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Focused Issue on Apoptosis and the Heart

Convergent signal transduction pathways controlling cardiomyocyte survival and function: the role of PI 3-kinase and Akt

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Abstract

Effective cardioprotection in clinical settings requires not only cardiomyocyte survival but also preservation of fonction. Multiple growth factors protect the heart from ischemic and other injury. While the downstream signaling pathways of these cardioprotective factors are complex, activation of phosphoinositide 3–kinase (PI 3–kinase) and its downstream effector, the serine-threonine kinase Akt (or Protein Kinase B), is a common feature in many cases. Genetic manipulations in cardiomyocytes both *in vitro* and *in vivo* suggest that acute activation of this pathway can promote both cardiomyocyte survival and function. Here, we review PI 3–kinase and Akt signaling, with a focus on their role in cardiomyocyte growth, survival, and function. Finally, the clinical implications of these studies will be considered.

Keywords: Apoptosis; Signal transduction; Cardiomyocyte; Growth factors; Cardioprotection; Akt; Phosphoinositide 3-kinase

1. Introduction

Cardiomyocyte death seen in clinical settings is an aggregate of multiple forms of cell death, including apoptotic and necrotic cell death, as well as intermediate forms with overlapping morphological features. Effective cardioprotection would require not only cardiomyocyte survival but also preservation of function. Several lines of investigation suggest this is feasible, at least in part because convergent intracellular signaling pathways appear to control not only the survival but also the function of cardiomyocytes in models of human cardiac diseases including ischemic injury and heart failure. In this review, we will focus on signaling through phosphoinositide 3-kinase (PI 3-kinase) and its downstream effector, the serine–threonine kinase Akt (or protein kinase B) as one such nodal point where critical determinants of cardiomyocyte survival and function converge.

Much of the clinical interest in cell death has resulted from studies documenting the presence of conserved morphological and biochemical markers of programmed cell death in clinical disease. Such studies provide an important clue to the relative contribution of different processes in the loss of cardiomyocytes seen in these settings. However, just as the seminal observations that delineated apoptosis in *C. elegans* required a functional and genetic dissection of pathways, an understanding of the importance of these pathways and their potential as therapeutic targets in disease requires a functional analysis. In this context, apoptosis provides a useful starting point because of the expanding information available about the specific mechanisms involved. However, as alluded to above, inhibition of apoptosis alone does not necessarily lead to meaningful rescue either in terms of survival or function. In other systems, some interventions can block morphological and biochemical manifestations of apoptosis (such as the DNA fragmentation) without preserving cell survival or function. In contrast, other interventions truly rescue cell survival and function. Thus, identifying interventions that not only inhibit apoptosis but mediate overall cardioprotection while preserving or improving cardiac function in clinically relevant models of disease will be critical to evaluating the therapeutic potential of this approach.

Initial interest in the PI 3-kinase and Akt signaling in this context evolved in parallel from two sources. First, elegant studies largely due to the work of Cantley et al. [1,2] had

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identified this pathway as a critical determinant of cell survival in a variety of other settings. Second, in the heart, a longstanding interest in cardioprotection had identified a variety of specific peptide hormones, growth factors, and cytokines (e.g. insulin, gp130-dependent cytokines, insulin-like growth factor I (IGF-I)) that could protect the heart from ischemic or other injury. Intriguingly, while the effector signaling pathways downstream of these cardioprotective factors are complex, activation of PI 3-kinase and Akt, was a common feature in many of these. These observations led us and others to evaluate the role of PI 3-kinase and Akt in the heart. As discussed in more detail below, we found that acute activation of PI 3-kinase or Akt is sufficient to inhibit cardiomyocyte apoptosis [3]. However, more importantly, acute activation of Akt also preserves function in surviving cardiomyocytes [4]. Such studies provide a proof-of-concept that intervening at specific points in complex signaling pathways can achieve these goals, as well as a rationale for further investigation of Akt signaling in the heart, its downstream effector mechanism, and the consequences of long-term activation. In this review, we will focus on what is know about Akt in other systems, as well as evidence regarding its role in controlling cardiomyocyte survival, growth, and function. Finally, we discuss the implications of such work for future therapeutic strategies.

2. Structure and activating mechanism of Akt

Akt1 and Akt2 were originally cloned as human homologues the *v-akt*, a retrovirus associated (Akt8) oncogene [5]. We now recognize three mammalian isoforms of Akt, known as Akt1 (PKBα), Akt2 (PKBβ), and Akt3 (PKBγ). These isoforms are encoded by distinct genetic loci but are closely related with approximately 80% homology of their amino acid sequences. Akt1 is ubiquitously expressed with notably high expression in brain, heart and lung among other tissues [6,7]. Expression of Akt2 varies more among different tissues, and is highly expressed in the muscle and brown fat [8,9]. Akt3 is expressed at high levels in the brain but at very low levels in skeletal muscle and the liver [10,11]. While their high degree of homology and in vitro studies suggest all three isoforms are capable of phosphorylating the same substrates, genetic analyses suggest that in vivo role of Akt1 and Akt2 are quite distinct [12,13].

All three isoforms of Akt share three domain structures consisting of an N-terminal pleckstrin homology (PH) domain, followed by a kinase domain related to protein kinases A and C (containing Thr^{308} in Akt1), and a C-terminal regulatory domain (containing Ser^{473} in Akt1). PH domains have high-affinity recognition of phosphoinositide head groups. Activation of PI 3-kinase leads to D3 phosphorylation of membrane phosphatidylinositol-(4,5)-bisphosphate [PtdIns(4,5)P_2], generating PtdIns(3,4,5)P_3, some of which is converted to PtdIns(3,4)P_2 by a phospholipid phosphatase such as SHIP, an Src homology 2 (SH2)-containing 5-phosphatase (Fig. 1). Accumulated PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3 recruit Akt containing PH domain to the plasma membrane [14] and PH domain covering Thr^{308} in a kinase domain is revealed (Fig. 1). Subsequently, phosphoinositide-dependent protein kinase-1 (PDK1) containing C-terminal PH domain phosphorylates Thr^{308} [15]. Although phosphorylation of Thr^{308} partially activates Akt [16], phosphorylation of Ser^{473} in a C-terminal regulatory domain is required in order to induce full activation in Akt [17,18] (Fig. 1). The mechanism of phosphorylation of Ser^{473} remains unresolved, although the "kinase" of this site is referred to as "PDK2". In some settings, PDK1 may phosphorylate both sites [19]. Autophosphorylation at the Ser site has also been reported [20]. Although the integrin-linked kinase (ILK) phosphorylates Ser^{473} in Akt C-terminal [21], it remains somewhat controversial whether ILK acts as a direct kinase to Ser^{473} ("PDK2") [22] (Fig. 1).

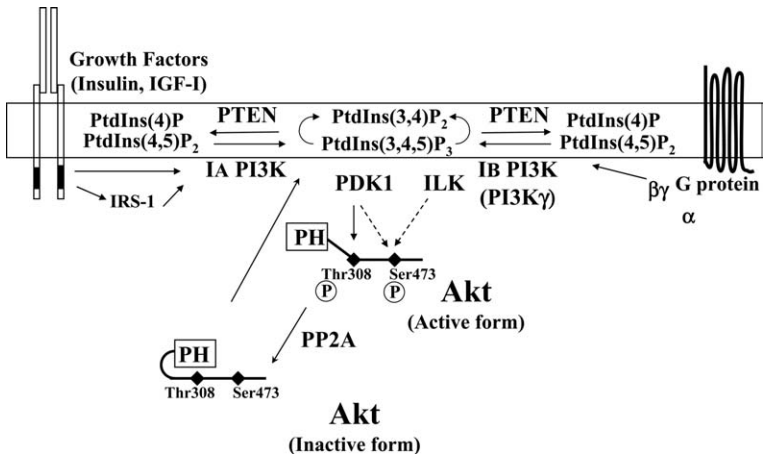

Fig. 1. Signaling pathway of PI 3-kinase and Akt. Signaling pathways are depicted schematically. PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3 are generated mainly by D3 phosphorylation on PtdIns(4)P and PtdIns(4,5)P_2, respectively, with activated class I_A or I_B (γ) PI 3-kinase. PtdIns(3,4)P_2 is partially produced by 5-dephosphorylation of PtdIns(3,4,5)P_3 by SHIP. PTEN reduces the levels PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3 by acting as a direct phosphatase. PtdIns(3,4)P_2 and PtdIns(3,4,5)P_3 bind to the PH domain of Akt and recruit Akt to the plasma membrane. PDK1 and other kinases (possibly including ILK) phosphorylate Thr^{308} and Ser^{473} to induce full activation of Akt. The general serine–threonine phosphatase, PP2A, dephosphorylates Akt and terminates activation of Akt.