Bcl-xL and E1B-19K Proteins Inhibit p53-induced Irreversible Growth Arrest and Senescence by Preventing Reactive Oxygen Species-dependent p38 Activation*

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In this study, we describe novel functions of the anti-apoptotic Bcl-2 family proteins. Bcl-xL and E1B-19K were found to inhibit p53-induced irreversible growth arrest and senescence, but not to inhibit transient growth arrest, implying that Bcl-xL and E1B-19K are specifically involved in senescence without participating in growth arrest. We provide several lines of evidence showing that the functions of Bcl-xL and E1B-19K to prevent generation of reactive oxygen species (ROS) are important to inhibit senescence induction. First, we found that ROS are increased during p53-induced senescence. Moreover, Bcl-xL and E1B-19K inhibit this p53-induced ROS generation. Second, antioxidants prevent the induction of senescence and ROS by p53, but not the persistence of the senescence phenotype. Third, the anti-senescence functions of Bcl-xL and E1B-19K were suppressed by adding exogenous ROS. These results suggest that Bcl-xL and E1B-19K inhibit senescence induction by preventing ROS generation. Furthermore, p38 kinase was found to be activated during p53-induced senescence, but not in cells expressing Bcl-xL or E1B-19K, or in cells treated with antioxidants. Consistently, a chemical inhibitor of p38 kinase, SB203580, was found to inhibit p53-induced senescence, but only when treated before the cellular commitment to senescence, implying that p38 kinase is necessary for senescence induction. Therefore, Bcl-xL and E1B-19K inhibit p53-induced senescence by preventing ROS generation. These results also suggest that the oncogenic potential of Bcl-2 is due to its ability to inhibit senescence as well as apoptosis.

Bcl-2 was originally identified at the chromosomal break point of t(14;18)-bearing B-cell lymphoma (1–3). Bcl-2 has been shown to contribute to neoplastic cell expansion by preventing normal cell turnover caused by physiological cell death mechanisms (4, 5). The Bcl-2 family includes both death antagonists such as Bcl-2, Bcl-xL, and E1B-19K and death agonists such as Bax, Bak, Bid, and Bad (6). High levels of Bcl-2 expression are found in a wide variety of human cancers (7). Furthermore, the expression levels of Bcl-2 proteins correlate with relative resistance to a wide spectrum of chemotherapeutic drugs (8).

Although the precise biochemical function of Bcl-2 family proteins remains controversial, Bcl-2 and Bcl-xL exert at least some of their anti-apoptotic effect by regulating mitochondrial homeostasis, such as regulation of mitochondrial membrane potential and maintenance of mitochondrial-cytosolic coupling of oxidative phosphorylation (9, 10). There are also some indications that Bcl-2 and Bcl-xL may function as anti-oxidants and in this way exert anti-apoptotic activity. Bcl-2 knockout mice are hypopigmented due to a defect in melanin synthesis, which itself is redox-regulated (11). Moreover, enhanced oxidative stress and a higher susceptibility to pro-oxidants are evident in the brains of Bcl-2 knockout mice compared with control mice (12). Bcl-2 protects cells from hydrogen peroxide- or thiol depletion-induced death and suppresses lipid peroxidation (13–16). Therefore, it is likely that Bcl-2 maintains cells in a more reduced state by scavenging ROS either directly or by up-regulating other ROS scavengers such as thiol compounds. Alternatively, or in addition, Bcl-2 functions to prevent the generation of ROS induced by various environmental stresses (13, 16).

The proliferative lifespan of normal mammalian cells is limited by replicative senescence (17, 18), a process that appears to be primarily mediated by gradual shortening of telomeres (19). Senescent cells withdraw irreversibly from the cell cycle but remain viable indefinitely and display characteristic phenotypic markers, such as enlarged and flattened morphology, irreversible growth arrest, and expression of the senescence-associated (SA)-β-galactosidase activity at pH 6.0 (20). Recently, it has been shown that expression of ras and raf oncogenes can induce a rapid onset of replicative senescence in normal fibroblast cells associated with induction of p53, p21, p16, and hypophosphorylation of Rb protein (21, 22), implicating that replicative senescence, like apoptosis, is a programmed response of the organism to potentially oncogenic impact.

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Tumor cells are capable of extended proliferation as if the capability to become senescent has been somehow repressed or lost. Recently we and other groups have reported that certain tumor cells enter into senescence state by expression of tumor suppressor genes such as p53 (23, 24), Rb (25), p21 (26), and p16 (27). Although these studies suggest that tumor suppressor genes are essential for oncogene-induced senescence in normal HDF and their expression can induce senescence in human tumor cells, detailed mechanisms of senescence induction have not been understood. There is therefore a great deal of interest in identifying genes that are involved in tumor suppressor genes such as p53 (23, 24), Rb (25), p21 (26), and p16 (27). Although these studies suggest that tumor suppressor genes are essential for oncogene-induced senescence in normal HDF and their expression can induce senescence in human tumor cells, detailed mechanisms of senescence induction have not been understood. There is therefore a great deal of interest in identifying genes that are involved in tumor suppressor gene-induced senescence. In this study, we demonstrated that anti-apoptotic Bcl-2 family proteins inhibit p53-induced senescence and addressed the potential mechanisms involved.

EXPERIMENTAL PROCEDURES

Cell Culture and DNA Transfection—EJ human bladder carcinoma cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum (Invitrogen) and penicillin-streptomycin (50 units/ml). To establish EJ cells expressing Bcl-xL and E1B-19K, we transfected cells with pPuro-Bcl-xL and pPuro-E1B-19K and selected individual clones of stable transfectants (designated EJ-Bcl-xL and EJ-E1B-19K, respectively) for further analysis.

SA-β-Galactosidase Staining—Cells were washed in PBS and fixed with 0.25% glutaraldehyde in PBS/2 mM MgCl₂ for 20 min at room temperature. SA-β-galactosidase activity at pH 6.0 was detected as described previously (20).

Immunoblot Analysis—Cells were lysed in EBC lysis buffer (50 μM Tris-Hcl, pH 8, 120 μM NaCl, 0.5% Nonidet P-40, 100 μM sodium fluoride) 2 μM sodium vanadate, 2 μM phenylmethylsulfonyl fluoride, and 10 mg/ml aprotinin) (24). Protein quantification was performed using the protein assay kit (Bio-Rad, Hercules, CA). Approximately 40 μg of total cell protein per sample was subjected to SDS-PAGE and transferred to an Immobilon polyvinylidene difluoride filter (Millipore, Bedford, MA). The filter was then blocked in 5% nonfat dry milk/0.1% Tween/Tris-buffered saline followed by incubation with each antibody and immunodetection using the ECL system (Amersham Biosciences, Arlington Heights, IL). p53, p21, and actin proteins were detected by DO-1 (Santa Cruz Biotechnology, Santa Cruz, CA), WAF-1 (Oncogene Science, Cambridge, MA), C-11 (Santa Cruz Biotechnology), p-p38 (Cell Signaling Technology, Beverly, MA), p38 (sc-728, Santa Cruz Biotechnology), and p-ATF-2 (Cell Signaling Technology), respectively.

BrdUrd Incorporation Assay—EJ cells infected with a recombinant adenovirus encoding p53 (Ad-p53) or control virus (Ad-ΔE1) were seeded on coverslips at time 0. At 0, 2, 4, 6, 8, and 10 days, cells on each cover glass were labeled for 1 h with 10 μM BrdUrd (cell proliferation kit; Roche Molecular Biochemicals) and fixed with acetic acid/ethanol. BrdUrd-incorporated cells were counted after detection as described in the manufacturer’s instructions.

Measurement of ROS Levels—Cells were incubated with 10 μM dichlorodihydrofluorescein diacetate (Molecular Probes) for 30 min, then washed with PBS, trypsinized, and collected in 1 ml of PBS. Fluorescence-stained cells were transferred to polystyrene tubes with cellstrainer caps (Falcon) and subjected to fluorescence-activated cell sorter (FACS, BD Biosciences FACScan) using Cell Quest 3.2 (BD Biosciences) software for analysis.

RESULTS

Bcl-xL and E1B-19K Inhibit p53-induced Senescence—To examine whether Bcl-2 family proteins affect senescence, we employed EJ cells, in which p53 expression triggers a rapid onset of senescence (23, 24). We first established human bladder cancer cells, EJ expressing Bcl-xL and E1B-19K and named them EJ-Bcl-xL and EJ-E1B-19K, respectively (Fig. 1A). These cells were resistant to apoptotic stimuli, such as staurosporine and tumor necrosis factor α treatments (data not shown). To examine whether Bcl-2 family proteins affect p53-induced se-
Bcl-x<sub>L</sub> and E1B-19K Inhibit p53-induced Senescence

We previously reported that Bcl-x<sub>L</sub> and E1B-19K proteins inhibit entry to irreversible growth arrest by p53 (Fig. 1B). Consistent with SA-β-galactosidase activity, the morphological characteristics of senescent cells, large and flat morphology, were found in EJ cells infected with p53-adenovirus, but were rarely observed in EJ cells infected with the same virus but expressing Bcl-x<sub>L</sub> and E1B-19K (Fig. 1C). However, Bcl-x<sub>L</sub> and E1B-19K did not affect the expression of p53 and its target protein, p21 (Fig. 1D), indicating that Bcl-x<sub>L</sub> and E1B-19K do not inhibit p53-induced senescence by regulating the expression levels of p53 and p21.

**Bcl-x<sub>L</sub> and E1B-19K Proteins Inhibit Irreversible Growth Arrest by p53**—To examine whether Bcl-2 family proteins affect the growth inhibition caused by p53, a BrdUrd incorporation assay was performed (Fig. 2A). Regardless of Bcl-x<sub>L</sub> and E1B-19K, BrdUrd incorporation was significantly reduced 2–4 days after infection with p53-adenovirus (Fig. 2A), implying that Bcl-2 family proteins do not affect the cell cycle arrest induced by p53. Moreover, p53 expression peaked 2 days after virus infection and then decreased presumably because of the replication deficiency of the viral genome in the cell (Fig. 2B).

**Bcl-x<sub>L</sub> and E1B-19K Proteins Inhibit an Increase in ROS Levels by p53**—We next addressed the question of how Bcl-2 family proteins inhibit cellular senescence. ROS induction in response to various stimuli (14, 36). Based on these studies, we examined ROS generation during p53-induced senescence. The ROS levels were found to increase significantly and to reach a maximum 4 days after virus infection. In contrast, ROS levels in cells expressing Bcl-x<sub>L</sub> or E1B-19K did not change significantly after p53 expression, versus p53-expressing EJ cells (Fig. 3), implying that Bcl-x<sub>L</sub> and E1B-19K prevent ROS production by p53.

**Bcl-x<sub>L</sub> and E1B-19K Inhibit p53-dependent ROS induction**—Cells of EJ, EJ-Bcl-x<sub>L</sub>, and EJ-E1B-19K were infected with p53-adenovirus (p53) or a control adenovirus (ΔE1), cultured for indicated times, and 5 × 10<sup>5</sup> cells were subjected to FACS analysis after staining with dichlorodihydrofluorescein diacetate, a fluorescent probe. Rectangles and error bars represent the mean values and the standard deviations of five independent experiments, respectively.

Consistently, increases in the intracellular levels of ROS were prevented in part when either NAC or PDTC was treated, but these increases were completely inhibited when the two antioxidants were added in combination (Fig. 4B).

We next examined whether ROS is required to induce and to maintain senescence. The two anti-oxidants were added for 24 h at the indicated time points and then removed (Fig. 5). In combination, NAC and PDTC significantly prevented the appearance of SA-β-galactosidase activity only when they were treated 2 and 3 days after p53 virus infection (Fig. 5). These results suggest that ROS generation is necessary for the induction of senescence by p53 but not for the maintenance of the senescence phenotype. Therefore, the prevention of ROS induction by either these anti-oxidants or Bcl-2 family proteins is likely to inhibit the induction of senescence from the reversible growth arrest state. To support this notion, we next examined whether a pro-oxidant such as tert-butyl-H<sub>2</sub>O<sub>2</sub> (t-BTH) can induce senescence in cells expressing Bcl-x<sub>L</sub> or E1B-19K after the level of p53 proteins decreased (Fig. 2). These results suggest that Bcl-x<sub>L</sub> and E1B-19K proteins prevent the cellular commitment to the senescence.

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To examine whether ROS induction by p53 is critical for senescence and Bcl-x<sub>L</sub> and E1B-19K inhibit p53-induced senescence by preventing ROS generation, we examined the effects of anti-oxidants, N-acetyl-L-cysteine (NAC) and 1-pyrroldine dithiocarbamate (PDTC). Like Bcl-x<sub>L</sub> and E1B-19K, the anti-oxidants also blocked appearance of SA-β-galactosidase activity (Fig. 4A) and senescence-specific morphological changes (Fig. 4C). Furthermore, the two anti-oxidants, NAC and PDTC, showed a synergistic effect on senescence inhibition (Fig. 4A). Consistently, increases in the intracellular levels of ROS were prevented in part when either NAC or PDTC was treated, but these increases were completely inhibited when the two anti-oxidants were added in combination (Fig. 4B).

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override the anti-senescence effects of Bcl-xL and E1B-19K. To this end, we treated the cells with t-BTH for 48 h from 2 to 4 days post virus infection, because anti-oxidants were known to exert their anti-senescence effects during this period (Fig. 5). SA-β-galactosidase activity was found to be dramatically increased in both EJ-Bcl-xL and EJ-E1B-19K when t-BTH was added after p53 expression (Fig. 6). As a control experiment, we treated normally growing EJ cells with t-BTH but found no SA-β-galactosidase activity. These results suggest that the addition of pro-oxidant overcomes the anti-senescence functions of Bcl-xL and E1B-19K but that pro-oxidants cannot promote senescence in the absence of p53 expression.

ROS Induction Is Essential for Activation of p38 Kinase by p53—Recent studies reported that p38 kinase is essential for oncogene-induced senescence in human diploid fibroblasts (37). It has been also reported that ROS induction leads to activation of p38 kinase (38). Based on these studies, we examined whether p38 kinase is activated during p53-induced senescence. Fig. 7A shows that the phosphorylation of p38 is slightly increased at 2 days and most prominently increased at 4 days, and then is significantly reduced, although it remained detectable 6 days after p53 virus infection (Fig. 7A). However, p38 phosphorylation in cells expressing Bcl-xL or E1B-19K was significantly inhibited (Fig. 7A). To further examine whether phosphorylation of p38 kinase is dependent on ROS induction, we treated cells expressing p53 with anti-oxidants, NAC and PDTC. The anti-oxidants inhibited phosphorylation of p38 kinase (Fig. 7A) as they did induction of senescence phenotypes (Fig. 4). In parallel with p38 phosphorylation, ATF2, which is a phosphorylation target of p38 kinase, was found to be phosphorylated after p53 expression, but its phosphorylation was significantly inhibited in cells expressing Bcl-xL or E1B-19K or in cells treated with the anti-oxidants (Fig. 7A). Because the cells expressing Bcl-xL or E1B-19K became senescent upon adding t-BTH (Fig. 6), we examined whether p38 phosphorylation is recovered in these cells in parallel with their ability to become senescent. Cells were treated with t-BTH as shown in Fig. 6. Although the control virus-infected cells did not phosphorylate p38 kinase, p38 phosphorylation was recovered in cells expressing Bcl-xL or E1B-19K after treating with t-BTH (Fig. 7B).

We next examined whether activation of p38 kinase is re-
quired for p53-induced senescence. Like the anti-oxidants, a chemical inhibitor of p38 kinase, SB203850, inhibited the appearance of SA-β-galactosidase activity (Fig. 8A) and senescence-specific morphological changes. However, SB202474, an analogue that does not inhibit p38 kinase (39), had no effect on SA-β-galactosidase activity (Fig. 8A). Furthermore, SB203850 did not affect ROS levels (Fig. 8C), implying that p38 kinase is not upstream regulator of ROS. To identify the time points at which SB203580 inhibits p53-induced senescence, SB203580 was added for 24 h at indicated times (Fig. 8B). SB203580 significantly prevented the appearance of SA-β-galactosidase activity only when they were treated 2 or 3 days after p53 virus infection. These results suggest that ROS-dependent p38 activation is necessary for senescence induction rather than cell cycle arrest or the persistence of the senescence phenotype.

DISCUSSION

Since we reported that p53 could induce a rapid onset of senescence in human tumor cells lacking wild type p53 (23), we have focused on a mediator involved in p53-induced senescence. Because cells enter the senescent state after cell cycle arrest, there is a great deal of interest in identifying regulators that are specifically involved in senescence without participating in cell cycle arrest. Here, we reported that Bcl-xL and E1B-19K inhibit p53-induced irreversible growth arrest and senescence but not cell cycle arrest (Figs. 1 and 2). These results suggest that Bcl-xL and E1B-19K abrogate the cellular commitment to senescence and the transition from reversible to permanent growth arrest.

To elucidate molecular mechanisms by which Bcl-2 family
proteins regulate p53-induced senescence, we focused on the functions of p53 and Bcl-2 family proteins to regulate ROS generation (13, 16, 34, 35). The present study shows that ROS induction by p53 is essential for senescence induction (Fig. 4). Several lines of evidence suggest that ROS is involved in the cellular commitment to senescence induction. First, ROS levels reached a maximum 4 days after p53 virus infection (Fig. 3). Second, reversible growth arrest became irreversible within 4 days after p53 virus infection (Fig. 2). Third, anti-oxidants exerted their anti-senescence effects when they were treated 2–4 days after virus infection (Fig. 5). Although many previous studies have suggested that ROS is involved in the senescence of normal and immortal tumor cells (28–31) and in vivo aging (32, 33), we suggest that ROS is involved in the cellular commitment to senescence induction and in the transition from reversible growth arrest to permanent one.

Because Bcl-xL and E1B-19K appear to inhibit p53-induced senescence, it is likely that Bcl-xL and E1B-19K inhibit senescence induction by preventing p53-induced ROS generation. This is further supported by the finding that the anti-senescence functions of Bcl-xL and E1B-19K were overridden by exogenous ROS (Fig. 6). Because normally growing cells did not respond to exogenous ROS (Fig. 6), senescence induction requires not only ROS generation, but also other functions of p53. Because growth of the cells expressing Bcl-xL or E1B-19K was arrested by p53, the growth arrest state may be a prerequisite of the pro-senescence functions of ROS. This notion is further supported by previous reports that ROS can trigger senescence when the growth of normal diploid fibroblasts is arrested by cell-contact inhibition (40).

Recent studies have reported that p38 kinase is activated in responses to cellular and environmental stresses. Hyper-mitogenic signals by expression of oncogenic ras leads to induction of premature senescence through activation of negative cell cycle regulators such as p53, Rb, and p16 (22, 41). Wang et al. (37) reported that expression of oncogenic Ras results in activation of MEKK3/6-p38 pathway, which in turn leads to activation of negative regulators of the cell cycle, such as p53 and p16, eventually, premature senescence. Recently, it has been reported that p38 kinase directly phosphorylates N-terminal serine residues of p53, which in turn activate the p53 signaling pathway (42–44). Therefore, it has been suggested that p38 kinase links mitogenic signals to tumor suppressor genes. In support of the role of p38, it was reported that constitutive activation of p38 kinase also induces cell cycle arrest, which becomes permanent and irreversible in association with bio-

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**Fig. 8. The role of p38 in p53-induced senescence.** A, proportion of SA-β-galactosidase-positive cells after treatment with SB203580 (SB). EJ cells were infected with Ad-p53 and cultured with or without 20 μM of either SB203580 or SB202474 for 4 days. Results represent the mean values and the standard deviations of three independent experiments. B, time at which SB203580 affected p53-induced senescence. Cells were treated for 24 h at the indicated times after p53 virus infection, and SA-β-galactosidase-stained cells were counted 6 days after virus infection. C, ROS levels in cells treated with SB203580.
expressing Bcl-xL or E1B-19K or in cells treated with anti-arrest. We found that p38 kinase is activated during p53-induced senescence but that this activation is blocked in cells expressing Bcl-xL or E1B-19K or in cells treated with anti-oxidants (Fig. 7A), which implies that ROS, which are generated by p33, lead to p38 phosphorylation. Furthermore, the phosphorylation of p38 kinase was paralleled by the induction of ROS, and this peaked 4 days after p53 virus infection (Fig. 7A). Consistently, a chemical inhibitor of p38 kinase, SB203580, was found to inhibit p53-induced senescence, but not ROS generation (Fig. 8). Moreover, the times at which SB203580 exerted its anti-senescence function were found to coincide with those at which anti-oxidants function (Figs. 5 and 8D). Thus, p38 kinase activation is likely to be due to ROS induction and to be required for the induction of senescence rather than cell cycle arrest or the persistence of the senescence phenotype.

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