Akt/Protein Kinase B Up-regulates Bcl-2 Expression through cAMP-response Element-binding Protein*

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In our previous study we showed that insulin-like growth factor-I induces a cAMP-response element (CRE) site-containing Bcl-2 promoter through a novel signaling pathway involving mitogen-activated protein kinase kinase 6/p38β mitogen-activated protein kinase/MAP kinase-activated protein kinase-3/cAMP-response element-binding protein (CREB) (Pugazhenthi, S., Miller, E., Sable, C., Young, P., Heidenreich, K. A., Boxer, L. M., and Reusch, J. E.-B. (1999) J. Biol. Chem. 274, 27529–27535). In the present investigation, we define a second pathway contributing to CREB-dependent up-regulation of Bcl-2 expression as a novel anti-apoptotic function of Akt signaling. To examine the role of Akt on Bcl-2 expression, a series of transient transfections using a luciferase reporter gene driven by the promoter region of Bcl-2 containing a CRE were carried out. Pharmacological inhibition of phosphatidylinositol (PI) 3-kinase, the upstream kinase of Akt, with LY294002 led to a 45% decrease in Bcl-2 promoter activity. The reporter activity was enhanced 2.3-fold by overexpression of active p110 subunit of PI 3-kinase and inhibited 44% by the dominant negative p85 subunit of PI 3-kinase. Cotransfection with 3-phosphoinositide-dependent kinase (PDK1), which is required for the full activation of Akt, resulted in enhanced luciferase activity. Insulin-like growth factor-1-mediated induction of Bcl-2 promoter activity was decreased significantly (p < 0.01) by the dominant negative forms of p85 subunit of PI 3-kinase, PDK1, and Akt. These data indicate that regulation of Bcl-2 expression by IGF-I involves a signaling cascade mediated by PI 3-kinase/PDK1/Akt/CREB. Furthermore, we measured the Bcl-2 mRNA in PC12 cells overexpressing Akt by real-time quantitative reverse transcription-polymerase chain reaction using the TaqMan™ fluorogenic probe system. We observed a 2.1-fold increase in Bcl-2 mRNA levels in the Akt cell line compared with control PC12 cells, supporting the observation that enhanced CREB activity by Akt signaling leads to increased Bcl-2 promoter activity and cell survival.

The serine threonine kinase Akt/protein kinase B is an important mediator of metabolic as well as survival responses to insulin and growth factors (1). Akt is activated by translocation to plasma membrane when the PI 3-kinase-generated 3-phosphoinositides bind to its pleckstrin homology domain (2). For its full activation it needs to be further phosphorylated by 3-phosphoinositide-dependent kinase1 (PDK1) at Thr-308 and by PDK2 at Ser-473. The metabolic actions of insulin mediated by Akt include stimulation of GLUT4 translocation and activation of glycogen synthase and the glycolytic enzyme 6-phosphofructose-2-kinase (1).

In addition to its metabolic actions, Akt/protein kinase B has been shown to promote cell survival by growth factors against several apoptotic stimuli (3, 4). The Bcl-2 family of proteins consisting of pro-apoptotic Bad, Bik, Bid, etc. and anti-apoptotic Bcl-2 and Bcl-xL are important regulators of mammalian apoptosis (5). Bcl-2/Bcl-xL prevents the activation of caspase-9 by Apaf-1 and cytchrome c (6). Bcl-2 and Bad heterodimerize and neutralize each other’s function. The fate of cells exposed to apoptotic signal is determined by the balance between pro- and anti-apoptotic proteins. One mechanism by which Akt prevents apoptosis is considered to proceed through phosphorylation of the pro-apoptotic protein Bad on Ser-136 (7). Phosphorylated Bad is sequestered by 14-3-3 protein, leading to its down-regulation. It has been also suggested that additional mechanisms might exist for the cell survival-promoting action of Akt (8, 9).

Up-regulation of Bcl-2 expression has been identified as a critical mechanism by which growth factors promote cell survival (10–13). The promoter region of Bcl-2 contains a CRE-response element (CRE) site, and the transcription factor CREB has been identified as a positive regulator of Bcl-2 expression (13, 14). Akt, a target of IGF-I signaling, has been shown to activate CREB (15). Thus, it seemed possible that Akt activation through PI 3-kinase could mediate regulation of Bcl-2 expression by IGF-I.

In our previous studies in PC12 cells, we identified that three post-receptor pathways activated by IGF-I through extracellular-regulated kinase, p38β MAPK, and PI 3-kinase are capable of mediating Ser-133 phosphorylation of CREB (13, 16). However, in the context of CREB-driven Bcl-2 promoter, activation of the extracellular-regulated kinase pathway has been shown to have a negative regulatory effect through Ets domain transcription factors (14). We identified a novel IGF-I-mediated signaling cascade involving MAP kinase kinase 6/p38β MAPK/
MAP kinase-activated protein kinase-3/CREB, leading to the induction of Bcl-2 promoter (13). However, SB203580, the p38 MAPK inhibitor blocked IGF-I-induced Bcl-2 promoter activity only partially. Earlier work in our laboratory demonstrated that IGF-I-mediated CREB phosphorylation and activation of CRE site-containing chromogranin A promoter requires PI 3-kinase (16). In that study, a dominant negative form of the regulatory subunit of PI 3-kinase was able to block IGF-I-mediated induction of a CRE site-containing promoter of chromogranin A, a neuroendocrine-specific gene. Du and Montminy (15) demonstrated recently that Akt stimulates the phosphorylation and the transcriptional activity of the CREB in HEK 293 cells. These reports clearly raise the possibility that Akt could mediate part of the IGF-I-induced increase in the expression of Bcl-2 at the transcriptional level. The objective of the present study was to examine whether IGF-I-mediated signaling through PI 3-kinase and Akt leads to a CREB-dependent increase in Bcl-2 promoter activity.

EXPERIMENTAL PROCEDURES

Materials—The pharmacological inhibitors LY294002 and rapamycin (LC laboratories,Millis, MA) and the hormone IGF-I (Peninsula Laboratories, Belmont, CA) and the CREB/CRE reporter plasmid pIR-A-CRE (4) were purchased from Stratagene (La Jolla, CA). Plasmids for transfection experiments were purified using Qiagen’s (Valencia, CA) maxi kit. Antibodies specific for Phospho (Ser-133) CREB and CREB were from New England Biolabs (Beverly, MA). The luciferase assay kit was purchased from Pharmingen (San Diego, CA).

Cell Culture—Rat pheochromocytoma (PC12) cells (provided by Dr. Derek LeRoith (NIDDK, National Institutes of Health, Bethesda, MD) were maintained in Dulbecco’s modified Eagle’s medium containing 10% fetal bovine serum, 5% heat-inactivated horse serum, 100 U/ml penicillin, 100 μg/ml streptomycin, and 100 μm/ml mycophenolic acid at 37 °C in a humidified atmosphere at 8% CO2. A CAG encoding Akt with the Sre myristoylation sequence at the N terminus (17) in the retroviral vector pLNCX (18) was packaged into replication-defective retrovirus using 293T cells and the virus obtained was used to infect PC12 cells. Ten days post-infection, the cells were harvested and lysates were prepared for western blotting.

Immunoblotting—PC12 cells were cultured in poly-L-lysine-coated 60-mm dishes under appropriate conditions were washed twice with ice-cold PBS, and the cell lysates were prepared. Protein content of lysates was measured (23), and appropriately diluted samples (containing equal amounts of protein) were mixed with 2× Laemmli sample buffer containing 100 mM dithiothreitol. The proteins resolved on a 12% SDS-

- polycrylamide gels were transferred to polyvinylidene difluoride membranes. After blocking with Tris-buffered saline with Tween (20 mM Tris-HCl (pH 7.9), 8.5% NaCl, and 0.1% Tween 20) containing 5% non-fat dry milk at room temperature for 1 h, the blots were treated with the primary antibody in blocking buffer at 4 °C overnight. The blots were washed with blocking buffer and incubated with anti-rabbit IgG conjugated to alkaline phosphatase for 1 h at room temperature. After further washings with blocking buffer and with 10 mM Tris-HCl (pH 9.5), 10 mM NaCl, 1 mM MgCl2, the blots were developed with CDP-Star reagent (New England Biolabs) and exposed to x-ray film.

Transfection Procedure—Transient transfections were carried out by the method described earlier using LipofectAMINE Plus reagent (Life Technologies, Inc.) (13). The cells were cultured to around 70% confluence in 6 × 35-mm plates. One μg of plasmid, 3 μl of Plus reagent, and 10 μg of LipofectAMINE reagent were used for each well. To normalize the transfection efficiency, the plasmid containing β-galactosidase gene driven by SV40 promoter was included. DNA and the LipofectAMINE reagent diluted in 100 μl of serum and antibiotic-free medium were mixed together and incubated at room temperature for 30 min. After washing the cells with PBS, 800 μl of serum and antibiotic-free medium was added. The plasmid and LipofectAMINE mixture was added to each well and incubated for 5 h. Then the cells were cultured in regular medium for 24 h before appropriate treatment. The cells were washed with cold PBS and lysed with 100 μl of reporter lysis buffer. After freezing and thawing, the lysate was centrifuged at 14,000 rpm for 30 min to collect the supernatant. Luciferase was assayed using the enhanced luciferase assay kit (Pharmingen) on a Monolight 2010 luminometer. The β-galactosidase assay was carried out as described earlier (13). Statistical analysis was performed by Student’s t test.

RESULTS

Modulation of PI 3-Kinase Impacts Basal and IGF-I-stimulated Bcl-2 Promoter Activity—To investigate the role of PI 3-kinase in the regulation of Bcl-2 expression, PC12 cells transfected with a Bcl-2 promoter construct containing a CRE site were treated with the PI 3-kinase inhibitor LY294002. There was a 45% decrease (p < 0.01) in the reporter activity in the presence of the inhibitor (Fig. 1A), suggesting a positive role for PI 3-kinase. To confirm these observations, a series of transient transfections with constitutively active p110 subunit and the dominant negative p85 subunit of PI 3-kinase were carried out. Fig. 1B demonstrates the ability of PI 3 kinase activation to augment basal and IGF-1-stimulated Bcl-2 promoter activity. The basal activity increased by 2.3-fold in the presence of p110, whereas it decreased by 56% of control by Δ p85. IGF-1-mediated regulation of Bcl-2 promoter activity was similarly affected. These observations indicate that IGF-I-induced Bcl-2 expression proceeds in part through activation of PI 3-kinase. Rapamycin did not inhibit the Bcl-2 promoter activity (Fig. 1A), suggesting a role for Akt rather than p70 s6 kinase in mediating PI 3-kinase action.

Full activation of Akt is known to require phosphorylation on Thr308 by PDK-1, a kinase downstream of PI 3-kinase (1). We therefore examined the impact of PDK1 and dominant negative PDK1 on Bcl-2 promoter activity. Cotransfection of PC12 cells with PDK1 resulted in a 2.0-fold increase in reporter activity (Fig. 1C). The increase in reporter activity by PDK1 was further enhanced 66% by IGF-I, probably due to its induction through p38 MAPK mediated pathway (13). In contrast, kinase dead PDK1 decreased basal and IGF-1-mediated reporter activity by 37 and 62%, respectively. These data demonstrate important roles for PI 3-kinase and PDK1 in the transcriptional regulation of Bcl-2 expression.

Akt Regulation of Bcl-2 Expression Requires CREB—Akt is one of the downstream targets of PI 3-kinase signaling. Du and Montminy (15) recently reported the positive regulation of CREB activity by Akt. To explore whether Akt regulation of Bcl-2 required CREB, we examined the impact of dominant negative form of CREB, KCREB, on the Akt-stimulated Bcl-2 promoter activity. As shown in Fig. 2A, Akt-stimulated Bcl-2 reporter activity is decreased by KCREB. However, KCREB did...
not completely block Akt-mediated activation of the reporter. This could be due to the CREB-independent component in the activation of Bcl-2 promoter (14). In our previous study, we observed that the promoter retained modest activity after deletion or mutation of the CRE site (13). Furthermore cotransfection of the reporter with the dominant negative Akt (T308A; S473A) decreased basal and IGF-I-stimulated luciferase activity by 40% \( p < 0.01 \) (Fig. 2B). These data support a role for the PI 3-kinase/PDK1/Akt/CREB pathway as a second signaling pathway important for IGF-I regulation of bcl-2 gene expression. However PDK1 is known to have potential targets such as p90rsk and protein kinase C isoforms in addition to Akt that are capable of activating CREB. Hence we examined the effect of dominant negative Akt on PDK1-mediated induction. We did observe that PDK1 mediated stimulation of Bcl-2 promoter activity in the absence and presence of IGF-I to be decreased by 51 and 48%, respectively, when the dominant negative Akt was included in the cotransfection experiments. The possibility of PDK1 modestly activating Bcl-2 promoter through other pathways involving p90rsk and protein kinase C isoforms cannot be ruled out. Further studies are needed to explore these pathways in detail.

Increased CREB Activity and Bcl-2 Expression in PC12 Cell Line-expressing Akt—The results of previous experiments clearly demonstrated that Akt-mediated signaling activates Bcl-2 promoter through CREB, and this transcription factor needs to be phosphorylated for its activation. We therefore examined whether CREB phosphorylation on Ser-133 activation site is increased in PC12 cells expressing myristoylated Akt. We noted a significant (90%; \( p < 0.01 \)) increase in CREB phosphorylation in these cells in the absence of IGF-I (Fig. 3, A and B). When these cells were treated with IGF-I (100 ng/ml) for 10 min, CREB phosphorylation increased from 2.2-fold in control cells to 2.9-fold in Akt-expressing cells. This enhanced PCREB formation could be due to growth factor action through p38 MAPK-mediated pathway as shown in our previous study (13). The CREB protein levels did not change significantly after the growth factor stimulation.
under different experimental conditions (Fig. 3B). Hence Akt seems to activate CREB at the post-translational level. We next examined the CREB activity in the cells expressing Akt using a luciferase reporter driven by a CRE site-containing Bcl-2 promoter. The promoter activity was elevated in Akt cells both in the absence and presence of IGF-I (Fig. 3C), correlating with the increased CREB phosphorylation observed in the previous experiment (Fig. 3A). Interestingly, culturing transfected control cells in low serum medium resulted in a 40% decrease in promoter activity, whereas cells expressing Akt maintained its activation in the presence of low serum (Fig. 3C). Similar results were obtained with a luciferase reporter driven by four tandem repeats of CRE sites (results not shown). Furthermore, PC12 cells expressing Akt were found to have increased survival after serum withdrawal and exposure to UV (Table I). After 72 h of culture in serum-free medium, the survival rate was as high as 86% in the Akt clone as compared with 26% control cells. In addition, Akt increased survival in UV-exposed PC12 cells to 76% from 38% seen in control cells.

Data from the studies described above demonstrate the impact of PI 3-kinase/PDK1/Akt on the luciferase reporter construct driven by Bcl-2 promoter. To confirm the role of Akt in the up-regulation of endogenous Bcl-2 expression, we used the PC12 cell line overexpressing constitutively active myristoy-
lated Akt. We measured Bcl-2 mRNA levels in these cells by a sensitive real-time quantitative RT-PCR using the TaqMan™ fluorigenic probe system. Applied Biosystems prism model 7700 sequence detection instrument was used to measure the reporter fluorescence emission. As shown in Fig. 3D, there is a 2.1-fold increase in Bcl-2 mRNA level in Akt clone as compared with the control vector-only clone. Treatment of these cells with 100 ng/ml IGF-I increased the Bcl-2 mRNA level further to 3.0-fold, which could be due to IGF-I action through p38 MAPK (13). This experiment clearly provides a physiological relevance to the significance of Akt-mediated CREB activation.

**DISCUSSION**

Great insight has been gained over the recent few years regarding the mechanism of neuronal programmed cell death and the ability of growth factors to serve as anti-apoptotic agents. The majority of the data has suggested post-translational modification of the apoptotic machinery (7). The importance of PI 3-kinase and Akt for these effects has been reported by a number of groups (3, 4). The present study defines an additional critical regulatory function for Akt involving transcriptional regulation of the anti-apoptotic protein Bcl-2. We recently reported the induction of Bcl-2 by IGF-I through a novel signaling pathway mediated by MAP kinase kinase 6/p38 MAP kinase kinase/MAP kinase-activated protein kinase-3 (13). Now we identify an additional pathway involving Akt for IGF-I-mediated activation of Bcl-2 promoter.

Regulation of neuronal survival by growth factors is known to proceed through the PI 3-kinase-mediated signaling (3). Low potassium-induced apoptosis in cerebellar granule neurons has been shown to be prevented by synthetic lipid products of PI 3-kinase when added to the culture medium (24). Downstream of this kinase, two signaling pathways involving Akt and p70 s6k when added to the culture medium (24). Downstream potassium-induced apoptosis in cerebellar granule neurons has been shown to be prevented by synthetic lipid products of PI 3-kinase when added to the culture medium (24). Downstream of this kinase, two signaling pathways involving Akt and p70 s6k have been identified. Dudek et al. (3) show that dominant negative Akt is able to induce apoptosis in rat cerebellar granular neurons, and rapamycin, an inhibitor of p70 s6k, suggests that Akt is likely to be involved in CREB activation (16). In a recent study, Du and Montminy (15) demonstrated that Akt/protein kinase B stimulates the phosphorylation of CREB on serine 133 and promotes the recruitment of the coactivator CREB-binding protein (15). They also showed that Akt-mediated induction of CRE-driven gene expression is blocked by a serine to alanine mutation at position 133 using the Gal4 CREB system. In the present investigation, we further demonstrate the physiological importance of this signaling pathway in the activation of an endogenous CRE site-containing Bcl-2 promoter. When the luciferase reporter construct driven by Bcl-2 promoter was cotransfected with p110, PDK1, and Akt, there was significant stimulation of basal and IGF-I-induced luciferase activity. The dominant negative forms of the regulatory subunit of PI 3-kinase, p85, and Akt were able to decrease the promoter activity, suggesting that growth factor-mediated signaling through PI 3-kinase/PDK1/Akt could be involved in the induction of Bcl-2 expression. Hence Akt seems to promote cell survival through inactivation of Bad by phosphorylation and up-regulation of Bcl-2 by transcriptional activation.

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