased levels of Lmcd1 exacerbate the hypertrophic response, whereas an inhibition strategy shows that hypertrophy can be blocked by targeting Lmcd1. The novel findings provided by this study indicate that Lmcd1 may be a relevant therapeutic target for hypertension-induced cardiac hypertrophy.

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