Gadd45b Mediates Fas-induced Apoptosis by Enhancing the Interaction between p38 and Retinoblastoma Tumor Suppressor

Gadd45b has been known as a positive mediator of apoptosis induced by certain cytokines and oncogenes. Here, we identified Gadd45b as an effector of Fas-induced apoptosis and found that p38-mediated Rb hyperphosphorylation is one of the mechanisms of Fas-induced apoptosis in murine hepatocyte AML12 cells. Gadd45b has been shown to activate p38 through its physical interaction with MTK1 and induce apoptosis. However, in this study, we have showed that the function of Gadd45b during Fas-induced apoptosis in AML12 cells is different from that reported in previous studies. Depletion of Gadd45b expression did not inhibit the phosphorylation of p38, but it suppressed p38-mediated Rb phosphorylation and apoptosis in response to Fas stimulation by reducing the interaction between p38 and Rb. Ectopic expression of Gadd45b was sufficient to enhance this interaction. These findings suggest that Gadd45b mediates p38-induced Rb phosphorylation by enhancing the interaction between p38 and Rb during Fas-induced apoptosis in murine hepatocytes.

Fas (CD95/APO1) is the prototypic representative of the death receptor subgroup that belongs to the tumor necrosis factor receptor family. Binding of Fas to its cognate ligand or antibody results in trimerization of the Fas receptors, which transduce death signals via the formation of a death-inducing signaling complex. In the context of this complex, procaspase-8 is activated by dimerization and converts to the processed heterotetrameric mature form of caspase-8, which is released into the cytoplasm, and then triggers the sequential activation of downstream caspses directly or via the mitochondrial pathway leading to the intermediate activation of caspase-9 (1, 2). Alternatively, Fas also can activate the p38 MAPK pathway through an adaptor protein, Daxx. p38 has been shown to inactivate Rb by hyperphosphorylation and to release free E2F1 to induce some proapoptotic genes or repress other antiapoptotic genes during Fas-induced apoptosis (3, 4).

The Gadd45 (growth arrest and DNA damage-inducible, 45) family proteins include three closely related members (a, b, and g) whose transcription is induced by a variety of genotoxic stresses as well as by terminal differentiation and apoptotic cytokines (5–7). The expression of these proteins has been implicated in cell cycle arrest (8), DNA repair (9), innate immunity (10, 11), maintenance of genomic stability (12), and apoptosis (13, 14). There is much evidence to suggest that the functions of Gadd45 family proteins are mediated via interactions with a wide spectrum of proteins, such as proliferating cell nuclear antigen (15), Cdc2-cyclin B1 complex (16), p21Waf1/Cip1 (17), and core histones (18).

One major property of Gadd45 family proteins is that overexpression of each individual Gadd45 protein activates p38/JNK MAPK and causes apoptosis, which can be partially suppressed by coexpression of a dominant inhibitory MTK1 protein, a MAPK kinase kinase upstream in the p38 pathway (11). Physical interaction of Gadd45 with MTK1 induces MTK1 N- to C-terminal dissociation, dimerization, and autophosphorylation and leads to the activation of the catalytic domain of the kinase (19, 20). These studies have suggested that Gadd45 proteins may mediate activation of the p38/JNK MAPK pathway through MTK1 in response to environmental stress. Because activation of the p38/JNK pathway can cause cell growth arrest and apoptosis (21), it is believed that some of the effects of Gadd45 proteins on cell growth and apoptosis are mediated by activation of the p38/JNK pathway. TGF-β-induced Gadd45b expression also activates p38 through MTK1 activation and induces apoptosis (22, 14). Moreover, ectopic expression of Gadd45b has been shown to sensitize H1299 human lung carcinoma cells to apoptosis induced by genotoxic stress (23).

In contrast to its role in apoptosis, Gadd45b has been implicated in promoting the survival of mouse embryo fibroblasts in...
response to tumor necrosis factor-α by suppressing JNK activation (24). Gadd45b directly associates with M KK7, an upstream activator of JNK MAPK, and inhibits its enzymatic activity by contacting critical residues in the catalytic domain (25). In addition, it has been reported that Gadd45b mediates the protective effects of CD40 against Fas-induced apoptosis in B lymphocytes (26). Additional evidence for an antiapoptotic function of Gadd45b has been supported by the fact that Gadd45b protects myeloid hematopoietic cells and fibroblasts from apoptosis induced by genotoxic stress (27) and serum withdrawal (28), respectively. These results reflect the multiple functions of Gadd45 family proteins in regulating intracellular processes and suggest that the function of Gadd45 family proteins might be dependent on the proteins that interact with them. In different types of cells or under different stimulation conditions, Gadd45b could interact with different proteins, leading to the differential regulation of their activities, and it may induce cell death or survival.

The Gadd45 family proteins have not been reported to have any enzymatic activity, and their functions are mediated via interactions with various other proteins. To find new functions of Gadd45b, we attempted to identify proteins that interact with Gadd45b by performing yeast two-hybrid screening. We found that p38 and Rb are binding partners of Gadd45b. In this report, we have demonstrated Gadd45b to be an effector of Fas-induced apoptosis in murine hepatocyte AML12 cells. The Fas antibody, Jo2, induced Gadd45b expression during apoptosis, and inhibition of Gadd45b expression suppressed Fas-induced apoptosis in AML12 cells. We also showed that ectopic expression of Gadd45b is sufficient to enhance the interaction between p38 and Rb, whereas inhibition of Gadd45b expression blocks p38-mediated Rb phosphorylation, which is critical for Fas-induced apoptosis in AML12 cells. These findings suggest that Gadd45b mediates p38-induced Rb hyperphosphorylation by enhancing the interaction between p38 and Rb during Fas-induced apoptosis in AML12 cells.

EXPERIMENTAL PROCEDURES

Cell Cultures and Reagents—AML12 murine hepatocytes were cultured in a 1:1 mixture of Dulbecco’s modified Eagle’s medium and Ham’s F12 medium containing insulin (5 μg/ml), transferrin (5 μg/ml), selenium (5 μg/ml), dexamethasone (40 ng/ml), 10% fetal bovine serum, and antibiotics. HEK293 cells were cultured in Dulbecco’s modified Eagle’s medium with 10% fetal bovine serum and antibiotics. SNU-719 human gastric cancer cells were cultured in RPMI with 10% fetal bovine serum and antibiotics. Antibodies used include anti-HA (Sigma); anti-p38, antiphospho-p38, anti-p-Rb Ser780, anti-ATF2, and anti- phospho-ATF2 (Cell Signaling); anti-Rb (BD Biosciences and Santa Cruz Biotechnology); mouse anti-Fas (Jo2, Pharmingen); human anti-Fas (CH11, Millipore). The p38 MAPK inhibitor, SB203580, was purchased from Calbiochem.

Co-immunoprecipitation and GST Pulldown Assays—For co-immunoprecipitation assays, HEK293 cells were transfected using FuGENE 6 (Roche Applied Science) with HA-Gadd45b, p38, and Rb as indicated. Cells were lysed in a lysis buffer (20 mM Tris (pH 7.4), 2 mM EDTA, 1% Triton X-100, 100 μg/ml bovine serum, and antibiotics). SNU-719 human gastric cancer cells were cultured in RPMI with 10% fetal bovine serum and antibiotics. Antibodies used include anti-HA (Sigma); anti-p38, antiphospho-p38, anti-p-Rb Ser780, anti-ATF2, and anti-phospho-ATF2 (Cell Signaling); anti-Rb (BD Biosciences and Santa Cruz Biotechnology); mouse anti-Fas (Jo2, Pharmingen); human anti-Fas (CH11, Millipore). The p38 MAPK inhibitor, SB203580, was purchased from Calbiochem.

In Vitro Kinase Assay—For the p38 kinase activity assay, 100 ng of active p38 protein (Upstate) was incubated with 200 ng of Rb protein in the presence of GST-Gadd45b or GST protein in 40 μl of kinase buffer (20 mM HEPES (pH 7.9), 20 mM MgCl₂, and 25 mM β-glycerophosphate) containing 50 μM ATP for 10 min at 30°C. Samples were immunoblotted with p-Rb Ser780 antibody.

Image Analysis—Intracellular localization of Gadd45b, p38, and Rb was determined with a confocal microscope (Olympus Fluoview FV1000). For imaging analysis, cells were plated onto poly-L-lysine-coated glass coverslips. After transfection of GFP- or red fluorescent protein-fused genes, the cells were cultured in RPMI with 10% fetal bovine serum and antibiotics. Antibodies used include anti-HA (Sigma); anti-p38, antiphospho-p38, anti-p-Rb Ser780, anti-ATF2, and anti-phospho-ATF2 (Cell Signaling); anti-Rb (BD Biosciences and Santa Cruz Biotechnology); mouse anti-Fas (Jo2, Pharmingen); human anti-Fas (CH11, Millipore). The p38 MAPK inhibitor, SB203580, was purchased from Calbiochem.

Apoptosis Detection—For detection of apoptosis using the TUNEL assay, cells were fixed and stained using the In Situ Cell Death Detection Kit (Roche Applied Science).
Fas-induced Apoptosis Is Mediated by Gadd45b

Death Detection kit, fluorescein (Roche Applied Science). The cell death detection ELISA kit (Roche Applied Science), which detects internucleosomal fragmentation of DNA, was used with lysates of transfected cells, according to the manufacturer's instructions. Results were read using an FL-600 microplate fluorescence reader (Bio-Tek).

RNA Interference Experiment—Two different siRNA oligonucleotide duplexes for targeting mouse Gadd45b (siGadd45b-1 and siGadd45b-2) and human Gadd45b (siGadd45b-A and siGadd45b-B) were purchased from Samchully (Seoul, Korea). The sequences of siRNA used in this study are described in supplemental Table S1. Transient transfection of each siRNA showed that Gadd45b could possibly regulate the function of p38 with p38 and Rb.

Total RNA Extraction and Reverse Transcription-PCR—Total RNA was extracted from the cultured cells using RNeasy mini kit (Qiagen) following the manufacturer's instructions. RT-PCR was performed using a Maxime RT-PCR PreMix kit (Intron, Taejon, Korea). The PCR primers used for the amplification of mouse Gadd45b mRNA were as follows: 5'-CTTCTGGTCGACCGGAAGG-3' and 5'-TCCTGAAAGAGATG-TAGGG-3'. The PCR primers used for the amplification of human Gadd45b mRNA were as follows: 5'-AGAAGATGCAGACGGTGA-3' and 5'-TCCTGAAGAGAGATG-TAGGG-3'. The amplification of β-actin was used as an internal control.

RESULTS AND DISCUSSION

Gadd45b Interacts with p38 and Rb—To identify novel Gadd45b-interacting proteins, we performed a yeast two-hybrid screen with a human HeLa cell cDNA library by using mouse Gadd45b as bait. We identified 12 human cDNA clones that interact with Gadd45b. Of these clones, three encoded p38 and two encoded Rb. To determine whether Gadd45b interacts with either p38 or Rb in mammalian cells, we carried out reciprocal immunoprecipitation using cell extracts from HEK293 cells containing HA-tagged Gadd45b (HA-Gadd45b) and p38 or Rb. HA-Gadd45b was coimmunoprecipitated with p38 and Rb with their specific antibodies, indicating the formation of Gadd45b-p38 and Gadd45b-Rb complexes (Fig. 1, A and B, left panels). Conversely, p38 and Rb were precipitated by anti-HA antibodies only when HA-Gadd45b was present (Fig. 1, A and B, right panels). To examine the subcellular localization of Gadd45b with p38 and Rb, HEK293 cells were cotransfected with an expression plasmid encoding Gadd45b-RFP and either a p38-GFP or an Rb-GFP fusion protein. p38-GFP and Gadd45b-RFP were mainly observed in the nucleus, but there also was significant expression in the cytoplasm (Fig. 1C, upper panels). Superimposing the expression patterns of p38 and Gadd45b indicated that the nuclear portions of their distributions were identical (Fig. 1C, upper panels). Rb-GFP was exclusively observed in the nucleus where it colocalized with Gadd45b (Fig. 1C, lower panels). To verify the direct binding of Gadd45b with p38 and Rb in vitro, commercially available purified p38 and Rb proteins were tested for their ability to bind to purified GST-Gadd45b fusion proteins. The results clearly showed that Gadd45b directly interacts with p38 and Rb without the help of any other proteins (Fig. 1D). These results suggest that Gadd45b could possibly regulate the function of p38 and Rb.

Gadd45b Is Required for p38-mediated Rb Phosphorylation during Fas-induced Apoptosis—To understand the significance of the interaction between Gadd45b and p38 or Rb, we examined the mechanism of Fas-induced apoptosis in murine hepa-
Fas-induced Apoptosis Is Mediated by Gadd45b

To address the question of whether endogenous Gadd45b is essential for Fas-induced p38 activation and apoptosis, AML12 cells were transfected with two different Gadd45b-specific siRNAs (siGadd45b-1 and -2), thereby blocking expression of the endogenous Gadd45b gene. In each transfectant, Gadd45b mRNA levels were assayed before and after Jo2 stimulation. Gadd45b mRNA was increased rapidly after treatment with Jo2, as well as TGF-β (Fig. 3A). The Gadd45b siRNAs effectively suppressed the up-regulation of Gadd45b expression by Jo2 (Fig. 3B) and markedly inhibited Fas-induced apoptosis (Fig. 3C) and PARP cleavage (Fig. 3D), indicating that the expression of endogenous Gadd45b is necessary to direct Fas signaling toward apoptotic end points.

We next investigated whether Rb is phosphorylated by Jo2 treatment, because Rb has been shown to be a potential target of p38 in Fas-induced apoptosis (3, 4), and we have shown direct interaction of Gadd45b with Rb (Fig. 1). We found that Rb phosphorylation was markedly increased after 2 h and sustained at 24 h after Jo2 treatment (Fig. 4A). The induction of Rb phosphorylation coincided with the onset of p38 phosphorylation (Fig. 2D), which suggests that phosphorylation of Rb might be crucial for Fas-induced apoptosis in AML12 cells. We also confirmed that down-regulation of Gadd45b expression markedly suppressed the phosphorylation of Rb but not p38 after Jo2 treatment (Fig. 4B). If Gadd45b regulates the upstream components of the p38 signaling pathway such as MTK1 during Fas-induced apoptosis, suppression of Gadd45b expression should inhibit the phosphorylation of p38 after treatment with Jo2. All of these results suggest that Gadd45b is required for p38-mediated Rb phosphorylation during Fas-induced apoptosis in AML12 cells by regulating p38 activity through the activation of p38 upstream kinase, but it might affect p38 activity more directly after p38 phosphorylation. We next determined whether Gadd45b could regulate the activity of p38 in vitro. p38-mediated phosphorylation of Rb was increased markedly in the presence of purified Gadd45b proteins (Fig. 4C), suggesting that Gadd45b could directly regulate the kinase activity of p38. As a complementary approach, we found that Fas-induced apoptosis and hyperphosphorylation of Rb are inhibited remarkably in AML12 cells transfected stably with antisense
**Fas-induced Apoptosis Is Mediated by Gadd45b**

---

**FIGURE 5. Gadd45b enhances interaction between p38 and Rb.** A, HEK293 cells were transfected with p38 and Rb alone or together with the HA-Gadd45b construct as indicated. Proteins were immunoprecipitated (IP) with anti-p38 or Rb and immunoblotted with Rb (left panel) or p38 (right panel) antibody, respectively. Cell lysates were analyzed for the expression of HA-Gadd45b, p38, and Rb by Western blotting (WB). B, interaction of purified p38 with Rb was tested in the presence or absence of GST-Gadd45b. The expression of p38, Rb, and GST-Gadd45b in 5% input was analyzed by Western blotting. C, total cell lysates were prepared from Jo2-treated AML12 cells for indicated times, and proteins were immunoprecipitated with anti-Rb and immunoblotted with p38 antibody. D, AML12 cells transfected with indicated siRNA were treated with Jo2 for 4 h, and proteins were immunoprecipitated with anti-Rb and immunoblotted with p38 antibody.

**FIGURE 6. Gadd45b mediates Fas-induced apoptosis and interaction of p38 with Rb in SNU-719 human gastric cancer cells.** A, SNU-719 cells were transfected with either control siRNA (siGFP) or two specific siRNA against human Gadd45b (siHGadd45b-1 and siHGadd45b-2). After 24 h, cells were treated with CH11 for 2 h, and expression of Gadd45b was analyzed by RT-PCR. B, percentage of TUNEL-positive Gadd45b-depleted SNU-719 cells after treatment of CH11 for 24 h. Non, non-treated. C, PARP cleavage was analyzed by Western blotting after treatment of CH11 for 24 h in Gadd45b-depleted SNU-719 cells. D, SNU-719 cells transfected with indicated siRNA were treated with CH11 for 4 h, and proteins were immunoprecipitated with anti-Rb and immunoblotted with p38 antibody. Data are mean ± SD of three individual experiments, each in triplicate.

---

Gadd45b cDNA, thereby blocking expression of the endogenous Gadd45b gene (supplemental Fig. S1).

Gadd45b Enhances the Interaction between p38 and Rb—To address the question of how Gadd45b regulates p38-mediated phosphorylation of Rb during Fas-induced apoptosis more precisely, we investigated the effect of Gadd45b on the interaction between p38 and Rb. We hypothesized that Gadd45b would act as an adaptor for the interaction between p38 and Rb because Gadd45b does not have enzymatic activity, and it directly interacts with p38 and Rb (Fig. 1). As shown in Fig. 5A, p38 interacts with Rb in vivo. Interestingly, the interaction between p38 and Rb was enhanced markedly in the presence of Gadd45b (Fig. 5A). Binding of purified p38 with Rb was clearly enhanced by the presence of purified Gadd45b (Fig. 5B). These results suggest that Gadd45b might act as an adaptor in the interaction between p38 and Rb.

We next examined whether the interaction between p38 and Rb is induced by Jo2 treatment in AML12 cells and whether such interaction is suppressed by the inhibition of Gadd45b expression. AML12 cells contained very little of the p38-Rb complex (Fig. 5C). Treatment with Jo2 increased the interaction of p38 with Rb within 2 h (Fig. 5C). Inhibition of Gadd45b expression strongly inhibited the interaction between p38 and Rb that had been induced by Jo2 treatment (Fig. 5D). These results suggest that Gadd45b plays a key role to stimulate the interaction between p38 and Rb, which is critical for Fas-induced apoptosis in AML12 cells.

We also confirmed the function of Gadd45b during Fas-induced apoptosis in SNU-719 human gastric cancer cells. Treatment of the human Fas antibody CH11 in SNU-719 cells markedly increased expression of Gadd45b mRNA (Fig. 6A). The human Gadd45b siRNAs (siHGadd45b-1 and -2) effectively suppressed the up-regulation of Gadd45b expression by CH11 (Fig. 6A) and inhibited Fas-induced apoptosis (Fig. 6B) and PARP cleavage (Fig. 6C). Depletion of Gadd45b expression inhibited Fas-induced interaction between p38 and Rb (Fig. 6D). These results suggest that Gadd45b is critical for interaction of p38 with Rb and Fas-induced apoptosis in human gastric cancer SNU-719 cells.

Taken together, our results suggest a new function of Gadd45b during Fas-induced apoptosis. Transcriptionally activated Gadd45b induced p38-mediated Rb phosphorylation, which is crucial for Fas-induced apoptosis in murine hepatocytes, by enhancing the interaction between p38 and Rb. Suppression of Gadd45b expression induced by Fas did not reduce the phosphorylation level of p38, but it inhibited p38 activity, interaction of p38 with Rb, p38-mediated phosphorylation of Rb, and apoptosis. Gadd45b interacted with p38 and Rb, and the expression of Gadd45b enhanced the interaction of p38 with Rb in vivo and in vitro. These results suggest that Gadd45b
can function as an adaptor between p38 and Rb to enhance p38-mediated phosphorylation of Rb, which is a critical step during Fas-induced apoptosis. In agreement with our results, there is a report showing that Gadd45a directly interacts with p38 and is required for the activation of p38 after oncogenic stress (29). Because Gadd45 family proteins have not been reported to have any enzymatic activity, these authors suggested that Gadd45a might be an adaptor or scaffold protein in a complex with p38 and other proteins. In this report, we have showed for the first time that Gadd45b could play a role as an adaptor protein in the complex of p38 and Rb during Fas-induced apoptosis.

REFERENCES
1. Fulda, S., Meyer, E., Friesen, C., Susin, S. A., Kroemer, G., and Debatin, K. M. (2001) Oncogene 20, 1063–1075
2. Hengartner, M. O. (2000) Nature 407, 770–776
3. Wang, S., Nath, N., Minden, A., and Chellappan, S. (1999) EMBO J. 18, 1559–1570
4. Hou, S. T., Xie, X., Baggley, A., Park, D. S., Chen, G., and Walker, T. (2002) J. Biol. Chem. 277, 48764–48770
5. Zhan, Q., Lord, K. A., Alamo, I., Jr., Hollander, M. C., Carrier, F., Ron, D., Kohn, K. W., Hoffman, B., Liebermann, D. A., and Fornace, A. J., Jr. (1994) Mol. Cell Biol. 14, 2361–2371
6. Fornace, A. J., Jr., Jackman, J., Hollander, M. C., Hoffman-Liebermann, B., and Liebermann, D. A. (1992) Ann. N.Y. Acad. Sci 663, 139–153
7. Papathanasiou, M. A., Kerr, N. C., Robbins, J. H., McBride, O. W., Alamo, I., Jr., Barrett, S. F., Hickson, I. D., and Fornace, A. J., Jr. (1991) Mol. Cell Biol. 11, 1009–1016
8. Kastan, M. B., Zhan, Q., el-Deiry, W. S., Carrier, F., Jacks, T., Walsh, W. V., Plunkett, B. S., Vogelstein, B., and Fornace, A. J., Jr. (1992) Cell 71, 587–597
9. Smith, M. L., Ford, J. M., Hollander, M. C., Bortnick, R. A., Amundson, S. A., Soo, Y. R., Deng, C. X., Hanawalt, P. C., and Fornace, A. J., Jr. (2000) Mol. Cell Biol. 20, 3705–3714
10. Yang, J., Zhu, H., Murphy, T. L., Ouyang, W., and Murphy, K. M. (2001) Nat. Immunol. 2, 157–164
11. Lu, B., Ferrandino, A. F., and Flavell, R. A. (2004) Nat. Immunol. 5, 38–44
12. Hollander, M. C., Sheikh, M. S., Bulavin, D. V., Lundgren, K., Auger-Henmueller, L., Shehee, R., Molinaro, T. A., Kim, K. E., Tolosan, E., Ashwell, J. D., Rosenberg, M. P., Zhan, Q., Fernández-Salguero, P. M., Morgan, W. F., Deng, C. X., and Fornace, A. J., Jr. (1999) Nat. Genet. 23, 176–184
13. Takekawa, M., and Saito, H. (1998) Cell 95, 521–530
14. Yoo, J., Ghiassi, M., Firmanova, L., Balliet, A. G., Hoffman, B., Fornace, A. J., Jr., Liebermann, D. A., Bottinger, E. P., and Roberts, A. B. (2003) J. Biol. Chem. 278, 43001–43007
15. Smith, M. L., Chen, I. T., Zhan, Q., Bae, I., Chen, C. Y., Gilmer, T. M., Kastan, M. B., O’Connor, P. M., and Fornace, A. J., Jr. (1994) Science 266, 1376–1380
16. Zhan, Q., Antinore, M. J., Wang, X. W., Carrier, F., Smith, M. L., Harris, C. C., and Fornace, A. J., Jr. (1999) Oncogene 18, 2892–2900
17. Kearsey, J. M., Coates, P. J., Prescott, A. R., Warbrick, E., and Hall, P. A. (1995) Oncogene 11, 1675–1683
18. Carrier, F., Georgel, P. T., Pourquier, P., Blake, M., Konny, H. U., Antinore, M. J., Gariboldi, M., Myers, T. G., Weinstein, J. N., Pommier, Y., and Fornace, A. J., Jr. (1999) Mol. Cell Biol. 19, 1673–1685
19. Mita, H., Tsutsui, J., Takekawa, M., Witten, E. A., and Saito, H. (2002) Mol. Cell Biol. 22, 4544–4555
20. Miyake, Z., Takekawa, M., Ge, Q., and Saito, H. (2007) Mol. Cell Biol. 27, 2765–2776
21. Davis, R. J. (2000) Cell 103, 239–252
22. Takekawa, M., Tatebayashi, K., Itoh, F., Adachi, M., Imai, K., and Saito, H. (2002) EMBO J. 21, 6473–6482
23. Zhang, W., Hoffman, B., and Liebermann, D. A. (2001) Int. J. Oncol. 18, 749–757
24. De Smaele, E., Zazzeroni, F., Papa, S., Nguyen, D. U., Jin, R., Jones, I., Cong, R., and Franzoso, G. (2001) Nature 414, 308–313
25. Papa, S., Zazzeroni, F., Bubici, C., Jayawardena, S., Alvarez, K., Matsuda, S., Nguyen, D. U., Pham, C. G., Nelsbach, A. H., Melis, T., De Smaele, E., Tang, W. J., D’Adamio, L., and Franzoso, G. (2004) Nat. Cell Biol. 6, 146–153
26. Zazzeroni, F., Papa, S., Algeciras-Schimnich, A., Alvarez, K., Melis, T., Bubici, C., Majewski, N., Hay, N., De Smaele, E., Peter, M. E., and Franzoso, G. (2003) Blood 102, 3270–3279
27. Gupta, M., Gupta, S. K., Balliet, A. G., Hollander, M. C., Fornace, A. J., Hoffman, B., and Liebermann, D. A. (2005) Oncogene 24, 7170–7179
28. Engelmann, A., Speidel, D., Bornkamm, G. W., Deppert, W., and Stocking, C. (2008) Oncogene 27, 1429–1538
29. Bulavin, D. V., Kovalsky, O., Hollander, M. C., and Fornace, A. J., Jr. (2003) Mol. Cell Biol. 23, 3859–3871

Fas-induced Apoptosis Is Mediated by Gadd45b