INTRODUCTION

The serine/threonine protein kinase, PKB/Akt, is one of the most multifaceted kinases in the human kinome. The Akt family includes three highly homologous members, referred to as PKBα/Akt1, PKBβ/Akt2, and PKBγ/Akt3, all of which are found in mammalian cells [1-3]. The activation of Akt is mediated by the growth factor receptor, tyrosine kinase-stimulated PI3K, which is known to be wortmannin-sensitive [4]. During its activation, Akt is recruited to the plasma membrane, where it binds to the PI3K products, P(3,4,5)P3 and P(3,4)P2, via its pleckstrin homology (PH) domain and exposes a pair of threonine-308 and serine-473 residues for phosphorylation. The Thr residue is targeted by 3-phosphoinositide-dependent kinase 1 (PDK1), which is also recruited to the plasma membrane by P(3,4,5)P3, [5] while the Ser residue is phosphorylated by mammalian target of rapamycin complex 2 (mTOR2) [6] under growth factor stimulation or by DNA-PK upon DNA damage [7,8]. These two phosphorylation events cause full activation of Akt [9, 10].

Akt is transiently localized to the plasma membrane during activation and, once activated, it induces the phosphorylation of a number of nuclear and cytosolic proteins that regulate diverse cellular functions including cell growth, survival, proliferation, and differentiation. Akt functions prior to the release of cytochrome c, via the exertion of regulatory effects on the activities of Bcl-2 family members and mitochondrial activity, and also operates after cytochrome c release, via the regulation of apoptosome components [11, 12]. Akt also directly phosphorylates CREB and inhibits the expression of caspase proteases, including caspase 9 [13, 14]. PI3K and Akt are predominantly located in the

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Neuroprotection Signaling of Nuclear Akt in Neuronal Cells

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Akt is one of the central kinases that perform a pivotal function in mediating survival signaling in a wide range of neuronal cell types in response to growth factor stimulation. The recent findings of a number of targets for Akt suggest that it prohibits neuronal death by both impinging on the cytoplasmic cell death machinery and by regulating nuclear proteins. The presence of active Akt in the nuclei of mammalian cells is no longer debatable, and this has been corroborated by the finding of multiple targets in the nucleus of PC12 cells. However, it is also clear that the nuclear Akt signaling exists independent of the cytosolic Akt signaling, thereby showing a distinctive feature of nuclear Akt signaling as opposed to its cytosolic counterpart. The principal objective of this review is to summarize our current state of knowledge regarding nuclear Akt signaling in neuronal survival, and to introduce current theories regarding the roles of nuclear Akt in neuron.

Key words: Akt, neuroprotection, nuclear Akt signaling

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cytoplasm, but have also been detected within the nucleus [15-17]. This indicates that they either originate in the nucleus, or are translocated into the nucleus upon stimulation [15, 16, 18]. As an example of this, Akt has been shown to translocate to the nucleus after 20–30 min of treatment with growth factors, and there it modulates Forkhead box transcription factors, including FKHR, FKHRL1, and AFX, via the phosphorylation of FOXOs, which results in the inhibition of their ability to induce the expression of death genes [19-21]. Akt has also been shown to both phosphorylate the p53 tumor suppressor, and inhibit its activity [22]. The nuclear targets of Akt include nuclear SRK (S6 kinase-related kinase) and Nur77, a transcription factor that has previously been implicated in T-cell receptor-mediated apoptosis [23, 24]. Acinus, which resides in nuclear speckles, and a focal adhesion protein zyxin, are other nuclear target of Akt [25, 26].

During embryogenesis, the neurons of the vertebrate sympathetic and sensory ganglia are dependent on the neurotrophic factors derived from their targets, for survival and maintenance of differentiated functions [27]. In the development of the mammalian nervous system, half of all generated neurons undergo apoptotic death, which is supposed to adjust the final number of neurons to the number of the target cells they are innervating [28]. Neurotrophins regulate neuronal apoptosis through the action of critical protein kinase cascades, such as the phosphoinositide-3-kinase/Akt through phosphorylation or interaction with its downstream target proteins. In addition to its vital roles in survival, Akt signaling is implicated in neuronal differentiation through glycogen synthase kinase 3b (GSK-3b).

It is now clear that Akt migrates to the nucleus, as a result of treatment with growth factors, in the neuronal cells and protects neurons from apoptotic stimulation in the nucleus [18, 29, 30]. In this review, we will focus on the existing evidence to highlight the putative functions of nuclear Akt in neuronal cells.

ROLE OF ACTIVE AKT IN THE NUCLEUS

Nerve Growth Factor (NGF) activates a variety of signaling cascades, but PI3k/Akt pathway is particularly important for mediating neuronal survival under a wide range of circumstances [5]. NGF stimulates phosphorylated Akt to translocate to the nucleus of PC12 cell [31]. Others and we have intensively studied the role of nuclear translocated Akt in the anti-apoptotic action of NGF in PC12 cells. We generated stably transfected PC12 cells with inducible forms of Akt constructs, which are expressing control, constitutively active, or dominant-negative Akt. Upon induction and NGF stimulation, the nuclei from cells transfected with empty vector or Myc-nuclear localization signal (NLS)-tagged constitutively active Akt (T308DS473D), designated as Myc-NLS-Akt-CA, display negligible DNA fragmentation, whereas, robust DNA fragmentation is observed in the nuclei of dominant-negative Myc-NLS-Akt transfected cells (two different stable clones KD1 and KD2). In the absence of NGF treatment, DNA cleavage is evident in the nuclei from cells transfected with all Akt constructs, though DNA fragmentation is slightly less in the constitutively active Akt cells. These observations indicate that the nuclear Akt is necessary, but not sufficient, to mediate the anti-apoptotic action of NGF, suggesting that presumably, other downstream effectors of the PI(3,4,5)P3, nuclear receptor cooperatively antagonize apoptosis with nuclear Akt [32].

KINASE ACTIVITY DEPENDENT TARGETS OF NUCLEAR AKT

In an effort to search for the downstream target of nuclear Akt that contributes to prevent apoptosis, acinus was discovered as a direct target of nuclear Akt [25]. Acinus is a nuclear factor that is required, after its cleavage by caspase-3, for apoptotic chromatin condensation [33]. However, Akt-mediated, Ser-422 and Ser-573 phosphorylation, of acinus abrogates caspase-3-mediated cleavage of acinus in the nucleus and thereby inhibits acinus-dependent chromatin condensation [25]. On the other hand, upon NGF stimulation of PC12 cells, nuclear Akt phosphorylates and interacts with nuclear-translocated zyxin, which possesses antiapoptotic activity [34, 35]. Akt-mediated phosphorylation of Ser-142 on zyxin elicits tight association with acinus, prevents apoptotic cleavage of acinus and inhibits acinus-dependent chromatin condensation. Thus, Akt controls zyxin/acinus complex formation in the nucleus and contributes to neuronal survival, besides direct phosphorylation of these two proteins, thereby providing alternative regulatory mechanism for apoptotic suppression.

Another intriguing Akt substrate for neuronal survival is ribosomal protein S3 (RPS3), a conserved, eukaryotic ribosomal protein of the 40S subunit, which is required for ribosome biogenesis. Although RPS3 is a ribosomal protein, it shuttles between the cytoplasm and the nucleus, and acts in both the compartments with extra-ribosomal functions including apoptosis. RPS3- is involved in the apoptotic process in NIH3T3 cells [36], and knockdown of RPS3 leads to a significant cell survival after hydrogen peroxide treatment [37]. Employing proteomic analysis with immunoprecipitated complex of anti-Akt in Myc-NLS-Akt-CA expressing PC12 cells, our recent study showed that RPS3 is a physiological substrate of Akt, and Akt-mediated phosphorylation of T70 on RPS3 augmented nuclear accumulation of RPS3 and ablated its pro-apoptotic effect [38].
Overexpression of RPS3 in the PC12 cells or in the primary hippocampal neurons induced neuronal apoptosis by cooperating with E2F1 and causing up-regulation of pro-apoptotic BH3-only proteins, Bim and death protein 5/harakiri (Dp5/Hrk). Akt-dependent phosphorylation of RPS3 T70 inhibited pro-apoptotic protein induction and led to nuclear accumulation of RPS3, thereby promoting neuronal survival. Thus, these findings suggest that upon growth factor stimulation not only Akt translocates itself into the nucleus, but also triggers its target proteins, that act as pro-apoptotic protein in the cytoplasm, to move into the nucleus in order to prevent neuronal death.

**PHYSICAL INTERACTION DEPENDENT TARGETS OF NUCLEAR AKT**

Besides specific phosphorylation of its target proteins, nuclear Akt regulates neuronal survival through protein–protein interaction. One interesting binding partner of nuclear Akt is ErbB3 binding protein 1 (Ebp1), a ubiquitously expressed protein, which distributed in both the nucleus and cytoplasm [39]. Earlier we identified that Ebp1 is expressed as two isoforms, p48 and p42, that correlate with two mRNA transcripts even though the gene possesses three in-frame ATG codons [40]. The p48 protein is initiated at the first ATG and is 54 amino acids longer than p42 at the N-terminus, while p42 initiates translation at the third ATG due to the skipping of a 29 nucleotide exon, eliminating the second ATG of the p48 mRNA. The crystal structures of the two isoforms revealed that p42 lacks one and a half helices present at the amino-terminus of p48 [41], suggesting that the conformational changes of p48 due to the 54 N-terminal amino acids may be responsible for the different cellular functions of p48 and p42. The longer p48 isoform is distributed in both the cytoplasm and the nucleus, whereas the shorter p42 isoform predominantly resides in the cytoplasm. We purified p48Ebp1, from NGF treated PC12 cell nuclear extracts, as an anti-apoptotic protein that prevents DNA fragmentation by inhibiting the activity of DNA fragmentation factor (DFF), which is the human homolog of caspase-activated DNase (CAD) [42]. Moreover we also found that Ebp1 binds to active Akt using IP/Mass analysis, p48Ebp1 (S360A), which cannot be phosphorylated by PKC, barely binds Akt or inhibits DNA fragmentation, whereas p48Ebp1 (S360D), that mimics phosphorylation, strongly binds Akt and suppresses apoptosis. In this p48Ebp1/Akt complex formation event, active nuclear, but not cytoplasmic, Akt interacts with p48Ebp1 and enhances its anti-apoptotic action independent of Akt kinase activity. Thus, nuclear Akt controls NGF-dependent cell survival through the association with its nuclear binding partner.

Another interesting binding partner of nuclear Akt is B23/Nucleophosmin (NPM). B23 is a major nucleolar phosphoprotein involved in ribosome biogenesis and it is also localized in the cytoplasm and mediates centrosome duplication [43-45]. B23 is a very dynamic multifunctional protein that is involved in diverse cellular functions including cell cycle progression, cell proliferation, and apoptosis [46, 47]. In neuronal cells, B23 is identified as a nuclear PI(3,4,5)P3 binding protein through a PI(3,4,5)P3 column and NGF-treated PC12 nuclear extracts [29]. B23 has been shown to mediate the anti-apoptotic effects of NGF by inhibiting DNA fragmentation activity of CAD. B23 mutants that cannot associate with PI(3,4,5)P3 fail to prevent DNA fragmentation, indicating that PI(3,4,5)P3/B23 complex regulates the anti-apoptotic activity of NGF in the nucleus. In a sequential study, we found that upon NGF stimulation, nuclear Akt directly interacts with the C-terminus of B23 and protects it from apoptotic cleavage by caspase-3, leading to increased neuronal survival [30].

Intriguingly, B23 K263R, a major sumoylation site mutant that is essential for B23 nucleolar localization and resistance against apoptotic cleavage, more strongly interacts with Akt regardless of sumoylation, implying presumably this interaction may occur in nucleoplasm to compromise B23 destabilization. Lysine-263 in B23 is involved in some important biological functions of B23 as it has been discovered as a major sumoylation site as well as an ATP binding site. Alteration of K263 residue ablate nucleolar retention of B23, distributing B23 to nucleoplasm where B23 stability decreases in accordance with the finding that B23 sumoylation and its interaction with ATP are essential for its nucleolar localization [48, 49]. Thus, the strongest interaction between the nuclear Akt and the nucleoplasmic B23 provide one of the possible mechanisms that nuclear Akt protects anti-apoptotic protein through direct interaction at the place where the anti-apoptotic protein is unstable.

On the other hand, as the C-terminus of B23 not only interacts with nuclear Akt but also provides binding site for nuclear PI(3,4,5)P3 binding in neuronal cells, nuclear Akt competes with nuclear PI(3,4,5)P3 binding to B23 in the nucleoplasm [50]. Mutation of Arg-23 and Arg-25 in the PH domain of Akt prevents its binding to PI(3,4,5)P3, but does not disrupt the interaction between Akt and B23, whereas with a high concentration of PI(3,4,5)P3, or treatment with PTEN or SHIP, both the phosphate moieties of PI(3,4,5)P3 abrogates the association between Akt and B23, suggesting that the precise control of the spatial and temporal dynamics of nuclear Akt and PI(3,4,5)P3 is critical for its biological functions.

Overall, the above highlighted findings presents convincing
evidence to suggest that the nuclear Akt inhibits neuronal apoptosis not only through phosphorylation of transcription factors but also through direct targeting of apoptotic effectors orchestrating apoptotic reactions in the nucleus. Neuroprotection signaling modulated by nuclear Akt in neuronal cells is summarized in Fig. 1.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The presence of active Akt in the nucleus has been reported since the late 1990s. Despite vast amounts of research, conducted over the last two decades, relatively little useful information is currently available regarding the nuclear Akt signaling, especially when compared to the great deal of information known about the cytosolic Akt signaling. Given this, we still have the following basic questions unanswered: (1) In what physical form do the nuclear Akt exist?; (2) How precisely Akt enters the nucleus?; (3) Or whether they are generated in the nucleus?; and finally, (4) How does its activity turned on/off in the nucleus?

Some nuclear Akt substrates have been identified and the functional consequence of their phosphorylation by Akt in the neuronal cells has been understood. Moreover, it is emerging that nuclear Akt could interact with anti-apoptotic proteins that are not kinase substrates, thereby enhancing neuronal survival. However, most of nuclear Akt substrates or binding partners are also ubiquitously expressed in various cell types other than neurons, and perhaps involves other cell survival signaling. Neuron-specific substrates of Akt are also identified, such as the intermediate filament protein peripherin [51], but yet we do not know how Akt phosphorylation could affect their functions. Thus, identification of additional neuron-specific targets or binding proteins of nuclear Akt may provide a better understanding of the neuroprotection mechanism that is modulated by Akt signaling in the nucleus.

A better knowledge of nuclear Akt is essential because, knowledge about its activation, that is distinct from its cytosolic counterpart, and regulated in a way peculiar to the nuclear compartment, would enable rational drug design to selectively

Fig. 1. Schematic diagram of neuronal survival function of nuclear Akt signaling. Upon growth factor stimulation, Akt is recruited to the plasma membrane by PIP3 binding where it can be fully activated through T398/S473 phosphorylation. Active Akt translocates into the nucleus and Akt phosphorylates its kinases substrate or forms complex with its binding partners to prevent neuronal death. Yellow arrows indicate positive regulation and red lines represent negative regulation. IRS (Insulin Receptor Substrate); ICAD (Inhibitor of Caspase Activated DNase)/CAD (Caspase Activated DNase); RTK (Receptor tyrosine Kinase).
inhibit the relevant nuclear isotypes while sparing Akt that is operating in the plasma membrane. Moreover, the manipulation of nuclear Akt activity in the neuron has therapeutic potential, particularly in brain injury and neurodegenerative disorders such as Alzheimer’s and Parkinson’s disease, due to the anti-apoptotic nature of this protein.

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