Apoptosis Review Series

The activation of Akt/PKB signaling pathway and cell survival

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Abstract

Akt/PKB is a serine/threonine protein kinase that functions as a critical regulator of cell survival and proliferation. Akt/PKB family comprises three highly homologous members known as PKBα/Akt1, PKBβ/Akt2 and PKBγ/Akt3 in mammalian cells. Similar to many other protein kinases, Akt/PKB contains a conserved domain structure including a specific PH domain, a central kinase domain and a carboxyl-terminal regulatory domain that mediates the interaction between signaling molecules. Akt/PKB plays important roles in the signaling pathways in response to growth factors and other extracellular stimuli to regulate several cellular functions including nutrient metabolism, cell growth, apoptosis and survival. This review surveys recent developments in understanding the molecular mechanisms of Akt/PKB activation and its roles in cell survival in normal and cancer cells.

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Introduction

Akt/PKB protein kinase, a serine/threonine kinase, belongs to the cAMP-dependent protein kinase A/ protein kinase G/ protein kinase C (AGC) super family of protein kinases that share structural homology within their catalytic domain and have the similar mechanism of activation. Deregulations of some of these kinases are frequently associated with human diseases including cancer and diabetes [1,2]. Akt/PKB was initially identified by three independent groups, based on its homology to protein kinase A (PKA) [3] and C (PKC) [4] or as the cellular homolog to the retroviral oncogene viral akt (v-Akt) [5]. In mammals, three Akt/PKB genes have been identified, termed PKBα/Akt1 [6], PKBβ/Akt2 [7] and PKBγ/Akt3 [8], located at chromosomes 14q32, 19q13, and 1q44, respectively.

Over the past decade, Akt/PKB has emerged as a central player in the signal transduction pathways activated in response to growth factors or insulin and is thought to contribute to several cellular functions including nutrient metabolism, cell growth, transcriptional regulation and cell survival [9]. In this review, we discuss the molecular mechanisms of Akt/PKB activation and its important functions in regulating cell survival particularly.

Structural features of Akt/PKB protein kinases

All three Akt/PKB isoforms consist of a conserved domain structure: an amino terminal pleckstrin homology (PH) domain, a central kinase domain and a carboxyl-terminal regulatory domain that contains the hydrophobic motif, a characteristic of AGC kinases. The major structural features of the Akt/PKB proteins are illustrated in Fig. 1.

The N-terminal PH domain consisting of approximately 100 amino acids was originally found in pleckstrin, the major phosphorylation substrate for PKC in platelets [10]. Recent detailed structural examination revealed that the PH domain of Akt/PKB shares similarity to those found in other signaling molecules that bind 3-phosphoinositides [11,12]. The PH domain interacts with membrane lipid products such as phosphatidylinositol (3,4,5) trisphosphate (PIP3) produced by phosphatidyli-

nositol 3-kinase (PI3-kinase). Biochemical analysis demonstrated that the PH domain of Akt/PKB binds to both PIP3 and PIP2 with similar affinity [13,14]. Recently, the crystal structure of the PH domain of Akt/PKB has been solved [15].

The kinase catalytic domain of Akt/PKB, located in the central region of the molecule, shares a high degree of similarity with other AGC kinases such as PKA, PKC, p70S6K and p90RSK [16]. Another feature in this region is a conserved threonine residue (T308 in PKBa/Akt1) whose phosphorylation can partially activate Akt/PKB [17].

Following the kinase domain there is a carboxyl terminal extension of around 40 amino acids. This region possesses the F-X-X-F/Y-S/T-Y/F hydrophobic motif (where X is any amino acid) that is characteristic of the AGC kinase family [16]. For all AGC family kinases, phosphorylation of the Serine or Threonine residue in this hydrophobic motif is necessary for full activation of the kinase. In mammalian Akt/PKB isoforms, this motif is identical (FPQFSY), and is thought to be critically important, because a deletion mutant of this motif completely abolishes enzymatic activity [18]. But the rat PKBγ/Akt3 and the human PKBα/Akt1 splice variant do not possess this motif, suggesting that these variant kinases are activated by mechanisms independent of phosphorylation of the Serine/Threonine residues in the hydrophobic motif [19,20].

Regulation of Akt/PKB activity

All Akt/PKB isoforms except the PKBg/Akt3 splice variant contain two regulatory phosphorylation sites, Thr308 in the activation loop within the kinase domain and Ser473 in the C-terminal regulatory domain (Fig. 2). Activation of Akt1/PKBa by growth factors involves a PI3-Kinase- and PH domain-dependent membrane translocation step, followed by phosphorylation of these two key regulatory sites. Phosphorylation of Thr308 partially activates Akt/PKB, while phosphorylation of both sites is required for full activation. Significantly, phosphorylation of Ser473 alone has little effect on Akt/PKB activity [17]. In addition, a number of novel Akt/PKB binding proteins have been identified and these proteins could regulate the activity of Akt/PKB (Table 1).
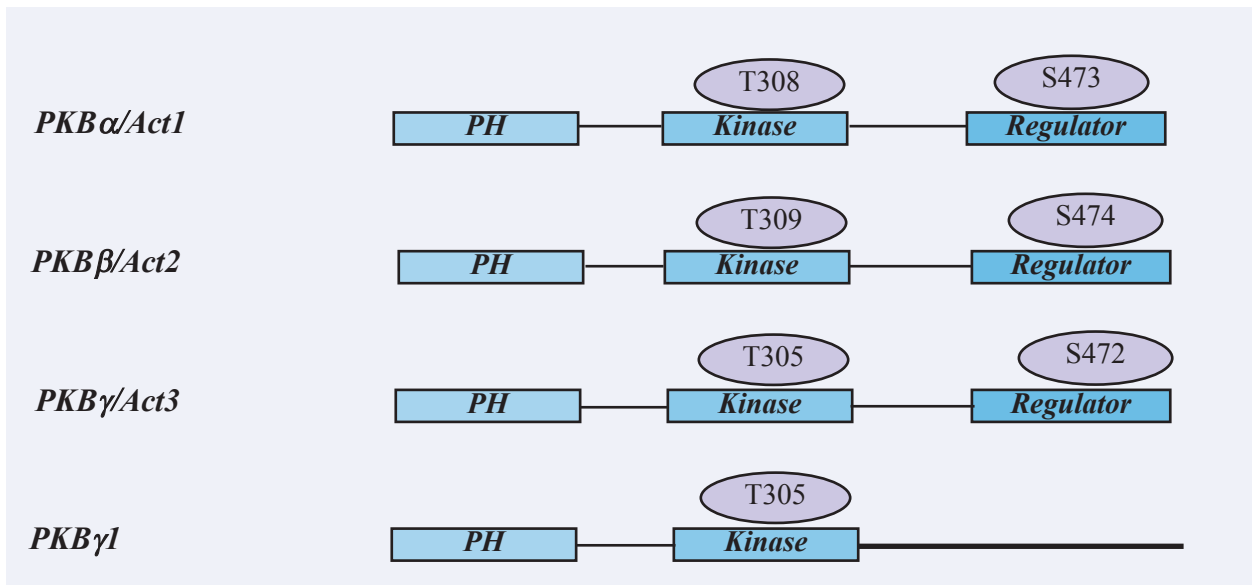
Fig. 1 Domain structure of human Akt/PKB isoforms and the PKBγ/Akt3 splice variant (PKBγ1).

Phosphoinositide 3-kinase (PI3-Kinase) -dependent activation of Akt/PKB

Membrane translocation

Akt/PKB, as the downstream effectors of PI3-Kinase, is activated by Class 1A and Class 1B PI3-Kinase, and Class 1A and Class 1B PI3-Kinase are activated by tyrosine kinase and G-protein-coupled receptors, respectively [21]. Following its recruitment to these receptors in the plasma membrane, PI3-Kinase is activated and PIP2 on the 3-OH group generates the second messenger PIP3. PIP3 levels are tightly regulated by the action of phosphatases such as PTEN, which removes phosphate from the 3-
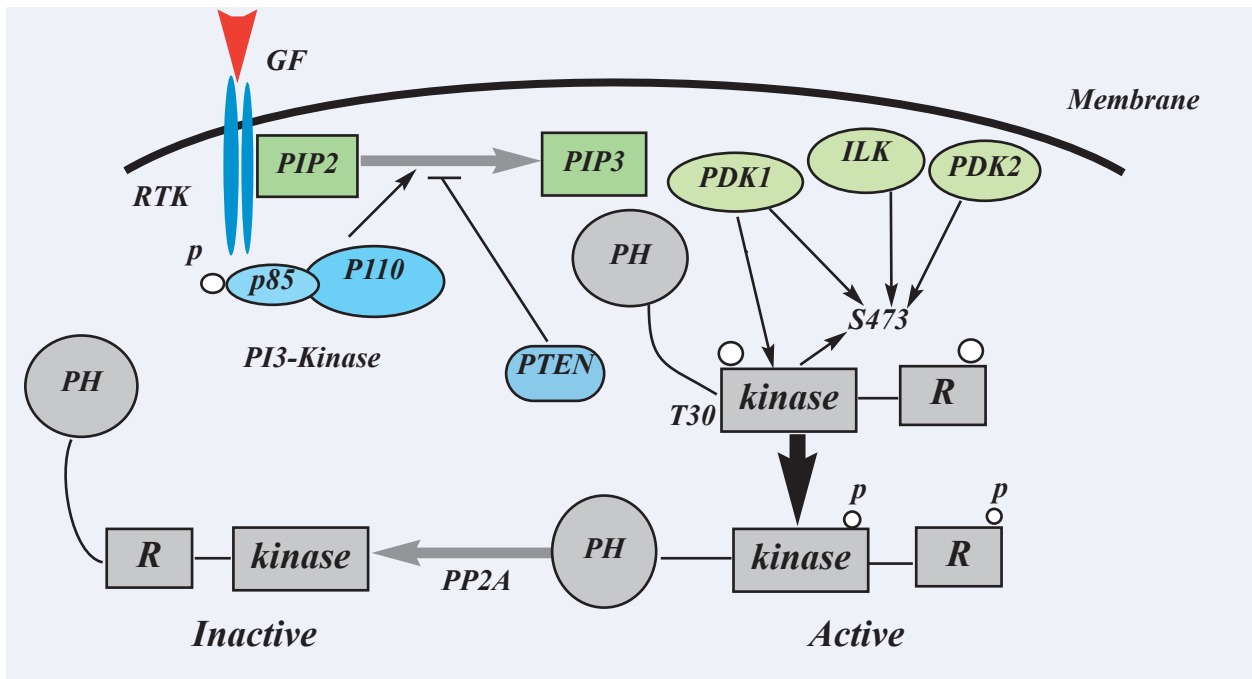

Fig. 2 Mechanism of Akt/PKB activation. GF: growth factor, p: phosphorylation, RTK: receptor tyrosine kinase, R.: regulator.

OH position [22]. The PH domains containing 100 amino acid modules found in many signaling proteins can mediate protein-lipid interactions [23]. In the case of Akt/PKB, the PH domain is required for its recruitment to the plasma membrane through high-affinity binding to PIP3 produced by activated PI3-Kinase [24]. PIP3 does not activate Akt/PKB directly, but instead appears to recruit Akt/PKB to the plasma membrane and to alter its conformation to allow subsequent phosphorylation by the phosphoinositide- dependent kinase-1 (PDK1).

Phosphorylation of Akt/PKB

Akt/PKB is activated by site-specific phosphorylation. For PKBα/Akt1, a main site of phosphorylation is within the activation T-loop at Thr308. There is convincing evidence that Thr308 is phosphorylated by the PDK1 [25]. The other phosphorylation site for PKB/Akt1 is Ser473, the mechanism of its phosphorylation is not completely understood. But there is evidence suggesting that the site can be autophosphorylated [26] or phosphorylated by distinct serine kinases including the integrin-linked kinase (ILK) [27]. Furthermore, several recent reports have investigated the possible role of tyrosine phosphorylation in Akt/PKB regulation [28,29].

Phosphorylation of Thr308

PDK1 is a 63-kDa serine/threonine kinase containing a C-terminal PH domain that binds with high affinity to 3-phosphoinositides. The primary structure of this kinase is similar to other AGC kinase family members, and it has a PH domain at its carboxyl-terminal [30]. When full-length of Akt/PKB is used as a substrate for PDK1, PIP3 is required for maximal activity. In contrast, when a PH domain deletion mutant of Akt/PKB, or a peptide substrate corresponding to the activation loop of Akt/PKB that contains a PDK1 phosphorylation site is used, the PIP3 dependency for PDK1 activity was completely abolished [31]. This indicates that the enzymatic activity of PDK1 is not a target of phosphoinositide and that the PH domain of Akt/PKB might act as an inhibitor for Thr308 phosphorylation by masking this residue from PDK1. The mechanism for phosphorylation of Akt/PKB on Thr308 seems to be different from other AGC kinases such as SGK, p70S6K and p90RSK [32,33]. For Akt/PKB, co-localization with PDK1 is necessary for phosphorylation on Thr308 [18,34].

Phosphorylation of Ser473

Although phosphorylation at T308 partially activates Akt/PKB [17], full activation of Akt/PKB requires phosphorylation on a second site (Such as S473 in PKBα/Akt1) located in the regulatory tail. The mechanism mediating Ser473 phosphorylation remains controversial. Since Ser473 phosphorylation is dependent on PI3-kinase, as well as Thr308, PDK1 was assumed to be the kinase for Ser473 phosphorylation [35]. However, PDK1 knockout ES cells disproved this prediction. In these cells, Ser473 was phosphorylated similar to wild-type cells, whereas Thr308 phosphorylation was completely abolished [36]. However, the phosphorylation level of Akt/PKB on Ser473 increases by overexpressing PDK1 in transfected cells [37]. This finding indicates that PDK1 may contribute indirectly in the process of Ser473 phosphorylation. Several groups reported that Akt/PKB itself could autophosphorylate Ser473 under certain conditions [38,39]. Other findings suggest that S473 is modified by a distinct kinase such as PDK-2 [40].

The integrin-linked kinase (ILK) was shown to phosphorylate Ser473 too [41]. But a subsequent report suggested that ILK acts only as a facilitator and does not phosphorylate Akt/PKB directly [42]. More recent studies showed that ILK could phosphorylate Akt/PKB on Ser473 and that the kinase activity of ILK was essential for Ser473 phosphorylation in cells. A novel ILK-specific inhibitor also blocked Ser473 phosphorylation of Akt/PKB [43]. These studies strongly suggest that ILK plays some roles in the activation process, but whether it phosphorylates Akt/PKB directly is controversial.

Phosphorylation of tyrosine residues

Several recent reports have described the possible role of tyrosine phosphorylation in Akt/PKB regulation [28,29]. One report indicated that two tyrosine residues located within the catalytic domain of Akt/PKB, Tyr315 and Tyr326, are phosphorylated following receptor activation and are required for activity, since mutation to phenylalanine abolished kinase activity [44]. Another

report identified Tyr474, based on phosphopeptide mapping, as a possible site of phosphorylation in response to insulin and pervanadate, and indicated phosphorylation at Tyr474 is required for full activation of Akt/PKB [28]. These observations indicated a novel regulatory mechanism for Akt/PKB. This tyrosine is conserved widely in the AGC family, suggesting that a possible mechanism of regulation could be a general feature. But further experiments are needed to evaluate the role of Tyr474 in Akt/PKB regulation.

Phosphoinositide 3-kinase (PI3-Kinase)-independent activation of Akt/PKB

Several reports have suggested that Akt/PKB could be activated in a PI3-kinase-independent manner. cAMP-elevating agents such as forskolin, chlorophenylthio-cAMP, prostaglandin-E1, and 8-bromo-cAMP were shown to activate Akt/PKB through PKA [45,46]. The PH domain of PKBa/Akt1 is not required for this activation and phosphorylation of Ser473 is not necessary for the PKA induced activation, while the phosphorylation of Thr308 is required. However, the mechanism by which PKA activates Akt/PKB is not fully clear [46]. PKA does not activate PI3-kinase and the cAMP-mediated activation of Akt/PKB is wortmannin resistant, so it was concluded that the activation is PI3-kinase independent [46].

It was also shown that Akt/PKB can be activated by Ca2+/calmodulin-dependent kinase directly in vitro [47]. Other reports idicated that Akt/PKB is activated by cellular stress and heat shock through association with Hsp27 [48] and that the β-adrenergic agonist, isoproterenol, can activate Akt/PKB in a wortmannin-resistant manner [49]. But the significance of these findings remains to be determined.

Proteins bind and regulate Akt/PKB

Many proteins have been reported to interact with Akt/PKB, but most of them are substrates for Akt/PKB and do not affect Akt/PKB kinase activity [50]. However, several proteins have been shown to regulate Akt/PKB activity, suggesting that there may be transient regulation of this kinase (Table 1). In recent studies, several proteins that bind to and inhibit the activation of Akt/PKB by reducing its phosphorylation on Thr308 and Ser473 have been identified. For example, carboxyl-terminal modulator protein (CTMP) is a novel protein identified as a binding partner for the carboxyl-terminal of Akt/PKB by yeast two-hybrid screening. It inhibits Akt/PKB signaling by reducing phosphorylation on Ser473 and reverses Akt/PKB dependent cancer cell growth and tumour formation in nude mice [51]. Trb3 is the mammalian homologue of tribbles, a cdc25 binding protein of Drosophila, identified by two-hybrid interaction cloning as a Akt/PKB binding protein [52]. Based on its functions, it is likely that Trb3 is a negative regulator of Akt/PKB activation. This protein binds to the central region of the kinase domain of Akt/PKB. Overexpression of Trb3 reduces phosphorylation and inhibits Akt/PKB activation in a Trb3-Akt/PKB interaction-dependent manner [52]. Keratin K10, a major component of intermediate filaments in the cytoskeletal structure, binds to Akt/PKB and sequestrates it to the cytoskeleton, and inhibits its intracellular translocation, which causes inactivation of Akt/PKB kinase activity and inhibits cell proliferation [53].On the other hand, positive regulators of Akt/PKB by several other proteins such as Hsp90, Hsp27, Tcl1, Grb10, Ft1, were identified to interact with different domains of Akt/PKB. The Hsp family of proteins is induced by heat shock and act as molecular chaperones that promote refolding and stabilization, or destabilization, of their client proteins in response to extracellular stresses. To date, two kinds of Hsp molecules have been reported to bind to Akt/PKB and regulate its activity. Hsp27 specifically binds to Akt/PKB isoforms following different stress treatments [54]. A recent report has shown that Hsp27-Akt/PKB interaction leads to activation of Akt/PKB and inhibition of apoptosis in neutrophils [55]. Hsp90 has been reported to act as a kinase chaperone for several tyrosine and serine/threonine kinases in cooperation with cdc37, and inhibitors of Hsp90 cause Akt/PKB degradation [56]. Grb10 is a member of the Grb family of proteins identified by their ability to bind to phosphorylated tyrosine residues in the

Table 1 Akt/PKB binding proteins

Binding proteins	Biological significance	Refs
Actin	Localization of Akt/PKB to the cytoskeleton; cdc42 is also involved	[62]
CTMP	Binds to the C-terminus of Akt/PKB and blocks phosphorylation and activation	[51]
Erk1/2	Akt/PKB binds a complex of ERK1/2, Rsk and PDK1 to regulate apoptosis	[63]
Ft1	Enhance the phosphorylation of Akt/PKB by promoting its interaction with the upstream kinase PDK1	[61]
Grb10	Recruit Akt/PKB to the plasma membrane in response to c-kit activation	[57,58]
Hsp90	Act as a kinase chaperone for several tyrosine and serine/threonine kinase in cooperation with cdc37	[56]
Hsp27	Specifically binds Akt/PKB isoforms following different stress treatments	[54,55]
Jip1	PKBa/Akt1 binding blocks JNK binding to JIP1 and delays apoptosis	[64]
Keratin K10	Inactivate of Akt/PKB kinase activity and inhibits cell proliferation	[53]
Periplakin	Binds to the PH domain of Akt/PKB and mediates localization to the intracellular network	[65]
Posh	PKBß/Akt2 binding blocks MLK-MKK-JNK complex formation and apoptosis	[66]
Tcl1	Positive regulator of Akt/PKB and overexpressed in several T or B cell malignancy	[39,59,60]
Trb3	Blocks Akt/PKB activation in hepatocytes	[52]

EGF receptor [57]. Grb10 constitutively forms a complex with Akt/PKB and interacts with the c-kit receptor tyrosine kinase in its ligand, in a stem cell factor (SCF)-dependent manner [58]. Tcl1 (T-cell leukaemia 1) is a 14-kDa protein. It was identified as an Akt/PKB binding protein by yeast two-hybrid screening. The mechanism for Tcl1-mediated activation of Akt/PKB requires further work because two different mechanisms have been proposed [39,59,60]. Ft1 was identified from a cDNA library screening using a green fluorescent protein-based protein-fragment complementation assay. Ft1 protein interacts directly with Akt/PKB to enhance the phosphorylation of both regulatory sites by promoting its interaction with the upstream kinase PDK1. Further, the modulation of PKB activity by Ft1 has a strong effect on the apoptosis susceptibility of T lymphocytes treated with glucocorticoids [61].

Regulation of cell survival by Akt/PKB

The Akt/PKB signaling pathway is now recognized as one of the most critical pathways in regulating cell survival. The activation of Akt pathway provides cells with a survival signal that allows them to withstand apoptotic stimuli [67]. Akt/PKB, a PI3-kinase activated protein kinase, is a principal mediator of cell survival. In recent years, many reports elucidate the important roles of Akt/PKB signaling pathway in cell survival in several cancers [68-71]. Recently, our lab in collaboration with Wang lab at Duke demonstrated that a secreted protein called periostin that is overexpressed in tumors can activate the Akt/PKB signaling pathway through the $\alpha_v\beta_3$ integrins to augment cancer cell and endothelial cell

survival and prevent stress-induced apoptosis, and dramatically enhance metastatic growth of colon [68]. Akt/PKB has direct effects on the apoptosis pathway, for example, targeting the pro-apoptotic Bcl-2 related protein, BAD. It also affects the transcriptional response to apoptotic stimuli, for example, by affecting on Forkhead factors and the activity of the p53 family. In addition, novel connections between the metabolic effects of Akt/PKB and its control of survival have recently been made. Targets of Akt/PKB signalling that are believed to promote cell survival are illustrated in Fig. 3.

Direct regulation of cell survival

A large amount of evidence has suggested that one of the major functions of Akt/PKB is to promote growth factor-mediated cell survival and to block apoptosis. Apoptosis in mammalian cells is a multistep process. In the current model, an early event is the loss of mitochondrial integrity fol-

lowed by cytochrome c release. The released cytochrome c then binds to the apoptotic protease-activating factor (Apaf-1) and activates it. Apaf-1 then binds to, cleaves and activates the cysteine protease, caspase-9. This initiates a caspase cascade culminating in the activation of the executioner caspases [72]. Critical regulators in this pathway are various members of the Bcl-2 family. These proteins include anti-apoptotic effectors such as Bcl-2 and Bcl-xL and their pro-apoptotic counterparts such as Bad, Bid, and Bik (the BH3 subfamily) and Bax and Bak (the Bax subfamily) [73].

BAD

BAD is a member of the Bcl-2 family of proteins that binds to Bcl-2 or Bcl-X and inhibits their anti-apoptotic potential. But when BAD is phosphorylated on Ser136 by Akt/PKB, it does not exhibit pro-apoptotic activity in cells, so it is thought to be one of the direct targets of Akt/PKB in promoting cell survival [74,75]. The potential of phosphorylated BAD to inhibit apoptosis might be regulated by its formation of complexes with other proteins.

Table 2 Some transcription factors regulated by Akt/PKB to control cell survival.

| Transcription factors	Phosphorylation site	Biological significance	Refs
Forkhead family	Thr24, Ser256, Ser319 (FKHR)	promotes nuclear exclusion;	
	(FKHR, FKHRL1, AFX) Thr32, Ser253, Ser315 (FKHRL1)	association with 14-3-3 proteins;	
	Thr28, Ser193, Ser258 (AFX)	prevention of transcription of proapoptotic genes	[85]
Ik-B kinase	Thr23	induction of NF-κB transcriptional activity	[87]
Mdm2	Ser166, Ser186	induction of its nuclear import or up-regulation of its ubiquitin ligase activity	[92,93]
CREB	Ser133	increased transcription of CREB-regulated survival genes	[94,95]
YAP	Ser127	acts as a suppressor of apoptosis	[96]
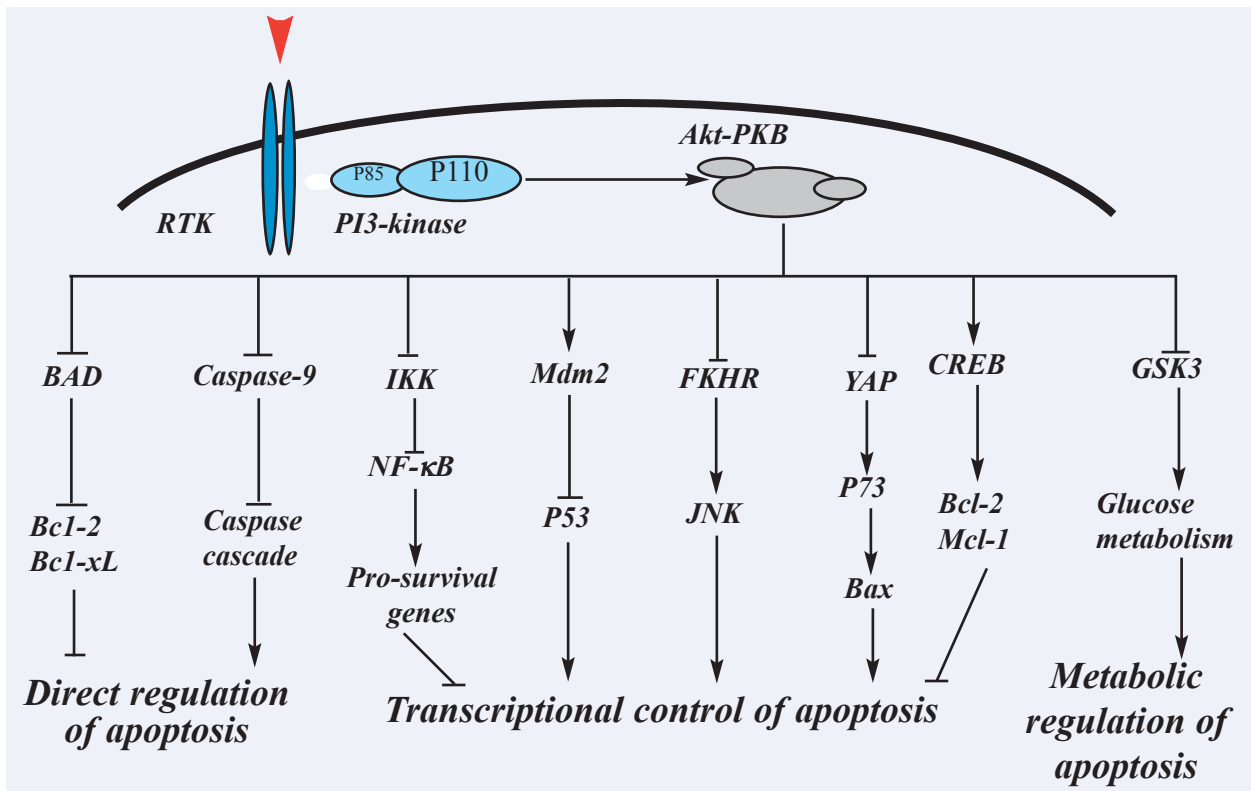
Fig. 3 Multiple mechanisms of cell survival regulation by Akt/PKB. GF: growth factor, p: phosphorylation, RTK: receptor tyrosine kinase.

Once phosphorylated, BAD is released from a complex with Bcl-2/Bcl-X that is localized on the mitochondrial membrane, and forms a complex with 14-3-3 proteins in the cytosol, thus inactivates its pro-apoptotic function [76].

Caspase-9

Caspase-9 acts as an initiator and an effecter of apoptosis [77]. Human caspase-9 has been reported to be phosphorylated on Ser196 by Akt/PKB, resulting in attenuation of its activity [78]. However, the site phosphorylated of caspase-9 is not conserved in other lower mammalian species such as mouse or rat, suggesting that this regulation of Akt/PKB is not likely to be a major physiological regulatory pathway or the phosphorylation of this site is specific for higher species [79].

SAPK

The stress-activated protein kinase (SAPK) pathway regulates cellular responses to stress or cytokines. The SAPK system consists of two groups of kinase, JNK and p38 MAP kinase pathways [80]. It has been reported that Akt/PKB can phosphorylate three kinases upstream of SAPK. Apoptosis signal-regulating kinase 1 (ASK1) is one of the MAP kinase kinase kinases (MKKK) that interacts with and is phosphorylated by Akt/PKB on Ser83, which results in the inhibition of apoptosis induced by ASK1 [81]. Akt/PKB can phosphorylate another MKKK upstream of SAPK, the mixed lineage kinase 3 (MLK3). Akt/PKB interacts with and phosphorylates MLK3 on Ser674 and this causes MLK3 inactivation and the promotion of cell survival [82]. Similar to the two MKKKs mentioned above, SEK1/ MKKK4 binds to and is phosphorylated on Ser78 by Akt/PKB, resulting in SEK1 inactivation and inhibition of ultraviolet (UV)-induced apoptosis [83]. The above observations suggest that the SAPK pathway is an important target for Akt/PKB regulation to promote cell survival.

Transcriptional control of cell survival

Recent studies have shown that Akt/PKB is able to regulate cell survival through transcriptional

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factors that are responsible for pro- as well as anti-apoptotic genes. Many of the recently identified substrates for Akt/PKB have been found to be involved in transcriptional regulation of cell survival (Table 2).

FoxO Forkhead
The Forkhead (FoxO or FH) family of transcription factors was first identified from the genetic analysis of C. elegans [84]. It has been found that all four isoforms of FoxO proteins (FKHR/FoxO1, FoxO2, FKHRL1/FoxO3 and AFX/FoxO4) could be phosphorylated by Akt/PKB directly. The phosphorylated FoxO proteins can regulate cell survival by operating their target genes. A number of FoxO target genes may be important in the inhibiting of cell survival. The target genes for the FoxO family are thought to be extracellular ligands, including the Fas ligand, TRAIL (TNF-related apoptosis-inducing ligand) and TRADD (TNF receptor type 1 associated death domain), and intracellular components for apoptosis like Bim (bcl-2 interacting mediator of cell death), a pro-apoptotic Bcl-2 family member, and Bcl-6 [85].

NF-kB
The transcription factor nuclear factor-κB (NF-κB) family is a key regulator of the immune response, and deregulation of its activity is implicated in the development of diseases such as autoimmune disease and cancer [86]. In most cases, the activation of NF-κB is dependent on the phosphorylation of IκB kinase (IKK) complex and degradation of IκB, an inhibitor of NF-κB. Akt/PKB has been shown to regulate IKK activity in both direct and indirect manner [87]. This leads to the nuclear translocation and activation of NF-κB, and transcription of NF-κB-dependent pro-survival genes, including Bcl-xL, caspase inhibitors and c-Myb [88,89].

Mdm2
Murine double minute 2 (Mdm2) is an oncogene product induced by p53 [90]. p53 is a major regulator of cell death in response to stresses, especially those involving DNA damage [91]. The level and function of the p53 protein is strongly inhibited through the action of the E3 ubiquitin ligase Mdm2. Akt/PKB has been reported to bind

to and phosphorylate Mdm2 on two residues, Ser166 and Ser186, resulting in induction of its nuclear import or up-regulation of its ubiquitin ligase activity [92,93]. Thus, Akt/PKB could result in promoting the inactivation or degradation of p53 and undermine the p53-mediated pro-apoptotic transcriptional response.

CREB
Cyclic AMP (cAMP)-response element binding protein (CREB) transcription factor is able to be phosphorylated by Akt/PKB on Ser133. This process results in increasing transcriptional activation of CREB and affinity of CREB to its co-activator CRB [94].CREB has also been shown to mediate Akt/PKB-induced expression of some antiapoptotic genes, such as bcl-2, mcl-1 [95].

YAP
Yes-associated protein (YAP) is a recently identified Akt/PKB substrate, purified from 14-3-3 binding proteins. Akt/PKB is able to phosphorylate YAP on Ser127 in a PI3-kinase-dependent manner. Phosphorylated YAP acts as a suppressor of apoptosis mediated by the transcriptional activity of p73 [96].

Metabolic regulation of cell survival

A major physiological function of Akt/PKB is the regulation of cell metabolism. When high levels of insulin are present, glycogen synthase kinase 3 (GSK3) is inhibited upon phosphorylation by Akt/PKB with the result that the storage of glucose as glycogen is promoted [97]. GSK3 is also involved in many other signaling pathways, including the β-catenin-TCF/LEF transcriptional pathway [98]. The inhibition of GSK3 has been found to be protective against apoptosis in many circumstances, although the molecular basis for this is not understood [99]. So an interesting hypothesis has been proposed that the effects of Akt/PKB on cell survival are connected with its effects on cell metabolism. Withdrawal of growth factors from cells leads to a reduction in their ability to utilize nutrients in the medium, resulting in a depletion of ATP and glucose-derived

metabolites within the cell [100]. Akt/PKB activation allows cells to continue to import glucose and amino acids [101,102]. In particular, the ability of Akt/PKB to promote glucose utilization can prevent the induction of conformational activation of Bax and subsequent cell apoptosis following treatment with apoptotic stimuli [103]. Although there are some mechanistic details missing in the metabolic connection between Akt/PKB and cell survival regulation, it is likely that these puzzles will be solved soon.

Conclusions

In the past decades, the mechanisms for Akt/PKB activation, the lipid second messenger-mediated phosphorylation of Akt/PKB, have been well characterized, and our knowledge of Akt/PKB in promoting cell survival and proliferation has expanded rapidly. Nevertheless, a number of major questions still remain unanswered. For example, the mechanism for the activation of Akt/PKB, particularly the regulation of the S473 site, is still not fully clear. In addition, although Akt/PKB is strongly implicated in the regulation of cell survival and growth, the physiological substrates of Akt/PKB that drive these processes remain to be completely identified. A number of strong candidates have emerged, such as GSK-3 and forkhead proteins, but their overall importance, compared to other potential substrates, is not yet clear. Akt/PKB has been an attractive therapeutic target. In recent years, specific Akt/PKB inhibitor has been identified, such as deguelin which proved a useful tool for cancer therapy [104,105]. So the progress of pharmaceutical compounds that specifically target Akt/PKB in tumor will be of interest to those in the field.

Acknowledgement

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