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COMMENTARY

A-Kinase-Anchoring Protein–Lbc Connects Stress Signaling to Cardiac Hypertrophy

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Heart failure often occurs as a consequence of persistent trauma to the myocardium. Cardiovascular pathologies, including hypertension, valvular disease, atherosclerosis, and ischemia, can all lead to pressure overload and myocardial dysfunction. In the face of such stressors, the heart attempts to maintain normal contractile function by initiating a complex remodeling process involving the reexpression of developmental genes. This process leads to an increase in cardiac muscle mass commonly referred to as pathological cardiac hypertrophy. If trauma is persistent or severe, such compensatory mechanisms are overwhelmed or become maladaptive and heart failure ensues. Stress signaling pathways play an important role in cellular responses to cardiotoxic insults such as mechanical shear and an overabundance of proinflammatory molecules. Moreover, recent development of effective drug therapies targeting these pathways has renewed interest in the role of stress signaling in ventricular cardiomyocyte hypertrophy (1, 2).

A variety of well-known signaling cascades underlie the onset of cardiomyocyte hypertrophy. Although the precise molecular details of these pathways are not clear, several groups have uncovered valuable clues that point to the complexity of the signaling events that lead to these phenotypes (3). Adrenergic agonists, acting through α1-adrenergic receptors (α1-AR) and Gα12, activate the small G protein RhoA, which then engages both the Jun N-terminal protein kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) kinase cascades (4–6). These studies point toward stress signaling as a major contributor to the hypertrophic response.

In this issue, del Vescovo et al. describe an intriguing new connection between adrenergic, small GTPase, and cytokine signaling that regulates stress effects on cardiac remodeling (7). del Vescovo and colleagues have identified a robust protein-protein interaction between A-kinase-anchoring protein (AKAP)–Lbc and IκB kinase β (IKKβ), a crucial regulator of NF-κB signaling. Interestingly, AKAP-Lbc is an AKAP that also possesses Rho guanine nucleotide exchange factor (GEF) activity and acts as a scaffold for multiple kinases involved in cardiomyocyte function (5, 8, 9). In this context, AKAP-Lbc promotes fetal gene reprogramming through a protein kinase D (PKD)-histone deacetylase 5 (HDAC5) pathway (10) and functions downstream of α1-adrenergic receptors to activate Gα12-mediated RhoA signaling (5). Through a combination of mass spectrometry and standard biochemical analyses, del Vescovo and colleagues showed that IKKβ binds to AKAP-Lbc. This stress-activated kinase phosphorylates and targets IκB for proteasomal degradation, releasing the transcription factor NF-κB from inhibition and allowing it to enter the nucleus (11). Once in the nucleus, NF-κB initiates a predetermined program of gene expression to combat cardiac stresses. More-detailed biochemical mapping experiments identified a short helical region at the end of the AKAP-Lbc pleckstrin homology (PH) domain that was responsible for interaction with IKKβ. Furthermore, a point mutation in AKAP-Lbc, W2328L, dramatically reduces IKKβ binding (7). Next, del Vescovo et al. showed that short hairpin RNA (shRNA)-mediated silencing of AKAP-Lbc impairs activation of an NF-κB reporter gene. Silencing AKAP-Lbc expression also reduced phenylephrine (PE)-induced IKKβ kinase activity. Thus, the anchoring of IKKβ by AKAP-Lbc permits transmission of adrenergic signals to NF-κB.

A previous report had implicated the RhoA effector Rho kinase as an activator of NF-κB (12). Consequently, del Vescovo et al. asked whether an AKAP-Lbc-associated RhoA pathway relayed signals to NF-κB. Using an AKAP-Lbc mutant with constitutive Rho GEF activity, they demonstrated that application of the Rho kinase inhibitor Y27632 impairs NF-κB transcriptional activity. This inhibitor also blocks AKAP-Lbc-mediated activation of IKKβ, as assessed by *in vitro* kinase assays. Moreover, these effects appear to be specific for the Rho pathway, as small molecule inhibitors of protein kinase Cη (PKCη), p38α, and MEK1, which are other kinases that associate with AKAP-Lbc, had no effects on the NF-κB transcriptional reporter (4, 7, 13). Finally, del Vescovo et al. demonstrated a requirement for an AKAP-Lbc/IKKβ subcomplex to initiate NF-κB transcription, as RNA interference (RNAi) rescue experiments were ineffective upon reexpression of the AKAP-Lbc W2328L mutant, which no longer anchors IKKβ (7). Thus, adrenergic and stress signaling pathways seem to converge at the level of the AKAP-Lbc signaling complex.

While the work of del Vescovo and colleagues provides clear evidence of a link between the adrenergic and stress signaling pathways in myocytes, several key questions still remain. For example, how does adrenergic signaling to NF-κB result in cardiomyocyte hypertrophy? One clue was provided by recent work demonstrating that α1-adrenergic signals promote expression of the cytokine interleukin-6 (IL-6) in an NF-κB-dependent manner (14). Importantly, del Vescovo et al. were also able to show that inhibition of IL-6 signaling impairs α1-AR-mediated induction of fetal genes, as indicated by atrial natriuretic factor (ANF) and β-myosin heavy chain (β-MHC) gene transcription. Taken together, these data suggest that IL-6 is produced and secreted downstream of AKAP-Lbc/RhoA/NF-κB, where it acts in a paracrine/autocrine manner to promote transcription of fetal genes characteristic of the hypertrophic response (Fig. 1). It will be in-

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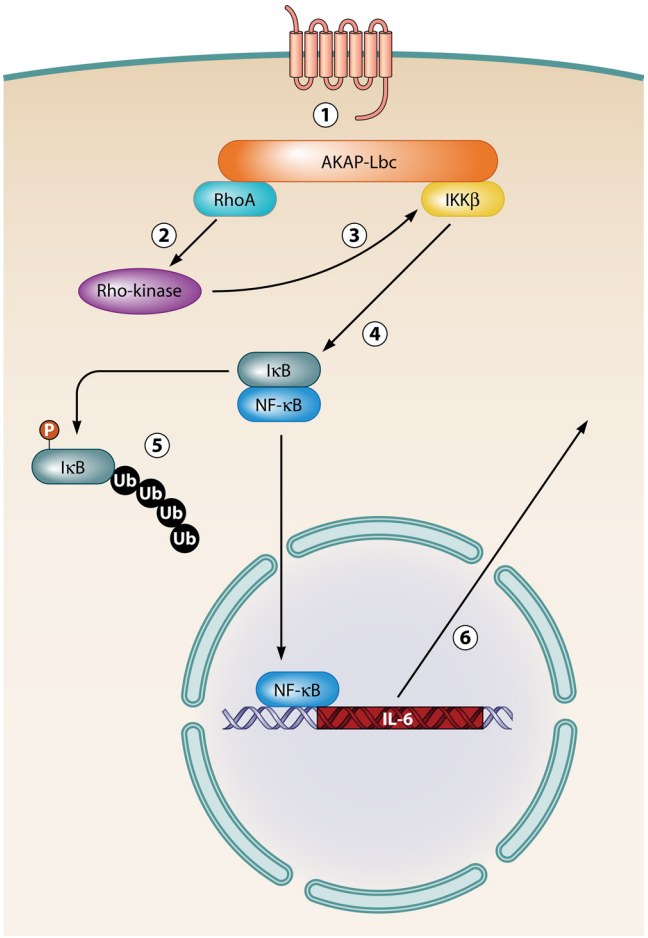

FIG 1 The AKAP-Lbc/RhoA/IKKβ complex acts downstream of α1-adrenergic receptors to relay hypertrophic signals to the transcription factor NF-κB. Adrenergic receptor signaling (1) leads to RhoA activation via the GEF AKAP-Lbc. Rho kinase, acting downstream of RhoA (2) phosphorylates IKKβ that is anchored by AKAP-Lbc (3). IKKβ disrupts IκB inhibition of NF-κB through phosphorylation of IκB (4), thereby targeting this subunit for proteasomal degradation (5). NF-κB then transits to the nucleus and activates the transcription of a number of genes involved in the cardiomyocyte stress response. One of these genes encodes IL-6 (6), and increased expression and secretion of this cytokine lead to paracrine/autocrine signaling that further propagates the hypertrophic phenotype. Ub, ubiquitin.

teresting to determine how IL-6 activates these genes, as it is attractive to hypothesize that IL-6 signals might also pass through the AKAP-Lbc complex to stimulate the PKD-HDAC5 pathway, which is known to control the developmental gene transcriptional program. Furthermore, this work and a recent report from Perez et al. (14) offer hope that targeting the IL-6 pathway during the onset of pathological trauma may represent a new avenue for therapeutic intervention in heart failure.

Another outstanding question in this field is whether the myriad signals that pass through the AKAP-Lbc complex are integrated or act independently. For example, AKAP-Lbc scaffolds that organize the PKD/HDAC5 pathway and/or the RhoA/Rho-kinase/IKKβ/NF-κB pathway both contribute to pathological hypertrophy. Thus, the next level of analysis will need to delineate between these pathways and establish the relative contribution of each enzyme subcomplex to the onset of pathological cardiac hypertrophy.

Finally, NF-κB was implicated in cardiomyocyte hypertrophy more than a decade ago (15), and attenuation of NF-κB-mediated transcription is known to reduce hypertrophy resulting from aortic banding in rats (16). These results, considered along with recent findings that gene silencing of NF-κB checks the onset of cardiac hypertrophy (17), point toward pharmacological manipulation of these events as a clinical option. Importantly the new information provided by del Vescovo et al. identifies the AKAP-Lbc–IKKβ interaction as a potential therapeutic target to interrupt hypertrophic signals from adrenergic receptors to NF-κB.

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