AMP Activated Protein Kinase 2 Protection During Hypertension-Induced Hypertrophy
A Common Mediator in the Signaling Crossroads

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Hypertension-induced pressure overload causes concentric left ventricular hypertrophy, which may induce arrhythmias or ultimately lead to congestive heart failure. Indeed, hypertension is a leading cause of heart failure in the United States. The cardiac response to pressure loading involves the intersection of multiple hypertrophic and metabolic signaling pathways. In cardiac myocytes, the major energy sensor is AMP activated protein kinase (AMPK), which is activated by increased ratios of AMP to ATP to turn off protein synthesis and to turn on the energy conservation mode. In this issue of Hypertension, Zhang et al examine the role of AMPKα2 in mediating cardiac hypertrophy. Using AMPKα2 null mice, they demonstrate that pressure overload (induced by 3 weeks of transverse aortic constriction) amplified the hypertrophic and fibrotic responses and further depressed cardiac function when compared with wild-type controls.

Although AMPK is ubiquitously expressed, concentrations of it are highest in skeletal and cardiac muscle. In cardiac myocytes, AMPKα2 is the dominant α catalytic subunit that complexes with 2 regulatory subunits (β and γ) to form the AMPK trimer. AMPK regulates fatty acid synthesis by phosphorylation of acetyl coenzyme A carboxylase to block malonyl-coenzyme A production. In addition, AMPK acts as a metabolic stress sensor in response to factors that limit fuel source, including hypoxia. Previous work has shown the following: (1) AMPK activity increases in pressure overload hypertrophy; (2) long-term activation of AMPK attenuates cardiac hypertrophy induced by aortic banding; (3) AMPK activation inhibits protein synthesis and hypertrophy in vitro in cardiac myocytes; and (4) the effects of AMPK activation in skeletal muscle are mediated through the Akt/mammalian target of rapamycin signaling pathway. Zhang et al extend these observations to show that deletion of AMPKα2 worsens remodeling after pressure overload. Their results complement a converse study published last year by Li et al in which AMPK activation by 5-aminimidazole 1 carboxamide ribonucleoside (AICAR) attenuated pressure-overload hypertrophy in rats. Because AICAR also lowers blood pressure, the work of Zhang et al provides supplemental evidence that the primary effect of AICAR is to activate AMPK.

Although AMPKα2 deletion did not produce changes in variables measured echocardiographically or at necropsy in unstressed mice, the null mice displayed exacerbated responses to 3 weeks of pressure overload. The increases in left ventricular and lung mass, as well as the decrease in left ventricular ejection fraction, were significantly greater in the null mice, and mortality was ≈20% higher in the null mice when compared with the wild-type controls. The fact that wall thickness was similarly increased and ejection fraction was still in the normal range in both groups indicates that the hearts were in a stage of compensatory hypertrophy at this time point and, therefore, did not show signs of failure. Fibrosis and myocyte cross-sectional areas also were amplified in the AMPKα2 null mice, suggesting that inactivation of AMPK mediates multiple downstream signaling pathways (Figure). It is interesting that AMPKα2 deletion further increased the expression of atrial natriuretic peptide, suggesting the extracellular signal regulated kinase and/or mitogen-activated protein kinase pathways were directly or indirectly upregulated by AMPK deletion. Although AMPKα levels rose in the null mice, the increase was not sufficient to compensate for the loss of AMPKα2, confirming that AMPKα2 is the major cardiac isoform. Using the same experimental design of 3 weeks of pressure overload, Liao et al showed previously a similar exacerbation of hypertrophy in adiponectin null mice. In the absence of adiponectin, AMPKα concentrations were depressed after banding, placing adiponectin as an upstream endogenous inducer of AMPK.

Furthermore, in vitro studies on isolated neonatal cardiac myocytes stimulated with phenylephrine in the presence or absence of AICAR or constitutively active AMPKα recapitulated the attenuated hypertrophic response seen in vivo. Future studies using this in vitro model to determine whether targeted disruption of Akt and p-70S6K is directly regulated by AMPK activation will help to further delineate the downstream pathways used by AMPK. The use of adult cardiac myocytes (rather than neonatal cells) would also confirm that adult cells behave in a similar manner. Because these same pathways are applicable in skeletal muscle homeostasis, studies that determine whether adverse effects occur after long-term treatment or whether cardiac-specific AMPK can be targeted are necessary.
An intriguing concept underscored by the results of this study is the fact that not every factor elevated in response to pressure overload has a negative consequence. These data provide an example of a factor for which the concentration is increased with hypertrophy and is protective, rather than deleterious, and they highlight the need to understand why a factor is expressed (and not just whether it is upregulated or downregulated) during hypertension and hypertrophy. AMPK levels increased in the wild-type mice after banding, indicating an endogenous protective mechanism. Another example of protection is the upregulation of the heat shock transcription factor-1 and its target heat shock proteins, which serve as key factors involved in the adaptive mechanism of cardiac hypertrophy.9

An additional concept raised by these results is that pressure overload induces a continuum of changes that begins with early compensatory hypertrophy and may end with heart failure. Although AMPKα2 may be protective in the short term, further studies of the temporal effects of activation or inactivation, especially at the juncture from acute to early and late chronic phases, are warranted. We have seen numerous examples in which inhibition is beneficial during the early stage and detrimental at a later stage of disease progression. An example of this is seen with matrix metalloproteinase inhibition after myocardial infarction in mice, where the short-term benefit of global matrix metalloproteinase inhibition shifts to a deleterious long-term outcome of increased mortality and more adverse remodeling.10 Thus, a temporal evaluation is needed to determine whether the absence of AMPKα2 accelerates the kinetics of progression to heart failure or whether later-phase deletion is beneficial.

In summary, the study by Zhang et al1 connects the results of several previously published works to highlight the role of AMPK in regulating the complex signaling cascade of LV hypertrophy. Inducing AMPK activation not only offers mechanistic insight into the hypertrophic signaling network but also may provide a novel therapeutic strategy in the treatment of patients with hypertension-induced hypertrophy.

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References


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