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The E2F-1 Transcription Factor Promotes Caspase-8 and Bid Expression, and Enhances Fas Signaling in T Cells

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The immune system depends on the extensive proliferation of rare Ag-specific precursor T lymphocytes, followed by their differentiation, the delivery of effector function, and finally death by apoptosis. T cells that lack the E2F-1 transcription factor, which is activated as cells pass the restriction point and enter S phase, show defects in activation-induced cell death. We now report that E2F-1 increases the activity of an apoptotic pathway that is important in murine primary T cells. Thus, E2F-1 promotes the transcription of Bid, a molecule that links death receptor signaling to the activation of apoptotic mechanisms in mitochondria. It also promotes the transcription of caspase-8, the enzyme that cleaves and activates Bid. Enforced expression of Bid can partially restore apoptosis in E2F-1-deficient T cells. Thus, E2F-1 integrates cell cycle progression with apoptosis. The Journal of Immunology, 2004, 173: 1111–1117.

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lonal expansion is a central operating principal of the immune system, but the immune system deletes most of the activated lymphocytes at the end of an immune response, thus maintaining the size of the lymphocyte pool (1, 2). Apoptosis is required for this process and also to eliminate autoreactive thymocytes by negative selection in the thymus (3, 4). Thus, T lymphocyte death protects animals from autoimmunity due to the survival of self-reactive T cells and from immunopathology due to the persistence of effector cells. There are two different mechanisms by which mature T lymphocytes can undergo apoptosis. One is activation-induced cell death (AICD),3 which functions mainly through death-promoting ligands, including FasL and TNF-\(\alpha\); these induce apoptosis by ligation of their receptors expressed on the T cell surface. The other is passive cell death, due to the lack of survival factors.

Upon engagement of Fas, the adaptor molecule Fas-associated death domain protein together with pro-caspase-8 is recruited to form the death-inducing signal complex, which activates caspase-8. The activated caspase-8 cleaves and triggers the activation of downstream effector caspases and also cleaves the BH-3 only Bcl-2 family member, Bid (5). The truncated Bid translocates into mitochondria and enhances the release of cytochrome c, which further amplifies the death signal (6, 7). Bid-deficient mice survived the injection of anti-Fas Ab, whereas wild-type mice died of massive liver damage (8). Defects in death receptor-mediated apoptosis lead to autoimmune diseases in both humans and mice. Fas-FasL interaction plays an important role in AICD of T cells (9, 10) as well as in T cell-mediated cytotoxicity. In mice, mutations of Fas or FasL lead to the lymphoproliferative (lpr) syndrome or generalized lymphoproliferative disease (gld), respectively, and both of these diseases are similar to the autoimmune lymphoproliferative syndrome in humans (11, 12), which is due to mutations in human Fas (13).

T lymphocytes also can undergo passive death induced by lack of extrinsic survival signals, as occurs in cytokine withdrawal. This process is Fas independent, because activated T cells from lpr/lpr and gld/gld mice can die in vivo in the absence of Fas or FasL.

The exact mechanism of this type of apoptosis is still poorly understood, but there is evidence that a calcium-dependent mitochondrial pathway is involved (14), and that Bcl-2 overexpression can overcome this type of cell death (10). The proapoptotic Bcl-2 family member Bim was recently shown to be required for staphylococcal enterotoxin B-induced AICD, which was independent of Fas or FasL (15). In addition, the Bcl-2 family members Bak and Bax play a role in passive cell death, but not in AICD (16).

Cell cycle progression is integrated precisely though the action of a family of transcription factors, the E2Fs (17, 18). These factors are repressed by the pocket proteins, p130, p107 and pRb, and are released from repression when pocket proteins are phosphorylated by cyclin-dependent kinases (cdk) (18, 19). E2F-1, -2, and -3 are transcription activators that mainly interact with pRb, and they have overlapping as well as distinct roles in the control of cell proliferation (20, 21). E2F-4 and -5 are transcriptional repressors and are essential for G1 control and cell cycle exit as well as for normal mouse development (22–24). E2F-1 transcriptional targets are involved in multiple cellular events, such as cell cycle checkpoint control, DNA damage, and apoptosis (25). E2F-1 is unique in having a well-documented dual role in both S phase progression and apoptosis. Thus, enforced overexpression of E2F-1 causes cell proliferation and cell death in multiple cell types (25), whereas E2F-1-deficient mice exhibit increased tumor formation accompanied by defects in thymocyte apoptosis and negative selection (26–28). E2F-1-induced apoptosis of cultured cells as well as AICD of T cells involves p73 (29–32), a homologue of the p53 tumor suppressor, but the mechanism of its action is still unknown. In T cells, E2F-1 and -2 are reported to control the threshold of Ag required for T cell activation (33). As AICD of T cells occurs from a late G1 phase check point (34), and E2F-1 has a role in controlling G1 to S progression, we tested the hypothesis that E2F-1 functions to link cell cycle progression to Fas-induced apoptosis of...
lymphocytes by regulating gene expression of proapoptotic molecules. We found that E2F-1 increases the expression of both caspase-8 and Bid, and that the cleaved Bid may act as a downstream effector of E2F-1 during AICD.

Materials and Methods

Mice and cell culture

E2F-1-deficient and wild-type control mice, both on the (C57BL/6 × 129F1) background, were from The Jackson Laboratory (Bar Harbor, ME) and were maintained in the specific pathogen-free animal facility at University of Rochester Medical Center. Lymphocytes from spleens and lymph nodes of 6- to 8-wk-old mice were cultured in RPMI 1640 cell growth medium (In Vitrogen, Carlsbad, CA) containing 10% FBS (In Vitrogen), 2 mM L-glutamine (In Vitrogen), 50 μM 2-ME (Sigma-Aldrich, St. Louis, MO), 2 μg/ml Penicillin, and 2 μg/ml streptomycin, and 10 μl/ml recombinant mouse IL-2 (Endogen, Woburn, MA) for an additional 2-3 days.

Plasmids and retroviral transduction

Mouse E2F-1 cDNA was cleaved from pcDNA-E2F-1 vector using PmeI and NorI and inserted into the murine sarcoma virus-GFP (MSCV-GFP) vector. Wild-type Bid and the Bid variant with a caspase-8 cleavage site mutation (gift from A. Gross, Rehovot, Israel) cDNA were recloned from pcDNA-BID and pcDNA-D59A, respectively, by PCR and inserted into MSCV-GFP to form MSCV-BID and MSCV-D59A. Phoenix cells for retrovirus packaging were transiently transfected with the specific plasmids and the viral supernatant was harvested 48 h later. Virus titers were determined based on GFP expression of NIH-3T3 cells transduced by retrovirus-containing supernatant. Activated lymphocytes were infected with retrovirus on day 2, the medium was removed after 24 h, and cells were cultured with 40 U/ml recombinant mouse IL-2 (Endogen, Woburn, MA) for an additional 2-3 days.

Flow cytometry

For cell surface staining, cells were incubated with Abs in 500 μl of PBS (1 × 10^6 cells) containing 5% FBS for 30 min on ice in the dark. R-PE-conjugated anti-Cdx8a (53-6.7), FITC-conjugated anti-mouse Fas (J02), and PerCP-conjugated anti-Cd4 (RM4-5) were all obtained from BD Pharmingen. Fluorescence was detected using a FACScan flow cytometer (BD Biosciences, San Jose, CA). Annexin V and 7-AAD staining were conducted according to the manufacturer’s protocol (BD Pharmingen).

Western blots

Lymphocytes were lysed in lysis buffer containing 0.5% Nonidet P-40, 100 mM NaCl, 50 mM Tris-HCl (pH 7.4), and protease inhibitor mixture (Calbiochem, San Diego, CA) by three cycles of free-thaw. Cell lysates were resolved by 10% SDS-PAGE gel, transferred to Hybond ECL (Amersham Pharmacia Biotech, Arlington Heights, NJ) nitrocellulose membranes, and blocked with TBS containing 5% dry milk. Immunoblots were probed overnight with primary Abs in TBS with 0.05% Tween 20 containing 5% dry milk and washed three times, then incubated with peroxidase-conjugated goat anti-rabbit or goat anti-mouse Abs for 1 h. The blots were washed for five times and developed using ECL-Plus reagent (Amersham Pharmacia Biotech) following the manufacturer’s protocol. Mouse anti-E2F-1, anti-caspase-8, and anti-β-actin Abs were obtained from Sigma-Aldrich, and rabbit anti-Bid Ab was purchased from Cell Signaling Technology (Beverly, MA).

Quantitative RT-PCR

Total RNA from lymphocytes was prepared using TRIzol reagent (Invitrogen Life Technologies, Carlsbad, CA) according to the manufacturer’s protocol. Total RNA (1.5 μg) was digested with DNAse I, purified, and reverse transcribed with SuperScript First Strand Synthesis System (Invitrogen). PCR amplification was conducted using the following conditions: 94°C denatured for 3 min for one cycle, and 94°C for 1 min, 58°C for 1 min, 72°C for 1 min for 35 cycles. PCR products were confirmed on a 1.5% agarose gel and detected with ethidium bromide staining. Real-time PCR was performed using 2X SYBR Green PCR Master Mix (Applied Biosystems, Foster City, CA) on an ABI Prism 7900 sequence detector (Applied Biosystems). β-Actin cDNA was amplified as a control for RT-PCR (Promega, Madison, WI). Primers used for actin cDNA were: sense, 5’TCTAGAAGTGTCGCTGACATCGTGT-3’ and antisense, 5’CTTAGAAGCTTTGCGGCATCG-3’. Primers for Bid cDNA were: sense, 5’ACAGGGCACTGTGATTAGTAATGACT-3’ and antisense, 5’CTCGGTTCAGTGATGTAGTGCCTG-3’. Primers for caspase-8 were: sense, 5’-AAGGCACGACACACAAGGAAAGAAGG-3’ and antisense: 5’-TTCCAGCGGCTAGCATGCTAAG-3’.

Results

Defects of Fas-induced apoptosis in E2F-1−/− lymphocytes

To study the role of E2F-1 in the apoptosis of primary T cells, mouse spleen and lymph node cells were activated using anti-CD3ε mAbI45-2C11 (BD Pharmingen, San Diego, CA) for 2 days, then cultured with 40 U/ml recombinant mouse IL-2 (Endogen, Woburn, MA) for an additional 2-3 days.

Apoptosis assay

Activated lymphocytes were cultured until day 5, and live cells were purified using Lympholyte-M (Cedarlane Laboratories) gradient. Cells (1 × 10^6) were seeded in 2 ml of growth medium in 12-well plates with 1 μg/ml hamster anti-mouse Fas (Jo-2) Ab or hamster IgG as a control (both from BD Pharmingen) at 4°C for 30 min. To cross-link the Jo-2, medium was removed, and cells were washed twice with RPMI 1640, then resuspended in growth medium containing 1 μg/ml rabbit anti-hamster IgG (Sigma-Aldrich) and 10 U/ml IL-2 for 6 h. For IL-2 deprivation experiments, cells were harvested on day 4, and live cells were separated, washed, and then cultured in growth medium with or without 10 U/ml IL-2 for 36 h. Apoptosis was detected by annexin V staining.

Caspase activation assay

Caspase activity was examined using the CaspaTag caspase activity kit (BD Pharmingen). Activated lymphocytes were cultured with 40 U/ml IL-2 until the induction of apoptosis.

Reconstitution of E2F-1 restored Fas-stimulated apoptosis

To test whether the effects of E2F-1 deficiency were evident in alternative forms of T cell death, we subjected activated anti-CD3 blasts to IL-2 deprivation. The apoptosis of the entire lymphocyte population was ~35% in response to IL-2 deprivation, whereas the loss of viable CD8 T cells was ~60% (Fig. 1C). In contrast, CD4 T cells in the same culture were less subject to apoptosis in this assay. We therefore used CD8 T cells to assess effects on cell death due to IL-2 deprivation. Neither total lymphocyte apoptosis nor CD8 T cell apoptosis was different between wild-type (+/+) and E2F-1-deficient (−/−) lymphocytes (Fig. 1C), which indicates that E2F-1 does not play a role in this type of cell death.

Reconstitution of E2F-1 protein in Fas-induced apoptosis

To confirm the role of E2F-1 protein in Fas-induced apoptosis, E2F-1-deficient lymphocytes were transduced on day 2 with recombiant MSCV retrovirus expressing both GFP and E2F-1 or...
with GFP only as a control. Previous studies in multiple cell types showed that overexpression of E2F-1 can induce spontaneous apoptosis; thus, we first tested whether the overexpression of E2F-1 by retrovirus in lymphocytes could cause cell death. By comparing the percentage of GFP-positive cells 24 and 48 h postinfection as well as the apoptosis by annexin V staining, we observed that retrovirus-mediated overexpression of E2F-1 in normal lymphocytes did not adversely affect cell survival or induce spontaneous apoptosis (Fig. 2A). In addition, the introduction of exogenous E2F-1 into activated E2F-1−/− lymphocytes did not affect the apoptosis of CD8+ T cells induced by IL-2 withdrawal (Fig. 2B). In contrast, the reconstitution of E2F-1 in E2F-1-deficient lymphocytes restored the extent of CD4+ T cell death due to Jo-2 anti-Fas treatment to a level comparable to that in wild-type cells (Fig. 2C), suggesting that E2F-1 has a specific function in promoting the Fas signaling pathway in peripheral T lymphocytes.

**Defects of caspase activation in E2F-1−/− lymphocytes**

To clarify the difference in apoptosis between lymphocytes from E2F-1 wild-type and deficient mice, we examined the kinetics of apoptotic signaling during Fas killing by Western blot. We detected the disappearance of full-length caspase-8 protein 2 h after Jo-2 treatment (Fig. 3A); in addition, the full-length caspase-9 and Bid proteins disappeared, suggesting a mitochondrial component in the apoptotic process activated by Fas in primary T cells.

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**FIGURE 1.** Lack of E2F-1 inhibits death receptor-induced apoptosis, but not passive apoptosis. A, Deficiency of E2F-1 did not affect Fas expression on activated T lymphocytes. Lymphocytes were activated for 2 days, and culture was continued in the presence of 40 U/ml IL-2. On day 5, cells were stained with PE-conjugated anti-Fas Ab. B, Anti-CD3-activated lymphocytes from wild-type or E2F-1-deficient mice were treated with Jo-2 anti-Fas Ab for 30 min, which was cross-linked using an anti-hamster IgG for various time intervals. Apoptosis was evaluated by annexin V and 7AAD staining, and data were relative to Ab isotope control treatment to exclude the effect of natural death. Data are from four different mice for each group. C, Comparison of cell death induced by IL-2 deprivation between E2F-1 (+/+ ) wild-type and deficient (−/− ) lymphocytes. Activated lymphocytes were cultured until day 4, washed, and recultured with or without 10 U/ml IL-2 for 36 h. Data are representative of six independent experiments.

**FIGURE 2.** Enforced expression of E2F-1 in E2F-1-deficient T cell blasts restored Fas-induced cell death. A, Anti-CD3-activated, wild-type lymphocytes were infected on day 2 with an E2F-1-GFP-encoding MSCV construct or an MSCV control vector. GFP-positive cell survival was evaluated, and apoptosis was analyzed by annexin V staining. Data are from four individual mice tested in two separate experiments. B, The E2F-1 encoding vector had no effect on the loss of CD8+ T cells due to IL-2 deprivation. Data are from nine individual mice tested in five experiments. C, Reintroduction of E2F-1 in E2F-1-deficient T cells restored the susceptibility of CD4+ T cells to Fas-induced cell death. E2F-1-deficient and wild-type T cells were infected with retrovirus containing E2F-1-GFP or MSCV empty vector as a control, then treated with Jo2 Ab for 6 h to induce cell death. Data are from six individual mice in four retrovirus infection experiments.
whether such a disappearance was linked to the caspase activation, we stained cells using fluorogenic caspase substrates. Cells were treated with Jo-2 anti-Fas Ab plus cross-linker or with an isotype control plus cross-linker. The data are the excess caspase activity compared to that in wild-type T cells in caspase-3 activity as early as 30 min after Fas ligation, with similar effects on caspase-8 and caspase-9 (Fig. 3B). At the 1 h point, there were dramatic increases in all three caspase activities, whereas cells from E2F-1 wild-type mice showed significantly higher caspase activity than those from the E2F-1-deficient mice ($p < 0.01$ for all substrates).

It was recently shown that murine activated T cells may undergo Fas-induced apoptosis through the mitochondrial (i.e., type 2) pathway, in which Bid is cleaved (35). In this study, activation of protein kinase B inhibited the processing of both Bid and caspase-8. Although it is likely that T cells undergo apoptosis through both the type 1 and type 2 pathways, the cleavage of Bid and the prominent activation of caspase-9 in our experiments are consistent with a type 2 mechanism. We considered the possibility that the lack of E2F-1 might compromise the type 2 pathway.

To test for defects in the elements of this pathway, the endogenous protein levels of both caspase-8 and Bid from activated T cells were examined on day 5 (at the same time as Fas killing experiments) by Western blotting (Fig. 3C). The expression of caspase-8 and Bid protein in T cells from E2F-1-deficient mice was significantly decreased compared with that in cells from wild-type mice (the Western blot represents one of the three individual experiments giving similar results). This indicates that E2F-1 protein could affect the transmission of upstream signals from caspase-8 to mitochondria by controlling expression of both these proapoptotic molecules.

**E2F-1 up-regulates caspase-8 and Bid expression**

To determine whether E2F-1 affects the mitochondrial pathway by regulating the gene expression of molecules that function as a link between the death-inducing signal complex and mitochondria, activated lymphocytes from E2F-1-deficient mice were transduced with retrovirus expressing E2F-1 and GFP or with GFP alone as a control. In cell lines, caspase-8 mRNA can be up-regulated by overexpression of E2F-1 (37). In the present studies in primary T cells, the mRNA level detected by RT-PCR showed that both caspase-8 and Bid mRNA expression were strongly induced by the reconstitution of E2F-1 (Fig. 4A), and real-time quantitative RT-PCR showed an average 4-fold induction of Bid mRNA and an average 5-fold induction of caspase-8 mRNA (Fig. 4B). Also, the endogenous mRNA level of both caspase-8 and Bid in E2F-1-deficient cells decreased by ~80% compared with that in wild-type controls (Fig. 4C). Western blotting revealed that the levels of E2F-1, caspase-8, and Bid proteins were up-regulated by enforced E2F-1 expression in E2F-1-deficient lymphocytes to levels comparable to those in wild-type cells. In the example shown, densitometry suggested that caspase-8 protein was up-regulated on the average of 2-fold, and Bid protein was up-regulated 4-fold, in the cells transduced with MSCV vector expressing E2F-1. As caspase-8 is likely to be regulated by cleavage, we would not be surprised if the effect of E2F-1 expression on caspase-8 protein was less dramatic than the effect on message. Despite the caveats associated with the quantitation of Western blots, we found that the E2F-1-induced up-regulation of Bid protein was comparable to the up-regulation of Bid message. We conclude that E2F-1 promotes
The linearity of amplification was also confirmed by a serial dilution of target cDNA (shown on the left). B, Real-time quantitative RT-PCR for detection of mRNA level of caspase-8 and Bid of infected E2F-1-deficient T cells. Real-time PCR revealed that the mRNA level of caspase-8 was increased 5.3- and 5.8-fold in two independent experiments, whereas Bid mRNA increased 3.4- and 4.3-fold in E2F-1 retrovirus-infected cells compared with cells infected with empty vector. The levels of cDNA for caspase-8 and Bid were normalized to β-actin. C, The relative levels of endogenous caspase-8 and Bid mRNA in E2F-1 deficient T cells, detected by real time RT-PCR were 30% and 16% those in wild-type cells, respectively. D, Western blot for caspase-8 and Bid in cells infected with E2F-1 protein. The full-length Bid was reported to be able to induce apoptosis without cleavage when overexpressed in certain cell types (38). To exclude this as a complicating factor in our experiments, we studied the influence of overexpression of full-length Bid in activated lymphocytes. Fig. 5A shows that introduction of exogenous Bid into normal lymphocytes did not affect the survival of transfected cells expressing GFP (Fig. 5A, left) nor the frequency of cells undergoing apoptosis, as evaluated by annexin V staining (Fig. 5A, right). In contrast, overexpression of wild-type Bid in E2F-1−/− CD4+ T cells increased apoptosis due to Fas ligation (Fig. 5B), whereas the caspase-8-resistant D59A mutant of Bid had a much smaller effect. These experiments show that Bid acts in Fas-induced apoptosis in T cells, and that its cleavage at the caspase-8 site is important. Taking the data together, we concluded that E2F-1 potentiates death receptor-induced apoptosis of T lymphocytes by modulating the gene expression of two proapoptotic molecules: caspase-8, which is required for the transmission of extrinsic signal to the downstream apoptotic machinery, and Bid, which is specifically important in enabling the mitochondria pathway by passing on the upstream signal from activated caspase-8. In addition, the effect of Bid depends on its cleavage by caspase-8, rendering the effects on caspase-8 and Bid synergistic.

Discussion

E2F-1 plays a central role in controlling cell cycle progression as well as apoptosis. In this study we show that it also affects the susceptibility of primary T cells to Fas-induced apoptosis. Signals from the TCR cause cell cycle progression from G0 to G1 phase of the cycle, and then the autocrine growth factor IL-2 causes the phosphorylation, ubiquitination, and breakdown of the cdk inhibitor, p27-kip1. This allows cdk-2 to phosphorylate pRb, leading to the derepression of E2F-1 activity. In addition to its effects on DNA synthesis, we now show that the transcriptional activity of E2F-1 increases the levels of caspase-8 and Bid in normal murine lymphocytes. In the absence of Fas ligation, the net result is cell proliferation, but if Fas ligand is present, a signaling pathway is enabled, leading to caspase activation, Bid cleavage, and activation of the mitochondrial amplification loop involving the release of cytochrome c and the activation of downstream caspases, including caspase-9 and caspase-3 (Fig. 6).

The Fas death receptor kills some cells (type I cells) via activation of caspase-8 leading directly to the cleavage of caspase-3. In other cells (type II cells), much of the killing action of Fas is transmitted via Bid cleavage and the induction of cytochrome c release. This study reveals a novel mechanism by which E2F-1 controls Fas-induced apoptosis in cycling T cells. E2F-1 regulates the gene expression of many proapoptotic molecules in different cell lines, and E2F-1-induced apoptosis can occur through both p53-dependent and independent pathways. How these molecules
vector encoding Bid, a Bid mutant (D59A) that resists caspase-8 cleavage, activated E2F-1-deficient lymphocytes were infected with an MSCV vector encoding Bid, a Bid mutant (D59A) that resists caspase-8 cleavage, or MSCV empty vector. Fas-induced apoptosis of CD4<sup>+</sup> T cells was increased in Bid-transduced cells, but not in cells transduced with the caspase-8-resistant mutant. Thus, Bid is an important effector in the Fas pathway, and cleavage of Bid is important. Data were plotted from three independent experiments.

FIGURE 5. Enforced expression of Bid can partially complement E2F-1 deficiency. A, Activated lymphocytes were infected with retrovirus containing wild-type Bid or empty vector. Cells were removed 24 or 48 h postinfection and stained with annexin V for analysis of apoptosis. This shows that Bid expression had no effect on spontaneous death of T cells. Results are representative of three independent experiments. ■ E2F-1<sup>−/−</sup> T cells with empty MSCV vector; □, E2F-1<sup>−/−</sup> T cells with MSCV-Bid. B, Activated E2F-1-deficient lymphocytes were infected with an MSCV vector encoding Bid, a Bid mutant (D59A) that resists caspase-8 cleavage, or MSCV empty vector. Fas-induced apoptosis of CD4<sup>+</sup> T cells was increased in Bid-transduced cells, but not in cells transduced with the caspase-8-resistant mutant. Thus, Bid is an important effector in the Fas pathway, and cleavage of Bid is important. Data were plotted from three individual experiments.

FIGURE 6. The central role of E2F-1 in enabling the type II pathway of Fas-induced apoptosis. In parallel with integrating cell cycle progression signals, E2F-1 both increases Bid expression and makes available the caspase that cleaves and activates Bid. Thus, T cells about to enter S phase become more susceptible to Fas-induced apoptosis.

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References


