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Review

The critical role of Akt in cardiovascular function

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ABSTRACT

Akt kinase, a member of AGC kinases, is important in many cellular functions including proliferation, migration, cell growth and metabolism. There are three known Akt isoforms which play critical and diverse roles in the cardiovascular system. Akt activity is regulated by its upstream regulatory pathways at transcriptional and post-translational levels. Beta-catenin/Tcf-4, GLI1 and Stat-3 are some of few known transcriptional regulators of AKT gene. Threonine 308 and serine 473 are the two critical phosphorylation sites of Akt1. Translocation of Akt to the cell membrane facilitates PDK1 phosphorylation of the threonine site. The serine site is phosphorylated by mTORC2. Ack1, Src, PTK6, TBK1, IKBKE and IKKε are some of the non-canonical pathways which affect the Akt activity. Protein–protein interactions of Akt to actin and Hsp90 increase the Akt activity while Akt binding to other proteins such as CTMP and TRB3 reduces the Akt activity. The action of Akt on its downstream targets determines its function in cardiovascular processes such as cell survival, growth, proliferation, angiogenesis, vasorelaxation, and cell metabolism. Akt promotes cell survival via caspase-9, YAP, Bcl-2, and Bcl-x activities. Inhibition of FoxO proteins by Akt also increases cell survival by transcriptional mechanisms. Akt stimulates cell growth and proliferation through mTORC1. Akt also increases VEGF secretion and mediates eNOS phosphorylation, vasorelaxation and angiogenesis. Akt can increase cellular metabolism through its downstream targets GSK3 and GLUT4. The alterations of Akt signaling play an important role in many cardiovascular pathological processes such as atherosclerosis, cardiac hypertrophy, and vascular remodeling. Several Akt inhibitors have been developed and tested as anti-tumor agents. They could be potential novel therapeutics for the cardiovascular diseases.

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1. Introduction

Akt family kinases (also known as protein kinase B/PKB) are serine/threonine kinases that belong to the general class of AGC kinases (AMP/GMP kinase and PKC subfamily of proteins) which has 518 members in humans [1]. While there are Akt homologs from fly to human, structure and function of mammalian Akt are highly conserved [2–6]. General pathway of Akt is called phosphoinositide-3-kinase–protein kinase B/Akt (PI3K–PKB/Akt) pathway or PI3k/AKT/mTOR pathway, named after upstream and downstream proteins involved. It was discovered by three different groups at the same time. Two of those discoveries were based on PKA or PKC homology based approaches and the other is through retroviral cloning [7–9]. The name Akt stems from the retroviral strain Akt-8 which was used for the cloning experiments. There are three Akt isoforms: Akt1, Akt2 and Akt3 (also known as PKBα, PKBβ, and PKBγ, respectively). Akt1 and Akt3 are ubiquitously expressed while Akt2 is expressed in the insulin-responsive tissues such as brown fat, skeletal muscle and liver [10]. The upstream and downstream targets of these Akt isoforms are quite similar. But there seem to be functional differences between these isoforms in different cell contexts. They seem to be specific in their interactions with other proteins. For example, onco-protein TCL1b forms oligomers with Akt1, not Akt2 or Akt3 [11]. These differences can be observed in the cell cycle regulation. Akt2 accumulates in the cytoplasm during mitosis [12] and in the nucleus during muscle differentiation [13]. Differences in Akt isoforms are also evident in disease development. Akt2 is indicated in many different tumors [14,15]. Ectopic expression of Akt2 has been shown to induce metastasis and invasion in human breast cancer cells and induce malignancy in mouse fibroblasts [12,16]. In human thoracic aortic dissection (TAD) and aortic aneurysm and dissection (AAD), Akt2 phosphorylation level is higher while Akt1 phosphorylation levels remain the same between disease and healthy conditions [17]. These differences are also evident in Akt isoform knockout mice. Akt2 deficient mice show a diabetic phenotype which is not observed in Akt-1 knockout mice [18]. Importance of Akt3 in brain development has also been shown in Akt3 knockout mice. This isoform specific cell development causes smaller brain sizes in Akt3 knockout mice, but not in Akt1 knockout mice [19]. In addition, Akt1 promotes endothelial neoplasms while Akt3 acts in an opposite manner [20]. The reduction of phosphorylation of endothelial nitric oxide synthase (eNOS) by Akt1 knockout can be compensated by Akt2, though phosphorylation of angiogenic substrate by Akt1 seems to be essential for angiogenesis [21].

Since they are involved in signal pathways related to cell proliferation, cell growth, survival and aspects of intermediary metabolism, Akt has been the center of focus for many studies attempting to therapeutically control these aspects.

2. Akt protein structure

Akt has a characteristic pleckstrin homology (PH) domain at the amino terminal (~110 amino acids), a middle kinase domain (~260 amino acids) and a carboxy-terminal regulatory domain (~70 amino acids) (Fig. 1). Of these, pleckstrin homology domain controls the membrane translocation of Akt. This structure is conserved in diverse species from flies to man. Akt has a higher sequence identity to other AGC family member proteins which made therapeutic strategies and developing specific inhibitors more challenging [22]. The region homology varies among the isoforms. Pleckstrin domain is 80% identical between Akt isoforms, while this being 30% identical to pleckstrin domains of other proteins. The region between PH domain and the catalytic domain is called the linker (LINK). This link is poorly conserved among Akt isoforms and lacks similarities to other human proteins. The catalytic domain shares a higher similarity within Akt isoforms (90%) and a significant similarity to other AGC family proteins. Because of the difficulty of obtaining crystal structure of the linker region, the structures of Akt protein is speculative [23].

3. Upstream regulatory pathways of Akt

In the cardiovascular system, Akt is activated by several stimuli such as insulin, platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) [24,25]. In addition, some phosphatase inhibitors also activate Akt [26]. Reactive oxygen species (ROS) have been shown to activate Akt through angiotensin II [27,28]. These growth factors regulate Akt activity through transcriptional or post-translational mechanisms (Fig. 2).

3.1. Transcriptional regulation of Akt

Transcriptional regulation of Akt genes remains largely unknown. It has been shown that upregulation of total Akt protein results in an increase in Akt activity, though the expression of a kinase may not be necessarily a reflection of its activity level [29]. Akt gene promoters contain binding sites for several signaling molecules such as Stat3, β-catenin/Tcf-4, and GLI1, indicating that Akt gene transcription may be regulated by these molecules.

The 4.2-kb region upstream of the transcription start site of the *AKT1* promoter contains five putative Stat3-binding motifs. However, the promoter is not induced by Stat3 and/or Src. The major Stat3 response elements are located within exon 1 and intron 1 regions of the *AKT1* gene, which is upstream of the AKT1 translation initiation site. Stat-3 interacts with this region and increases the Akt1 gene transcription [30].

The transcription of Akt1 gene is induced by β-catenin/Tcf-4 [29]. Nine putative b-catenin/Tcf/Lef-binding sites (TBE) in the AKT1 gene have been found to show a high degree of homology to the core consensus sequence AGATCAAAGGG [29]. Four of these TBEs are located upstream of the transcriptional start, whereas five TBEs are situated in Exon 1. Moreover, the promoter region of the AKT2 gene contains six potential TBEs

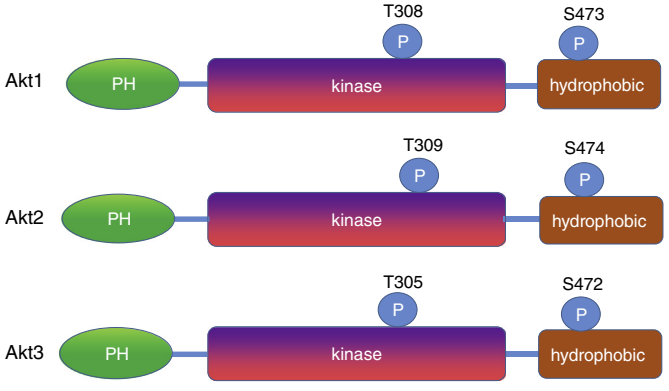

Fig. 1. Human Akt protein structure. Akt has a characteristic pleckstrin homology (PH) domain at the amino terminal (~110 amino acids), a middle kinase domain (~260 amino acids) and a carboxy-terminal regulatory domain (~70 amino acids).

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