The mechanisms by which cAMP mediates apoptosis are not well understood. In the current studies, we used wild-type (WT) S49 T-lymphoma cells and the kin− variant (which lacks protein kinase A (PKA)) to examine cAMP/PKA-mediated apoptosis. The cAMP analog, 8-CPT-cAMP, increased phosphorylation of the cAMP response element-binding protein (CREB), activated caspase-3, and induced apoptosis in WT but not in kin− S49 cells. Using an array of 96 apoptosis-related genes, we found that treatment of WT cells with 8-CPT-cAMP for 24 h induced expression of mRNA for the pro-apoptotic gene, Bim. Real-time PCR analysis indicated that 8-CPT-cAMP increased Bim RNA in WT cells in <2 h and maintained this increase for >24 h. Bim protein expression increased in WT but not kin− cells treated with 8-CPT-cAMP or with β-adrenergic receptor agonist isoproterenol. Both apoptosis and Bim expression were reversible with removal of 8-CPT-cAMP after <6 h. The glucocorticoid dexamethasone also promoted apoptosis and Bim expression in S49 cells. In contrast, both UV light and anti-mouse Fas monoclonal antibody promoted apoptosis in S49 cells but did not induce Bim expression. 8-CPT-cAMP also induced Bim expression and enhanced dexamethasone-promoted apoptosis in human T-cell leukemia CEM-C7–14 (glucocorticoid-sensitive) and CEM-C1–15 (glucocorticoid-resistant) cells; increased Bim expression in 8-CPT-cAMP-treated CEM-C1–15 cells correlated with conversion of the cells from resistance to sensitivity to glucocorticoid-promoted apoptosis. Induction of Bim appears to be a key event in cAMP-promoted apoptosis in both murine and human T-cell lymphoma and leukemia cells and thus appears to be a convergence point for the killing of such cells by glucocorticoids and agents that elevate cAMP.

The second messenger cAMP alters the balance between cell growth and apoptosis in a cell type-dependent manner; cAMP stimulates growth arrest and apoptosis in certain lymphoid cells, especially poorly differentiated lymphoblastic cells, but promotes growth of other cell types (e.g. epithelial cells) and protects other cell types (e.g. neutrophils and eosinophils) from drug- and cytokine-promoted apoptosis (1–3). The greater susceptibility of certain tumor cells to cAMP-mediated growth and/or apoptosis has spurred interest in developing cAMP analogs or related agents as anti-cancer drugs (4–6), including those for glucocorticoid-resistant malignancies (4–7). The mechanisms of cAMP-mediated apoptosis are poorly understood, although PKA1 is known to be involved (5, 8, 9). Overexpression of certain anti-apoptotic proteins, such as Bcl-2, can protect lymphoma cells from cAMP-mediated apoptosis; such protection appears to be distinct from the effects of cAMP on cell cycle arrest (10). Although over-expression of Bcl-2 can protect cells from cAMP-mediated apoptosis, whether endogenous levels of Bcl-2 or other Bcl-2 family members are involved in cAMP-induced apoptosis is not known.

In the current study, we used murine S49 lymphoma cells and human CEM cells as model systems to investigate changes in gene expression that contribute to cAMP-promoted apoptosis. S49 cells, which arose in a Balb/c mouse as a transplantable T-cell tumor, grow in suspension culture with a doubling time of 16–18 h and respond to agonists that elevate cAMP by undergoing G1 arrest and apoptotic cell death (8, 10, 11). kin− S49 cells, isolated as a clonal variant by virtue of resistance to killing by cAMP analogs, lack PKA activity, cAMP-promoted G1 growth arrest, and apoptosis (8, 10–13). Thus, WT and kin− S49 cells are a useful system to use in defining PKA-dependent events involved in cell growth and death. CEM cells provide a model of human lymphoid tumor cells with glucocorticoid sensitivity or resistance, one in which cAMP can be used to enhance glucocorticoid sensitivity (14). We show here that the Bcl-2 family member, Bim, may be a key protein in both cAMP/PKA- and glucocorticoid-promoted apoptosis of both murine S49 and human leukemia cells.

**EXPERIMENTAL PROCEDURES**

Materials—Cell culture reagents and a SuperScript II reverse transcriptase kit were obtained from Invitrogen, mouse apoptosis GEArray Q series kit (MM-001 N) from SuperArray, annexin V-fluorescein isothiocyanate from BD Pharmingen, Master Mix SYBR green from Applied Biosystems, propidium iodide, 8-CPT-cAMP, isoproterenol, IBMX, and dexamethasone (Dex) from Sigma, caspase-3 colorimetric assay kit from R&D Systems, biotin-16-dUTP from Roche Applied Science, RNase inhibitor and Maloney murine leukemia virus reverse transcriptase from Promega, Bim primers and GAPDH primers from Integrated DNA Technologies, Inc., subcellular proteome extraction kit from Calbiochem, RestoreTM Western blot stripping buffer and BCA Protein Assay kit® from Pierce, and Immobilon-P® polyvinylidene difluoride membranes from Millipore. cAMP/PKA- and glucocorticoid-promoted apoptosis of both murine S49 and human leukemia cells.

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CAMP induces Bim expression and promotes apoptosis

Fluorescine membrane from Millipore. The following antibodies were used: CREB antibody, phospho-CREB antibody, anti-mouse IgG-horseradish peroxidase, and anti-rabbit IgG-horseradish peroxidase from Cell Signaling Technology; anti-mouse Fas monoclonal antibody, J02, and polyclonal rabbit anti-Bim from BD Pharmingen; and actin (mouse monoclonal IgG,) from Santa Cruz Biotechnology.

Cell Culture—S49 lymphoma cells (2–3 × 10⁶ cells/ml) were grown in suspension in Dulbecco's modified Eagle's medium supplemented with 10% heat-inactivated horse serum, 10 mM Hepes in a humidified atmosphere containing 10% CO₂ at 37°C. The CEM-C7–14 and CEM-C1–15 human acute T-cell leukemia cell lines were provided by Dr. E. Brad Thompson (University of Texas, Galveston) and were cultured and grown in RPMI medium supplemented with 2 mM L-glutamine, 10% fetal bovine serum. Cultures were initiated at a density of 2 × 10⁵ cells/ml and grown in a humidified 5% CO₂ incubator at 37°C.

Apoptosis assay and analysis of DNA content and cell cycle by flow cytometry—Apoptosis was evaluated by assessment of annexin V binding or by propidium iodide analysis of cells for apoptotic sub-G₁ levels of DNA.

Casparase-3 activity assay—Cells treated with 8-CPT-CAMP were collected by centrifugation at the appropriate times. Caspase-3 activity was assessed according to the manufacturer's instructions.

cDNA microarray analysis—Total cellular RNA was isolated by using a Qiagen RNeasy mini-column with extract prepared from cells treated with 8-CPT-CAMP (100 μM) or vehicle for 24 h. The biotin-dUTP-labeled cDNA probe was generated in the presence of a designed set of gene-specific primers using total RNA (5 μg/filter) and 200 units of Maloney murine leukemia virus reverse transcriptase. Hybridization of the array filters, washing conditions, and chemiluminescent detection steps were performed according to the manufacturer's instructions. Chemiluminescent signals were captured with a UVP Biolimaging system. WT and kin⁻ CAMP-treated DNA microarrays were performed twice, each time with new filters, and RNA was isolated at different times. 8-CPT-CAMP-treated DNA microarrays were analyzed once. Data were analyzed with a GEArray software (SuperArray Inc.) and Microsoft Excel software and normalized to GAPDH mRNA levels.

Preparation of cDNA and real-time PCR—Preparation of total RNA was performed as described above. Each cDNA template was made from total RNA with Superscript II reverse transcriptase kit according to the manufacturer's instructions. Quantitative analysis of cDNA amplification was assessed by incorporation of SYBR Green into double-stranded DNA. For mouse Bim we used 5'-CGACACGTCTCGAGAAGACCC-3' as the forward primer and 5'-CTTTCCTCATACCGAAGGAA-3' as the reverse primer. For mouse GAPDH we used 5'-ATACCTGGCCACCCAGAGGAC-3' as the forward primer and 5'-CAGATGGGTTGAGAGAGAAGAC-3' as the reverse primer. PCR containing 50 ng of cDNA template, 0.5 μM each of forward and reverse primers, and SYBR Green PCR Master Mix was performed in a total volume of 25 μl. Thermal cycling conditions were as follows: initial incubation of 10 min at 95°C followed by 45 cycles at 95°C for 1 min, at 57°C annealing and 30 s at 72°C. All cDNA samples were tested in duplicate using the ABI PRISM 7700 Sequence Detector (PE Applied Biosystems) and analyzed with ABI Prism Sequence Detection Software version 1.7 (PE Applied Biosystems).

Samples were compared using the relative Ct method. The Ct value, which is inversely proportional to the initial template copy number, is the calculated cycle number in er where the fluorescence signal is significantly above background levels. Fold induction or repression was measured relative to controls and calculated after adjusting for GAPDH using 2^(-ΔΔCt), where Δ Ct = Ct Bim − Ct GAPDH and ΔΔ Ct = Δ Ct control − Δ Ct treatment (15).

Cytosol and membrane extraction—We used a subcellular proteome extraction kit (S-PER) according to the manufacturer's instructions to extract cytosol and membrane/organelle fractions of S49 lymphoma cells. Cells were treated with 8-CPT-CAMP or vehicle, pelleted (4,000 g/filter) and 200 units of protease inhibitor mixture (10 mM Tris-HCl, pH 7.4, 150 mM NaCl, 5 mM EDTA, 1% Triton X-100, 0.1% SDS, and 0.5% sodium deoxycholate) containing protease inhibitor mixture tablets (for Bim protein expression) or 0.2 ml of SDS sample buffer (2% SDS, 10% glycerol, 0.01% bromphenol blue, 62.5 mM Tris-HCl, pH 6.8, 2.5% β-mercaptoethanol) (for CREB immunoblotting), incubated for 30 min on ice, sonicated three times for 10 s, and centrifuged (5 min at 4°C, 14,000 rpm); the resulting supernatants were used as cell lysates. Protein concentration, determined using a BCA protein assay kit, was equalized by the addition of ultrapure water. Lysates were treated and stripped in RestoreTM and reprobed with actin antibody (mouse monoclonal IgG) or anti-Bim antibody (mouse monoclonal IgG) as the reverse primer. After five washes in phosphate-buffered saline containing 0.75% Tween-20, filters were incubated with horseradish peroxidase-conjugated secondary antibodies at a final dilution of 1/8,000 and then washed five times. Protein was visualized by ECL (Amersham Pharmacia Biotech) using a UVP Biolimaging system. Filters were stripped in Restore™ and reprobed with actin antibody (mouse monoclonal IgG) or CREB antibody for normalization.

Statistical analyses—All determinations were performed in duplicate or triplicate, and each experiment was repeated at least three times. Values are the means ± S.E. Differences were statistically analyzed by one-way analysis of variance followed by Bonferroni’s post hoc test. Comparison between two groups was based on a one-tailed t test. A p value of <0.05 was considered significant.
**RESULTS**

8-CPT-cAMP Acts via PKA to Increase Caspase-3 Activity and Induce Apoptosis of WT S49 Cells—WT S49 cells undergo apoptosis in response to the agents that increase cAMP levels (8). We assessed the pro-apoptotic effects of the cAMP analog 8-CPT-cAMP (100 μM) on both WT and \( \text{kin}^- \) S49 cells. Recent work has indicated that among several cAMP analogs (e.g. 8-Cl-cAMP, 8-Br-cAMP, Bt\(_2\)-cAMP and 8-CPT-cAMP), only CPT-cAMP acts purely as a cyclic nucleotide, having no effect on S49 \( \text{kin}^- \) cells but strongly inhibiting growth of S49 WT cells (16). We found that 8-CPT-cAMP promoted apoptosis in WT but not \( \text{kin}^- \) S49 cells in a time-dependent fashion, akin to that of another cAMP analog, 8-Br-cAMP (8), with a prominent increase in apoptosis after 24 h (Fig. 1A). 8-CPT-cAMP also increased caspase-3 activity (which is activated during apoptosis (17)) of WT but not \( \text{kin}^- \) S49 cells by 24 h of 8-CPT-cAMP treatment (Fig. 1B). As a further confirmation that this effect of cAMP is through PKA, we tested the compound 8-pCPT-2′-O-Me-cAMP, a cyclic AMP analog that does not activate PKA but instead activates Epac, a guanine nucleotide exchange factor for the small GTP-binding protein Rap (18). This analog failed to elicit apoptosis (n = 3, data not shown). Results shown in Fig 1A and in subsequent figures with detection of apoptosis by propidium iodide were confirmed by use of an annexin V binding assay (data not shown).

8-CPT-cAMP/PKA Induce Bim expression in WT but Not \( \text{kin}^- \) S49 Cells—Because of the relatively slow time course of 8-CPT-cAMP-promoted caspase-3 activation and apoptosis, we hypothesized that cAMP/PKA-promoted apoptosis may result from changes in gene expression. Consistent with this hypothesis, 8-CPT-cAMP increased phosphorylation of the CREB protein in WT but not \( \text{kin}^- \) S49 cells (Fig. 1A, inset). Enhanced phosphorylation of CREB by cAMP/PKA would be expected to stimulate gene expression in WT but not \( \text{kin}^- \) S49 cells. To document this effect, we isolated total RNA from WT and \( \text{kin}^- \) cells, either treated with vehicle or with 8-CPT-cAMP for 24 h, and used a GEArray Q series mouse apoptosis cDNA expression array to assess gene expression. This array assesses the expression of 96 murine genes involved in apoptosis and has been shown to be 98% reliable as confirmed by real-time PCR (19). We found that WT and \( \text{kin}^- \) S49 cells show similar “basal” gene expression pattern as assessed by this array (data not shown). After 8-CPT-cAMP treatment of WT but not \( \text{kin}^- \) cells for 24 h, the expression of Bim (Bcl-2-interacting mediator of cell death) increased 3-fold; this was the greatest increase in mRNA expression of pro-apoptotic genes in the microarray. We did not observe a change in Bcl-2 expression, a result confirmed by real-time PCR analysis (data not shown). Based on these data, we hypothesized that Bim contributes to cAMP/PKA-mediated apoptosis, because Bim acts as a “death ligand” that can neutralize members of the pro-survival Bcl-2 subfamily (20). To test this hypothesis, we quantified expression of Bim mRNA by preparation of cDNA for real-time PCR using total RNA from WT and \( \text{kin}^- \) cells treated with 8-CPT-cAMP. Bim was induced as early as 2 h following 8-CPT-cAMP treatment and remained elevated for at least 24–48 h in WT but not \( \text{kin}^- \) S49 cells (Fig. 2A). Bim possesses a hydrophobic C terminus,
localizes to intracytoplasmic membranes including mitochondrial membranes, and exists in three main isoforms (BimEL, BimL, and BimS), all of which promote apoptosis (20–23). Using immunoblot analysis, we detected BimEL and BimL protein in S49 membrane but not cytosol fractions and found that 8-CPT-cAMP increased expression of both BimEL and BimL in WT but not kin− cells (Fig. 2, B and C). Thus, Bim expression induced by 8-CPT-cAMP in S49 cells depends on PKA activity, whereas basal levels of Bim mRNA and protein expression did not differ between WT and kin− S49 cells (data not shown).

Bim Expression Increases with cAMP Analog, Isoproterenol-, and Dexamethasone-promoted Apoptosis but Not with UV Light- or anti-Fas Antibody-promoted Apoptosis—To test whether a G protein-coupled receptor that increases cAMP in S49 cells would lead to apoptosis and Bim expression in a manner akin to 8-CPT-cAMP, we used the β-adrenergic agonist isoproterenol (10 μM, in the presence of 0.2 mM IBMX). As shown in Fig. 3, isoproterenol increased apoptosis and Bim protein expression in WT but not kin− cells over a time course akin to that observed with 8-CPT-cAMP. Not only cAMP, but also glucocorticoids, UV light, and anti-Fas antibody promote apoptosis of S49 cells (Fig. 4A). As shown in Fig. 4B, left panels, Dex prominently induced expression of BimEL and BimL protein. Although UV light and anti-Fas antibody promoted apoptosis more rapidly and vigorously than did 8-CPT-cAMP (Fig. 4A, right panel), these treatments did not induce Bim protein expression (Fig. 4B, right panels).

Sustained Treatment with 8-CPT-cAMP Is Necessary for cAMP-promoted Apoptosis and Increased Expression of Bim mRNA—We undertook studies to assess the reversibility of the response to 8-CPT-cAMP as well as the time required to “commit” cells to apoptosis. Cells were incubated with 8-CPT-cAMP for various times, washed to remove 8-CPT-cAMP, and then returned to culture for up to 48 h. The results (Fig. 5A) show that a 2- or 6-h incubation with 8-CPT-cAMP was too short a period to promote apoptosis; cells appeared to require >6 h treatment with 8-CPT-cAMP to commit to apoptosis. As shown in Fig. 5B, in parallel with the reversal of apoptosis, washout of 8-CPT-cAMP returned Bim mRNA expression to basal levels.
Synergy between CPT-cAMP/PKA and Dex on Apoptosis and Bim Expression in Human CEM Cells—To assess whether induction of Bim by cAMP occurs in other lymphoid cells and in other species, we assessed apoptosis and Bim expression in response to 8-CPT-cAMP, Dex, and the combination of 8-CPT-cAMP and Dex in the human acute leukemia CEM cell line, in particular CEM-C7–14 (glucocorticoid-sensitive) and CEM-C1–15 (glucocorticoid-resistant) cells (24). Previous data have shown that treatment with cAMP analogs enhances glucocorticoid sensitivity in CEM-C1–15 cells (24). We found that Dex induced apoptosis in CEM-C7–14 but not in CEM-C1–15 cells (Fig. 6A, left panel), whereas 8-CPT-cAMP (100 μM), alone or together with Dex, yielded similar results in the two cell lines (Fig. 6A, middle and right panels). 8-CPT-cAMP acted synergistically with Dex to promote apoptosis, even in the Dex-resistant cell line CEM-C1–15. Western blots revealed that all three isoforms of Bim were induced by 8-CPT-cAMP in CEM-C7–14 and CEM-C1–15 cells but that Dex induced Bim only in
CEM-C7–14 cells. The combination of 8-CPT cAMP and Dex also synergistically induced Bim expression (Fig. 6B). Thus, the results in human leukemia CEM cells show a similar ability of cAMP to promote apoptosis and increase Bim expression as observed in murine lymphoma S49 cells.

DISCUSSION

Although the second messenger cAMP was shown to regulate cell growth and cell death many years ago (e.g. Refs. 11 and 25), the precise determinants of cAMP-promoted cell death are poorly understood. Previous studies in the S49 cell system have documented that cell death promoted by cAMP analogs occurs via apoptosis (8) and that apoptosis and G1 growth arrest are independent events that occur in WT but not kin− cells (10, 11), thus implicating activation of PKA in the apoptotic process. In the current studies we show that the cAMP analog 8-CPT-cAMP increases phosphorylation of CREB and activates caspase-3, as well as promoting apoptosis in WT but not kin− S49 cells (Fig. 1). Using a commercial cDNA microarray to define cAMP/PKA-mediated changes in gene expression, we found that mRNA expression for Bim yielded the greatest change among pro-apoptotic genes in WT S49 cells in response to 8-CPT-cAMP. Real-time PCR and immunoblotting confirmed the induction of Bim mRNA and protein by 8-CPT-cAMP in WT S49 cells and in human CEM leukemia cells. In addition, we found that the β-adrenergic agonist isoproterenol promoted apoptosis and enhanced expression of Bim protein over a time course similar to that of 8-CPT-cAMP, implying that G protein-coupled receptors that increase cAMP levels have an action similar to the cAMP analog. Taken together, the results show a close correlation between Bim expression and apoptosis in both murine and human lymphoid cells and, as will be discussed subsequently, are consistent with the idea that Bim mediates apoptosis.

Bim is a member of the Bcl-2 family, which regulates apoptosis. This family is characterized by at least one of four conserved Bcl-2 homology domains present in Bcl-2 (26). Some members, such as Bcl-2 and Bcl-XL, promote cell survival, whereas others, e.g. Bax, Bak, Bad, Bik, and Bim, are pro-apoptotic. Bim, Bad, and Bik contain a single Bcl-2 homology 3 domain and appear to promote cell death by neutralizing prosurvival Bcl-2 family members and activating pro-apoptotic family members (27). Bim is expressed as three major splice variants, BimEL, BimL, and BimS; BimS is the most potent in promoting apoptosis (20, 28). Lymphocytes from Bim−/−/− knock-out mice survive 10–30 times better than cells from Bim−/− mice following cytokine withdrawal or in response to apoptotic stimuli (29, 30). Interleukin-3 withdrawal from murine hematopoietic progenitor cells results in an up-regulation of Bim expression and induction of apoptosis (31, 32). Enforced expression of Bim induces apoptosis in the absence of other signals (32), and expression of Bim isoforms can occur several hours prior to caspase activation (33, 34).

Bim appears to be required for certain apoptotic responses but not others. Compared with Bim−/− cells, Bim−/− pre-T cells are refractory to Dex and γ-irradiation but are equally sensitive to treatment with phorbol 12-myristate 13-acetate or Fas ligand (29). Consistent with those observations, we found that Dex- and 8-CPT-cAMP-promoted apoptosis of WT S49 cells were accompanied by increases in Bim expression, but anti-Fas- and UV radiation-induced apoptosis were not (Fig. 4, A 5).
However, sustained treatment with 8-CPT-cAMP appears to be necessary for cAMP-promoted apoptosis and increased Bim mRNA expression (Fig. 5, A and B). Importantly, in the S49 cell system, responses promoted by 8-CPT-cAMP and isoproterenol, i.e. Bim protein expression and apoptosis, both depend on the presence of PKA activity (Figs. 1–3). To our knowledge, this is the first report to show that cAMP/PKA-induced apoptosis closely correlates with Bim expression.

The precise mechanism by which cAMP/PKA increases Bim expression in WT S49 cells will require further study. Such regulation might be transcriptional or post-transcriptional (22, 23, 35). Transcriptional regulation by cAMP is often mediated...
through the interaction of cREB with a cAMP response element (CRE) in the promoter of target genes but the mouse Bim promoter lacks a consensus CRE (36). However, this promoter contains two potential c-Myb binding sites and multiple potential binding sites for the Sp1 transcription factor (36). It is possible that cAMP/PKA regulates Bim expression by c-Myb or Sp1. Farrar et al. (37) found that 8-Br-cAMP stimulated c-Myb mRNA accumulation. We, too, have found that 8-CPT-cAMP can increase c-Myb mRNA expression in WT (but not kit−) S49 cells as early as 2 h with sustained expression for 24 h (data not shown). Perhaps 8-CPT-cAMP increases c-Myb expression and c-Myb then binds to the Bim promoter to stimulate expression of Bim mRNA. An alternate hypothesis would be if the CREB-binding protein (CBP), which serves as a co-activator of CREB and c-Myb (38), was to stimulate c-Myb-dependent transcriptional activation. CBP preferentially interacts with the phosphorylated (activated) form of CREB; the domain of CBP that interacts with c-Myb is also required for binding to CREB (38). Because Sp1 is also a CREB-responsive transcription factor, it provides another means by which expression of Bim might be regulated via cAMP/PKA (39).

Our studies with human leukemia CEM cells show that cAMP-induced Bim expression is not unique to murine lymphoma S49 cells. CEM cells, T-lymphoblasts derived from a child with acute lymphocytic leukemia, show glucocorticoid-cAMP interaction; activators of cAMP/PKA synergize with glucocorticoids in promoting apoptosis, perhaps via cooperative effects on gene transcription by glucocorticoid receptors and the PKA pathway (24). Our results confirmed that the glucocorticoid Dex promotes apoptosis of S49 cells and CEM cells, T-lymphoblasts derived from a child with acute lymphocytic leukemia, show glucocorticoid-cAMP interaction; activators of cAMP/PKA synergize with glucocorticoids in promoting apoptosis, perhaps via cooperative effects on gene transcription by glucocorticoid receptors and the PKA pathway (24). Our results confirmed that the glucocorticoid Dex promotes apoptosis of S49 cells and CEM cells and induces Bim expression in these cells (40, 41). Murine thymocytes and T-lymphocytes can show a decrease in glucocorticoid sensitivity with a loss in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activity (42) and enhancement in PKA activ
The Pro-apoptotic Protein Bim Is a Convergence Point for cAMP/Protein Kinase A- and Glucocorticoid-promoted Apoptosis of Lymphoid Cells
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