Akt Signaling and Growth of the Heart

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Physiological and pathological stimuli produce clinically and molecularly distinct forms of cardiac growth. Physiological cardiac growth is a feature of normal postnatal development in which an increase in cardiac muscle cell diameter is observed as infants mature to adults. This nonpathological heart growth, sometimes referred to as physiological hypertrophy, is similar to the growth observed in the hearts of trained athletes in whom the adaptation to increased workload leads to increased vascularization of the myocardium and more forceful ejection. In contrast, pathological hypertrophy occurs in patients with hypertension or valvular heart disease. A number of molecular distinctions can be made between physiological and pathological cardiac hypertrophy. For example, pathological cardiac hypertrophy is associated with interstitial fibrosis, activation of a fetal gene program, and myocyte apoptosis, whereas physiological cardiac growth does not display these features. Most studies have focused on elucidating mechanisms of pathological heart growth, whereas the molecular regulation of physiological cardiac growth is less understood. In this issue of Circulation, an article by DeBosch et al sheds light on the role of Akt1 signaling in the promotion of physiological growth and inhibition of pathological hypertrophy.

The Akt (also referred to as protein kinase B) family of serine/threonine protein kinases is highly conserved in evolution. Akt1 and Akt2 share extensive sequence homology at the amino acid level, whereas Akt3 is slightly more divergent in structure and is expressed as a splice variant that lacks a regulatory phosphorylation site. Akt protein kinases are stimulated by a number of receptor tyrosine kinases, and this is mediated by the action of phosphatidylinositol 3-kinase (PI3K). PI3K phosphorylates inositol lipids that activate Akt directly by binding to its pleckstrin homology domain and indirectly by activating the protein kinases that phosphorylate Akt. In the heart, Akt activation is regulated by insulin and nutritional status, exercise training, pressure overload, and advanced disease. In turn, Akt signaling regulates myocyte size, at least in part, through activation of mTOR-dependent progrowth pathways and suppression of GSK3β- and FOXO-dependent atrophy programs.

Studies in Drosophila melanogaster show that PI3K/Akt signaling is an essential component of the growth response of the organism to nutritional input. Unlike mammals, Drosophila Akt contains a single Akt gene. Loss-of-function mutations in Drosophila Akt lead to embryonic lethality and are associated with ectopic apoptosis. Importantly, mosaic flies containing Akt-deficient cells display smaller cells and organs. Likewise, flies deficient for S6 kinase, a downstream target of Akt, have smaller bodies comprising smaller cells rather than fewer cells. These data clearly document the importance of the Akt regulatory pathway in the physiological growth response in simple animals. Similarly, numerous lines of data also suggest that this pathway is of critical importance in mammalian growth and metabolic responses. Gene ablation studies in mice have shown that Akt1 deficiency results in slightly diminished growth, and these mice exhibit increased frequencies of spontaneous and stress-induced apoptosis. Akt3-deficient mice display a selective reduction in brain size resulting from fewer and smaller cells. In contrast, Akt2-deficient mice have a normal body size but are mildly insulin resistant. However, the combined deletion of Akt1 and Akt2 genes results in perinatal lethality with multiple developmental defects, indicating a large degree of functional overlap between the different Akt isoforms. Nevertheless, studies have documented functional differences between the Akt1 and Akt2 isoforms with regard to insulin-dependent glucose uptake.

DeBosch et al now show that Akt1-deficient mice are resistant to swim training–induced cardiac hypertrophy. Furthermore, they find that adult murine cardiac myocytes are resistant to insulin-like growth factor–1–stimulated protein synthesis in vitro, suggesting that Akt1 deficiency in myocytes accounts for the reduction in heart growth in this mouse model. These data are consistent with a growing body of evidence indicating that the PI3K-Akt signaling pathway is important for physiological growth of the heart. For example, insulin-mediated activation of this signaling pathway has been shown to regulate cardiac growth in response to diet-induced changes in body size. This study also showed that the overexpression of a constitutively active form of Akt1 in cultured rat cardiomyocytes leads to an increase in cell growth in the absence of atrial natriuretic peptide gene induction and reorganization of the actin cytoskeleton, which generally are associated with pathological hypertrophy.

In light of these new observations in Akt1-deficient mice, it also is relevant to consider the findings of gain-of-function experiments in which modified Akt isoforms are overexpressed in the hearts of mice. Overexpression of the E40K mutation of Akt1 leads to modest hypertrophy (~40% increase in heart size), and these hearts do not exhibit features...
of pathological hypertrophy or any defect in contractility.29 In fact, these hearts display improved contractile properties and can be viewed as being similar to the “athlete’s heart.” In contrast to these findings, cardiac-specific Akt1 or Akt3 transgenic mice, constructed with myristoylated or phosphomimetic forms of these proteins, can display very large increases in heart size that correspond to the development of interstitial fibrosis and cardiac dysfunction.13,14,30 How can one explain the divergent phenotypes of the Akt transgenic mice? Recently, studies with an inducible, cardiac-specific Akt1 transgenic mouse line have shown that short-term Akt activation is associated with modest growth of the heart with preserved contractile function, whereas long-term Akt expression leads to excessive cardiac hypertrophy that is associated with pathological remodeling and loss of contractile function.15 These data indicate that the overall extent of cardiac growth resulting from Akt activation is a critical determinant of the difference between physiological and pathological cardiac hypertrophy. Furthermore, it was shown that a deficiency in vascular endothelial growth factor–mediated angiogenesis plays a pivotal role in promoting the transition from physiological or pathological growth in the inducible Akt model.15 Thus, the impairment in contractile function is not caused by the extent of Akt-mediated cardiac hypertrophy per se but by an imbalance between tissue growth and angiogenesis as the heart enlarges.

The most intriguing aspect of the study by DeBosch et al14 is the demonstration that Akt1-deficient mice show an exaggerated growth response to pathological stimuli. These effects are likely to be a direct effect of Akt1 deficiency in the heart because myocytes isolated from adult Akt1-deficient mice also display enhanced protein synthesis in response to endothelin-1 treatment. Thus, it appears that Akt signaling actively suppresses signaling pathways that promote pathological hypertrophy, in addition to its actions in promoting physiological growth. Although the mechanisms by which this occurs in the heart are unknown, cross-talk between Akt and the ERK31,32 and p3833 signaling pathways has been documented in other cell types, and ERK and p38 signaling has been implicated in pathological hypertrophy in heart. In addition to its growth regulatory properties, it is widely recognized that Akt1 signaling confers cytoprotection to the myocardium in both acute and chronic models of cardiac injury.34,35 Recently, it was reported that overexpression of wild-type Akt1 exclusively in the nucleus of cardiac myocytes in transgenic mice protects the heart from ischemia-reperfusion injury.36 Of particular interest, the cytoprotective actions of chronic Akt1 activation occurred in the absence of detectable cardiac growth, indicating that the growth and protective phenotypes conferred by Akt may depend on its subcellular distribution. One also should consider the possible contributions of the Akt2 and Akt3 isoforms in the heart. In this regard, the expression of Akt2 is relatively high in heart, in addition to “metabolic” tissues such as skeletal muscle and liver.37 Furthermore, although Akt3 is expressed at low levels in nonstressed heart, both Akt3 splice variants are upregulated in diseased human heart, but the levels of Akt1 and Akt2 do not change.13 However, in contrast to Akt1, relatively little is known about the roles of Akt2 and Akt3 in the heart.

The findings of DeBosch et al14 and others provide a framework indicating that Akt1 signaling is a key regulator of physiological heart growth, whereas other signaling pathways may predominate in pathological growth. However, a number of questions remain. First, does Akt2 have a metabolic role in the heart that can be critical under conditions of stress? Do the different Akt isoforms have an adaptive or maladaptive role when they are upregulated in the diseased heart? Finally, it will be important to dissect the different downstream signaling pathways that confer growth and cytoprotective actions of this signaling step to determine how the subcellular localization of Akt influences these processes. Therefore, despite numerous studies on Akt action in the heart, it appears that continued research in this area will provide important new information about cardiac growth and function.

Disclosures

None.

References


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