Effects of Akt on Cardiac Myocytes

Location Counts

Daniele Catalucci, Gianluigi Condorelli

“Akt quisque ipse faber fortunae suae...” (Each Akt makes its own destiny. . . .)

During the last few years, Akt (protein kinase B [PKB]) has become among the most studied signal-transduction molecules in cardiac biology. Akt is, in fact, at the crossroads of the insulin- and insulin-like growth factor-1 (IGF-1)–activated signal-transduction pathways. After insulin or IGF-1 interacts with its respective receptor, phosphatidylinositol 3-kinase (PI3K) phosphorylates inositol lipids that then bind to the pleckstrin domain of Akt, inducing its translocation to the plasma membrane. Here, Akt becomes the substrate of 3’-phosphoinositide-dependent kinase-1 (PDK-1), which activates it through phosphorylation of Thr308. Once active, Akt phosphorylates a number of “effector” substrates throughout the cell after migrating to subcellular organelles, including nuclei and mitochondria and other cytosolic locations. Therefore, the regulation of specific cellular functions is exerted by Akt at the level of the plasma membrane, nucleus, mitochondria, and cytosol in multiprotein complexes (Figure).

Models for studying the role of Akt, or its upstream molecules, in cardiac biology include cardiac-specific transgenic and knockout mice. Akt harboring mutations in either its pleckstrin or kinase domain, or containing different subcellular localizing signals, has been used for the generation of cardiac-specific mouse models. This approach, however, has led to controversies because of the variability of the phenotypic effects of Akt overexpression, which can also depend on the different methodologies applied for phenotypic analysis. Nonetheless, common results to most models include cardiac hypertrophy (increased cardiomyocytic size; reviewed by Walsh) and maintenance or improvement of cardiac function; in only 1 model, overexpression of Akt was found to be detrimental for cardiac function. Therefore, Akt is critical for the type of hypertrophic adaptation underlying physical training, and this has been further demonstrated by reports in which overexpression of a dominant-negative PI3K mutant or ablation of Akt prevented increased cell size and cardiac function. Moreover, the fundamental role of Akt in maintaining basic cardiomyocytic function has been demonstrated by cardiac-specific knockout of PDK-1, which induced heart failure associated with a decreased capacity of cardiomyocytes to cope with hypoxia.

Isolated cardiac myocytes from physically trained mice have increased inotropism, lusitropism, and calcium transients. These are determined by both entrance of Ca\(^{2+}\) from L-type Ca\(^{2+}\) channels (\(I_{\text{CaL}}\)) and release of Ca\(^{2+}\) from the sarcoplasmic reticulum (SR). An increase in \(I_{\text{CaL}}\) consequentially augments SR-Ca\(^{2+}\) release. Akt is activated during physical training, and this seemingly enhances \(I_{\text{CaL}}\), which in turn improves SR-Ca\(^{2+}\) release. That Akt is involved in the fine-tuning of \(I_{\text{CaL}}\) was, in fact, first suggested by phenotypic analysis of E40K Akt transgenic mice, which showed cardiac hypertrophy and enhanced inotropism, and by analysis of Ca\(^{2+}\) metabolism in myocytes isolated from these mice, which had enhanced \(I_{\text{CaL}}\) and SR-Ca\(^{2+}\) release.

Very recently in this journal, further proof has been documented for the role of Akt in regulating \(I_{\text{CaL}}\). PTEN (Phosphatase and TENsin homolog deleted on chromosome 10) antagonizes the activity of PI3K by catalyzing conversion of active inositol lipids into inactive ones. In PTEN knockout mice, both PI3K\(\gamma\) and PI3K\(\alpha\) activities are therefore increased. Interestingly, PTEN\(^{-/-}\) mice have increased cardiomyocyte size but also a depressed cardiac function, in contrast to the expected positive inotropic effect that follows activation of Akt. The negative inotropic effect was found to be dependent on decreased cAMP levels secondary to inhibition of adenylyl cyclase by an uncontrolled PI3K\(\gamma\) activity, whereas the effects on cell size were subsequent to the increase in PI3K\(\alpha\). However, measurements of \(I_{\text{CaL}}\) from PTEN knockout cardiomyocytes revealed an increment of Ca\(^{2+}\) flux, which was prevented by inhibition of either PI3K\(\gamma\) or Akt, thus confirming that Akt controls \(I_{\text{CaL}}\.

Along this line, a previous report from Sussman, Anversa, and colleagues showed that overexpression of a cardiac specific Akt mutant containing a nuclear localization signal (nuclear Akt) has important effects on survival and inotropism. In this model, cardiomyocytes are protected from cell death while hypertrophy is absent. The antiapoptotic effect of nuclear Akt is promoted by interaction with zyxin, which is recruited to the nucleus by activated nuclear-targeted Akt. The same authors found that overexpression of nuclear Akt affected Ca\(^{2+}\) by both increasing \(I_{\text{CaL}}\) and augmenting the phosphorylation of phospholamban (PLB), an inhibitor of the SR-Ca\(^{2+}\) pump, SERCA2a, with a result that closely resembles the phenotype of E40K Akt cardiomyocytes. However, in this case the mechanism through which nuclear Akt exerts its effects on Ca\(^{2+}\) and inotropism involves both
Akt: survival, metabolism, Ca\textsuperscript{2+}-handling

Binding of insulin (Ins) or IGF-1 activates PI3K and generates inositol lipids that bind to the pleckstrin domain of Akt, which is therefore localized to the plasma membrane where it becomes the substrate of PDK-1. Once activated, Akt migrates on plasma membrane itself, cytoplasm, mitochondria, and nucleus, phosphorylating key effector molecules. The result of this multitude of effects is improvement of metabolism, inotropism, and survival.

decreasing PP1A protein levels, a phosphatase that dephosphorylates PLB at residue Ser16 (the PKA kinase site), and increasing PKA activity.\textsuperscript{17}

Another important adaptive myocardial response during training is vascularization. Walsh and colleagues elegantly demonstrated the critical role of Akt in regulating myocardial capillary growth with an inducible model of active Akt overexpression. Here, activation of Akt-1 induces expression of vascular endothelial growth factor (VEGF) and angiopoietin-2,\textsuperscript{19} although long-term overexpression of active Akt-1 was deleterious for cardiac function. Thus, Akt increases cardiac cell size simultaneously with enhanced VEGF production, allowing appropriate energy supplies and expenditure through augmented vascularization.

A further important effect of Akt in the nucleus is the control of cardiac myocyte metabolism. This is at least partly dependent on cytoplasmic phosphorylation, sequestration, and consequential inhibition of the FOXO 3 transcription factor, which in turn controls the expression of multiple atrophy-related genes ("atrogenes"), including the ubiquitin ligase atrogin-1 (MAFbx), an enzyme enhancing muscle protein catabolism.\textsuperscript{20}

In this issue of Circulation Research, a report by Sussman, Anversa, and colleagues has added to the knowledge on the nuclear effects of Akt, determining that overexpression of Akt within the nucleus is associated with prolonged myocardial myocyte postnatal cell cycling 2 to 3 weeks after birth.\textsuperscript{21} The effects of Akt on the basal cell cycle machinery are well known in other systems and include activation of cell cycle–dependent kinases and inhibition of cell cycle–dependent kinase inhibitors.\textsuperscript{22} A study by Anversa and colleagues using cardiac-specific IGF-1–overexpressing mice has previously suggested that Akt affects components of the basal cell cycle machinery in cardiomyocytes.\textsuperscript{23} Now, the same authors\textsuperscript{24} show that nuclear targeting of Akt promotes expansion of c-kit+/Nhx 2.5+/MEF 2C+ cells, which they previously defined as a resident cardiac progenitor population.\textsuperscript{24} Therefore, according to the results of this and other studies from the same group, Akt is a key molecule for cell cycling of cardiac myocytes during differentiation and survival/proliferation of progenitor cells. Interestingly, gene expression array analysis has shown that nuclear Akt induces proproliferative cytokines including tumor-necrosis superfamily 8, interleukin-17e, and hepatocyte growth factor,\textsuperscript{17} thus shedding new light on the effects of Akt on survival and cell cycle during local cardiac stem cell growth and differentiation. As a corollary, it should therefore be possible to expand local cardiomyogenic progenitor cells by modulating Akt activity.

Acknowledgments
We thank Michael V. G. Latronico for critical reviewing.

Sources of Funding
G.C. is supported by the NIH (grant RO HL078797-01A1), European Community (EU FP6 grant LSHM-CT-2005-018833, EUGeneHeart), Italian Ministry of Health, and Italian Ministry of Research and University. D.C. is supported by a Marie Curie International fellowship within the 6th European Framework Programme.

Disclosures
None.

References


Effects of Akt on Cardiac Myocytes: Location Counts
Daniele Catalucci and Gianluigi Condorelli

Circ Res. 2006;99:339-341
doi: 10.1161/01.RES.0000239409.90634.a9
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/99/4/339

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/