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ER stress is involved in B cell antigen receptor ligation-induced apoptosis

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Abstract

Apoptosis of B cells upon ligation of the B cell antigen receptor (BCR) plays a role in elimination of self-reactive B cells. Previously, BCR ligation was shown to induce expression of the molecules involved in the unfolded protein response (UPR). However, the role of the UPR in BCR-mediated apoptosis is poorly understood. Here, we demonstrate that activation of various UPR molecules are induced when BCR ligation induces apoptosis in the B cell line WEHI-231 and mouse spleen B cells. BCR ligation-induced UPR is attenuated by survival signaling through CD40 in these cells. When overexpression of BiP suppresses the UPR in WEHI-231 cells, activation of p38 MAPK is blocked and apoptosis is reduced. Moreover, the p38 MAPK inhibitor SB203580 reduces BCR ligation-induced apoptosis. These results suggest that the UPR is involved in BCR ligation-induced apoptosis and that p38 MAPK is crucial for apoptosis during the UPR in B cells.

Keywords: UPR; ER stress; Apoptosis; B lymphocyte; BCR; p38 MAPK; CHOP

Metazoan cells react rapidly to dysfunction of the endoplasmic reticulum (ER) through a set of evolutionally conserved adaptive pathways known collectively as the unfolded protein response (UPR) [1,2]. In mammalian cells, three ER-resident membrane molecules, PERK, IRE1, and ATF6 sense perturbation of normal ER function, and then induce expression of UPR genes either directly or by activation of down-stream transcriptional factors such as the spliced form of XBP-1 (sXBP-1) generated by IRE1-mediated splicing of the XBP-1 mRNA. The UPR genes include those encoding chaperones such as BiP (also known as GRP78) and those involved in ER-associated degradation (ERAD). Further, PERK inactivates eIF2α required for protein synthesis thereby reducing protein loading on the ER. Although this set of responses normally restores ER homeostasis, persistent or intense ER stress can also trigger apoptosis. The ER stress-induced apoptosis involves the UPR gene product CHOP (also known as GADD153) and the stress kinase JNK that is activated by various cell stress including ER stress [2] and is induced in various diseases. In neurodegenerative diseases and diabetes, the UPR is induced at the site of cell death of neurons and pancreatic β-cells, respectively [1,3].

During B lymphocyte development, B cells with distinct developmental stages show distinct response to ligation of the B cell antigen receptor (BCR) [4]. In the bone marrow, newly generated immature B cells mature to transitional B cells, and then they migrate to the peripheral lymphoid organs such as spleen and lymph nodes where transitional B cells undergo maturation to mature B cells. When BCR is ligated by anti-Ig antibodies (Abs), transitional B cells undergo massive apoptosis, which is thought to recapitulate efficient elimination of self-reactive B cells at this stage by interaction with self-antigens [4,5]. Although ligation of

Abbreviations: BCR, B cell antigen receptor; ER, endoplasmic reticulum; UPR, unfolded protein response; QM, quasi-monoclonal; NP, (4-hydroxy-3-nitrophenyl) acetyl; Ab, antibody; mAb, monoclonal antibody; PI, propidium iodide.

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BCR by anti-Ig Abs induces survival and activation of mature B cells, antigen-induced BCR ligation causes extensive apoptosis [6], suggesting that antigen generates distinct BCR signaling from anti-Ig Abs and that self-reactive B cells may be eliminated at the mature B cell stage as well as at the immature and transitional B cell stages. Recently, Skalet et al. demonstrated that BCR ligation of anti-Ig Abs up-regulates distinct UPR genes in transitional and mature B cells [7] and suggested that BCR signaling induces partial and distinct UPR depending on developmental stages of B cells.

Here, we addressed BCR ligation-induced UPR, and its role in BCR ligation-mediated apoptosis in mouse spleen B cells that undergo apoptosis upon BCR ligation by antigens, and the B cell line WEHI-231. Our results indicated that BCR ligation-induced extensive UPR including induction of XBP-1 and BiP. Further, BCR ligation-induced apoptosis was reduced by either abrogation of the UPR through overexpression of BiP or inhibition of p38 MAPK, which is activated upon BCR ligation in an UPR-dependent manner. Collectively, our results strongly suggest that extensive UPR is induced by BCR ligation and is involved in BCR ligation-induced apoptosis.

Materials and methods

Mice and cells. QM mice were described previously [8] and were maintained in our animal facility. Spleen B cells were stained with anti-B220-biotin Abs (PharMingen, San Diego, CA) together with streptavidin-microbeads (Miltenyi Biotec, Auburn, CA) and purified by magnet sorting using autoMACS separator (Miltenyi Biotec). The mouse B-lymphoma line WEHI-231, BAL17 and K46μv were cultured as described previously [9,10]. Cells were stimulated with (4-hydroxy-3-nitrophenyl) acetyl (NP)-conjugated BSA, or $F(ab')_2$ fragments of goat anti-mouse IgM Abs (ICN Pharmaceuticals, Aurora, OH) in the presence or absence of anti-CD40 mAb FGK45 [11] (a gift of Dr. A. Rolink, Basel Institute for Immunology, Switzerland) at 37 °C.

RT-PCR. Total RNA was extracted using TriZol (Invitrogen, Carlsbad, CA) and first-strand DNAs were synthesized by reverse transcription using Oligo(dT) primer (Invitrogen). XBP-1 and G3PDH, and BiP cDNA fragments were then amplified by PCR using specific primers (5′-ACACG CTTGGGAATGGACAC-3′ and 5′-CCATGGGAAGATGTTCTGGG-3′ for XBP-1, 5′-AGGTCGGTGTGAACGGATTTG-3′ and 5′-TGTAG ACCATGTAGTTGAGGTCA-3′ for G3PDH, and 5′-ACTCGAGGC CGGCATGATGAAGTTCACTGTG-3′ and 5′-AGCGGCCGCCTACA ACTCATCTTTTTCTGATGT-3′ for BiP).

Plasmids. BiP cDNA fragments were digested with XhoI and NotI and subcloned into the XhoI–NotI digested pMXs-IG [12] (a gift of Dr. T. Kitamura, The University of Tokyo, Japan). Transfection of WEHI-231 cells was done as described previously [9].

Western blot analysis. Cells were lysed in SDS–PAGE sample buffer and proteins were separated by SDS–PAGE. Membranes were incubated with rabbit anti-XBP-1 Abs, goat anti-BiP Abs, anti-mouse CHOP mAb (Santa Cruz Biotechnology, Santa Cruz, CA), rabbit anti-phospho-eIF2α Abs, rabbit anti-phospho-JNK Abs, rabbit anti-phospho-p38 MAPK Abs (Cell Signaling Technology, Beverly, MA), or anti-β-tubulin mAb (Seikagaku Kogyo, Tokyo, Japan), followed by incubation with peroxidase-conjugated goat anti-mouse Ig Abs (Southern Biotechnology Associates, Birmingham, AL), sheep anti-mouse Ig Abs (Amersham Pharmacia Biotech, Uppsala, Sweden), donkey anti-goat IgG Abs (Santa Cruz Biotechnology), or goat anti-rabbit Ig Abs (Cell Signaling Technology). Proteins were then visualized by Chemi-Lumi One (Nacalai Tesque, Kyoto, Japan).

Apoptosis assay. Cells Apoptosis assay was performed as described previously [9].

Results

The UPR is associated with BCR-mediated apoptosis in the B cell line WEHI-231

To ask whether BCR ligation induces the UPR, we ligated BCR in the B cell lines WEHI-231, BAL17, and K46μv using anti-Ig Abs, and examined phosphorylation of eIF2α, production of unspliced XBP-1 (uXBP-1), and splicing of XBP-1 (sXBP-1) mRNA because these events are regulated by distinct UPR pathways involving PERK, ATF6, and IRE1, respectively [1,2]. We also examined expression of BiP, a representative chaperone induced by the UPR. When we stimulated B cells with anti-Ig Abs, most of the WEHI-231 cells underwent apoptosis, whereas apoptosis was not induced in both BAL17 and K46μv cells (Fig. 1A). Treatment with anti-Ig Abs markedly induced phosphorylation of eIF2α and increased the sXBP-1 protein, and moderately increased the uXBP-1 and BiP proteins in WEHI-231 cells (Fig. 1B). RT-PCR analysis revealed that BCR ligation increased the level of both total and spliced form of XBP-1 mRNA (Fig. 1C). These results indicated that BCR ligation induces phosphorylation of eIF2α, expression of XBP-1, and splicing of XBP-1 in WEHI-231 cells, suggesting that BCR ligation activates various distinct UPR pathways involving PERK, IRE1, and ATF6 in WEHI-231 cells.

In BAL17 or K46μv cells, phosphorylation of eIF2α and the BiP protein were not changed after BCR ligation (Fig. 1B). The levels of both sXBP-1 and uXBP-1 were not changed in BAL17 cells. A large amount of the sXBP-1 was produced in unstimulated K46μv cells, which are originally IgG^+ and thus are at the later stage of B cell differentiation than BAL17 [13], probably due to ER stress-independent expression of XBP-1 during B cell differentiation, and BCR ligation reduced the level of XBP-1, in agreement with the previous finding that BCR ligation blocks B cell differentiation to plasma cells [14]. In contrast, various BCR signaling pathways including calcium signaling and MAPK cascades were activated in these cells as well as in WEHI-231 cells (data not shown). This result indicated that BCR ligation does not induce the UPR in B cells that do not undergo apoptosis. Moreover, these UPR events were markedly reduced in WEHI-231 cells when BCR ligation-induced apoptosis was abrogated by treatment with anti-CD40 mAb (Fig. 1B). Thus, the UPR is not induced by BCR ligation in B cell lines that do not undergo apoptosis and is reduced when BCR ligation-induced apoptosis is abrogated by CD40 signaling.

Next, we examined expression of CHOP and the stress MAPKs JNK, and p38 MAPK because CHOP and prolonged activation of JNK were shown to be involved in ER stress-induced apoptosis [15–17]. In WEHI-231 cells, BCR ligation-induced expression of CHOP and prolonged

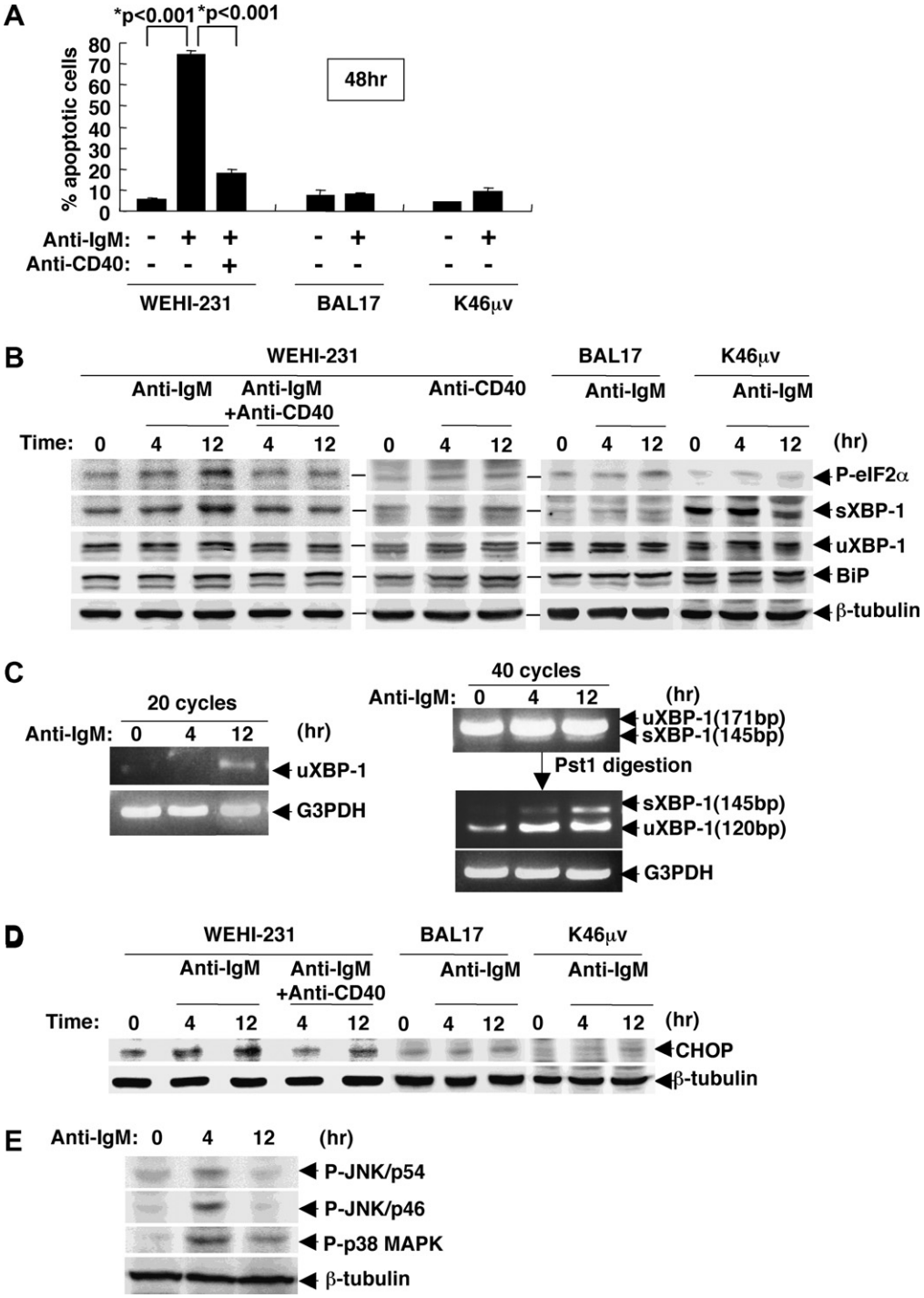

Fig. 1. BCR ligation induces UPR and is reversed by CD40 signaling in WEHI-231 cells. WEHI-231, BAL17, and K46μv cells were stimulated with 5 μg/ml of anti-IgM Abs in the presence or absence of 10 μg/ml anti-CD40 mAb for the indicated time periods. (A) Analysis of apoptosis. Cells were stained with propidium iodide (PI) and the percentage of cells with hypodiploid DNA was measured. The data represent means ± SD of triplicate and were analyzed by unpaired *t* test (*$p < 0.001$). (B) Western blot analysis for XBP-1, BiP, and phosphorylation of eIF2α. Whole cell lysates were probed with Abs specific for XBP-1 reactive to both the unspliced and spliced forms of XBP-1 (uXBP-1 and sXBP-1, respectively), BiP, or phosphorylated form of eIF2α (P-eIF2α). To verify equal loading, the membrane was reprobed with anti-β-tubulin mAb. (C) RT-PCR analysis of XBP-1 mRNA. XBP-1 DNA fragments were amplified by RT-PCR for 20 cycles or 40 cycles using total RNA as templates. Undigested or PstI-digested DNA fragments were analyzed on 3% agarose gels. Positions of unspliced and spliced form of XBP-1 are shown. As a control, RT-PCR product of G3PDH was analyzed. (D) Western blot analysis for CHOP. Whole cell lysates were probed with Ab specific for CHOP. To verify equal loading, the membrane was reprobed with anti-β-tubulin mAb. (E) Western blot analysis for phosphorylation of JNK and p38 MARK. Whole cell lysates were probed with Abs specific for phosphorylated p46 and p54 isoforms of JNK (P-JNK/p54 and P-JNK/p46) and phosphorylated p38 MAPK (P-p38 MAPK). To verify equal loading, the membrane was reprobed with anti-β-tubulin mAb. Representative data of at least three experiments are shown.

phosphorylation of both JNK and p38 MAPK (Fig. 1D and E). In contrast, CHOP expression was not induced in BCR-ligated BAL17 and K46μv cells and CHOP expression was reduced by anti-CD40 mAb in WEHI-231 cells. Taken together, BCR ligation induces extensive UPR including activation of the molecules involved in UPR-mediated apoptosis when BCR ligation induces apoptosis in WEHI-231 cells, whereas BCR ligation does not induce the UPR in B cell lines that do not undergo apoptosis or in which apoptosis is suppressed. These results indicate that the UPR is associated with BCR ligation-induced apoptosis of the B cell line and suggest that BCR ligation induces UPR-mediated apoptosis in B cells.

The UPR is induced in primary B cells that undergo antigen-induced apoptosis

To ask whether the UPR is induced in primary B cells that undergo BCR ligation-induced apoptosis, we stimulated spleen B cells from the quasi-monoclonal (QM) mice with the antigen NP-BSA because almost all the B cells express BCR reactive to NP [8]. Stimulation with the antigen NP-BSA alone induced apoptosis in most QM B cells, whereas antigen-induced apoptosis was markedly inhibited by treatment with anti-CD40 mAb (Fig. 2A) as described previously [6]. Treatment with NP-BSA alone markedly induced phosphorylation of eIF2α and increased the sXBP-1 protein, and moderately increased the BiP protein (Fig. 2B). Both phosphorylation of eIF2α and induction of sXBP-1 were markedly suppressed by treatment with anti-CD40 mAb, whereas the same treatment did not reduce the BiP level. BiP was induced by CD40 signaling and may contribute to suppression of the UPR (Figs. 1B and 2B). Thus, the UPR is induced in primary B cells that undergo antigen-induced apoptosis and is suppressed by survival signaling through CD40.

The UPR contributes to BCR ligation-induced apoptosis through activation of p38 MAPK at least in part

To address whether the UPR is involved in BCR ligation-induced apoptosis, we transfected BiP expression vector in WEHI-231 cells (Fig. 3A) because BiP is known to block the UPR by inactivating UPR sensors such as IRE1, ATF6, and PERK, and/or refolding of unfolded proteins [1,2]. In WEHI-231 BiP trasnfectants (WEHI-BiP), treatment with anti-Ig Abs no longer induced phosphorylation of eIF2α, splicing of XBP-1, or induction of CHOP and uXBP-1 (Fig. 3B), indicating that BiP overexpression abrogates the UPR induced by BCR ligation. Unexpectedly, phosphorylation of p38 MAPK but not JNK was reduced in WEHI-231 BiP transfectants compared to WEHI-231 cells tansfected with vector alone (WEHI-vector). Thus, the UPR induced phosphorylation of p38 MAPK but not JNK in B cells. In WEHI-BiP cells, BCR ligation-induced apoptosis was significantly reduced compared to the WEHI-vector cells (Fig. 3C). These results indicated that BCR ligation-induced apoptosis in WEHI-231 cells is reduced when the UPR is blocked by overexpression of BiP and suggested that the UPR is involved in BCR ligation-induced apoptosis.

Finally, we asked the role of JNK and p38 MAPK in BCR ligation-induced apoptosis. In WEHI-231 cells, treatment with the JNK inhibitor SP600125 and the p38 MAPK inhibitor SB203580 almost completely blocked phosphorylation of JNK and p38 MAPK, respectively (Fig. 4A). Treatment with SB203580 significantly suppressed BCR-mediated apoptosis in WEHI-231 cells whereas SP600125 rather enhanced apoptosis (Fig. 4B). These results indicated that p38 MAPK is activated by the UPR and is involved in BCR ligation-induced apoptosis in WEHI-231 cells, and suggested that p38 MAPK mediates apoptosis induced by the UPR in BCR-ligated B cells.

Discussion

Here, we demonstrate that BCR ligation generates extensive UPR when BCR ligation induces apoptosis in the B cell line WEHI-231 and primary mouse spleen B cells. In contrast, the UPR is reduced by survival signaling through CD40 in both WEHI-231 and spleen B cells and is not induced in B cell lines that survive BCR ligation. Thus, the UPR is induced by BCR ligation and is associated with BCR ligation-induced apoptosis. Overexpression

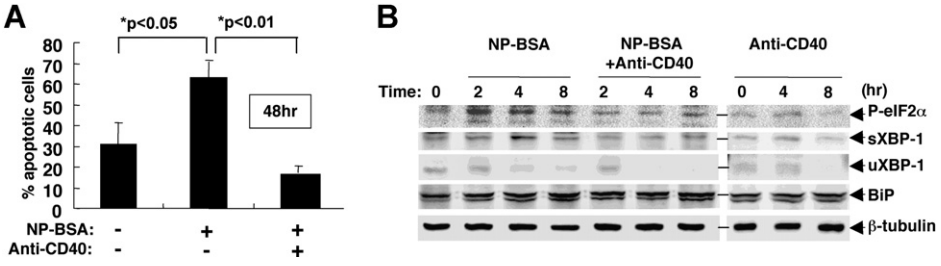

Fig. 2. BCR ligation induces UPR in primary B cells. Spleen B cells from QM mice were stimulated with 1 μg/ml of NP-BSA in the presence or absence of 10 μg/ml of anti-CD40 mAb for the indicated time periods. (A) Analysis of apoptosis. Cells were stained with PI, and the percentage of cells with hypodiploid DNA was measured by flow cytometry. The data represent means ± SD of triplicates and were analyzed by unpaired *t* test. Representative data of at least three experiments are shown. (B) Western blot analysis for XBP-1, BiP, and phosphorylation of eIF2α. Whole cell lysates were probed with Abs specific for XBP-1, BiP, or phosphorylated eIF2α (P-eIF2α). To verify equal loading, the membrane was reprobed with anti-β-tubulin mAb.

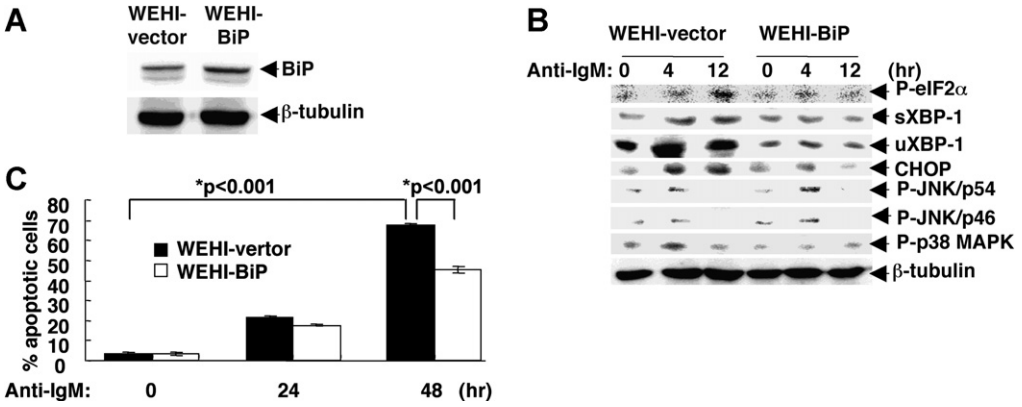

Fig. 3. Overexpression of BiP inhibits the UPR and reduces BCR-mediated apoptosis. WEHI-231 cells were transfected with the retrovirus vector expressing both BiP and GFP (WEHI-BiP), or GFP alone (WEHI-vector). (A) Western blot analysis for BiP. Whole cell lysates were probed with Ab specific for BiP. To verify equal loading, the membrane was reprobed with anti-β-tubulin mAb. (B, C) Analysis for the UPR and apoptosis. WEHI-BiP cells or WEHI-vector cells were stimulated with 5 μg/ml, anti-IgM Abs for the indicated time periods. Whole cell lysates were analyzed by Western blotting for XBP-1, CHOP, or phosphorylation of eIF2α, JNK, or p38 MAPK (B). To verify the equal loading, the membrane was reprobed with anti-β-tubulin mAb. Cells were stained with PI, and the percentage of cells with hypodiploid DNA was measured (C). The data represent means ± SD of triplicate samples and were analyzed by unpaired *t* test. Representative data of at least three experiments are shown.

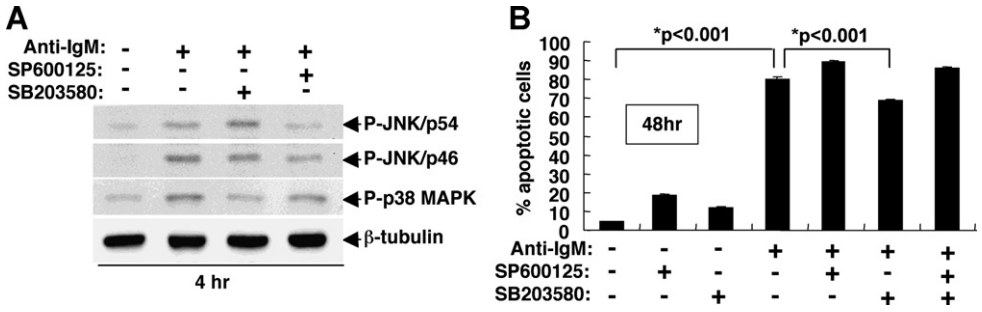

Fig. 4. Treatment with the inhibitor for p38 MAPK reduces BCR-mediated apoptosis in WEHI-231 cells. WEHI-231 cells were stimulated with 5 μg/ml, anti-IgM Abs in the presence or absence of 10 μM SP600125, or 10 μM SB203580 for the indicated time periods. (A) Western blot analysis for phosphorylated JNK and p38 MAPK. Whole cell lysates were analyzed by Western blotting with indicated Abs. To verify equal loading, the membrane was reprobed with anti-β-tubulin mAb. (B) Analysis of apoptosis. Cells were stained with PI and the percentage of cells with hypodiploid DNA was measured. The data represent means ± SD of triplicates and were analyzed by unpaired *t* test. Representative data of at least three experiments are shown.

of BiP blocks activation of p38 MAPK as well as various known mediators of the UPR in WEHI-231 cells. This suggests that p38 MAPK is activated by the UPR in B cells because BiP blocks the UPR by facilitating protein folding and inactivating the UPR sensors such as IRE1, ATF6, and PERK [18]. Further, both BiP overexpression and treatment with a p38 MAPK inhibitor significantly reduce BCR ligation-induced apoptosis in WEHI-231 cells. Thus, the UPR is induced by BCR ligation and is involved in BCR ligation-induced apoptosis in B cells through activation of p38 MAPK.

Here, we demonstrate that BCR ligation induces extensive UPR in B cells that undergo apoptosis. This is in contrast to the previous study by Skalet et al. in which BCR ligation activates a part of UPR molecules in mature B cells [7]. This is probably because we used the system in which BCR ligation induces apoptosis efficiently in WEHI-231 cells and mature B cells. However, Skalet et al. used anti-Ig Ab that does not induce apoptosis efficiently in mature B cells.

Here, we demonstrated that CD40 signaling blocks BCR ligation-induced UPR, which is involved in BCR ligation-induced apoptosis. Inhibition of the UPR may be involved in CD40-mdiated rescue of BCR-ligated apoptosis. This is consistent with the previous finding that CD40 signaling almost completely blocks apoptosis induced by thapsigargin [19]. Previously, CD40 signaling was shown to induce expression of various anti-apoptotic members of the Bcl-2 family including Bcl-xL and A1 [19–21]. Several lines of evidence suggest that the members of Bcl-2 family localize in ER as well as mitochondria and regulate apoptosis by controlling the UPR [22,23]. Thus, Bcl-xL and A1 up-regulated by CD40 signaling might also localize in ER and regulate the UPR.

Here, we demonstrate that BCR ligation induces expression of CHOP and phosphorylation of JNK, both of which are shown to be involved in ER stress-induced apoptosis [1,2]. However, previously CHOP-deficient B cells were demonstrated to undergo BCR ligation-induced apoptosis as efficiently as wild-type B cells [7], suggesting that CHOP

is not required for BCR ligation-induced apoptosis, although this does not necessarily exclude involvement of CHOP in this process. During UPR, prolonged JNK activation is induced by an ASK1-dependent pathway [15,16], in which IRE1 recruits TRAF2 and ASK1, resulting in activation of ASK1, which then triggers MAPK cascades activating both JNK and p38 MAPK. BCR ligation induces prolonged JNK activation in WEHI-231 cells. Nonetheless, prolonged JNK activation does not depend on the UPR in B cells, suggesting that JNK is not involved in BCR ligation-induced UPR-mediated apoptosis. In contrast, we demonstrate that p38 MAPK is phosphorylated after BCR ligation in an UPR-dependent manner and is involved in BCR ligation-induced apoptosis. p38 MAPK has been shown to be involved in apoptosis of various cell types including B cells by activating various different pathways [24,25]. Thus, p38 MAPK is activated by ER stress in BCR-ligated B cells probably through IRE1-ASK1 pathway [15] and plays an essential role in inducing apoptosis instead of JNK.

In this report, we demonstrate involvement of the UPR in BCR ligation-induced apoptosis of B cells and identify p38 MAPK as a mediator of UPR-mediated apoptosis. Since BCR ligation-induced apoptosis is implicated in deletion of self-reactive B cells, the UPR and p38 MAPK may play a role in maintenance of the normal immune system by controlling self-reactive B cells. Further elucidation of molecular mechanisms for induction of BCR ligation-induced UPR and its regulation may strengthen our understanding how B cell immunity is regulated.

Acknowledgments

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