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Forum Review

Redox Control of Cell Death

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ABSTRACT

Cellular redox is controlled by the thioredoxin (Trx) and glutathione (GSH) systems that scavenge harmful intracellular reactive oxygen species (ROS). Oxidative stress also evokes many intracellular events including apoptosis. There are two major pathways through which apoptosis is induced; one involves death receptors and is exemplified by Fas-mediated caspase-8 activation, and another is the stress- or mitochondria-mediated caspase-9 activation pathway. Both pathways converge on caspase-3 activation, resulting in nuclear degradation and cellular morphological change. Oxidative stress induces cytochrome *c* release from mitochondria and activation of caspases, p53, and kinases, including apoptosis signal-regulating kinase 1 (ASK1), c-Jun N-terminal kinase, and p38 mitogen-activated protein kinase. Trx inhibits apoptosis signaling not only by scavenging intracellular ROS in cooperation with the GSH system, but also by inhibiting the activity of ASK1 and p38. Mitochondria-specific thioredoxin (Trx-2) and Trx peroxidases (peroxiredoxins) are suggested to regulate cytochrome *c* release from mitochondria, which is a critical early step in the apoptotis-signaling pathway. dATP/ATP and reducing factors including Trx determine the manifestation of cell death, apoptosis or necrosis, by regulating the activation process and the activity of redox-sensitive caspases. As mitochondria are the most redox-active organelle and indispensable for cells to initiate or inhibit the apoptosis process, the regulation of mitochondrial function is the central focus in the research field of apoptosis and redox. *Antioxid. Redox Signal.* 4, 405–414.

REDOX CONTROL BY THIOREDOXIN AND GLUTATHIONE SYSTEMS

OXYGEN is indispensable for many creatures on the earth. However, reactive oxygen species (ROS) are harmful to cells. ROS are generated while oxygen is reduced to H_2O in the respiratory chain in mitochondria, which is the main source of intracellular ROS. External stress, such as ultraviolet (UV), ionizing irradiation, and drugs, also generates ROS. Cells have antioxidant systems to protect themselves against dangerous ROS. Although ROS have been considered only to damage cells, accumulating evidence shows that oxidative stress, ROS-inducible stress, evokes many intracellular events, such as proliferation, gene activation, cell-cycle arrest, and apoptosis (47, 54). Hydrogen peroxide activates nuclear factor-κB, and many oxidants induce protein tyrosine phosphorylation in immune cells (57, 58, 71).

Cellular redox is controlled by the thioredoxin (Trx) and glutathione (GSH) systems (27, 28). Trx is a small (12 kDa) ubiquitous protein having the -Cys-Gly-Pro-Cys- sequence in its conserved active site, and operates as a protein disulfide/dithiol reducing system coupled with Trx reductase and NADPH. Trx was originally identified as a proton donor to ribonucleotide reductase in *E. coli.* We cloned human Trx as adult T-cell leukemia-derived factor (ADF), which induces interleukin (IL)-2 receptor α chain (CD25) (78, 90). Trx protects cells against a variety of oxidative stress (52, 69, 79, 91). Trx translocates from cytoplasm to nucleus upon stress, and activates the function of transcriptional factors by enhancing their binding activity to the target DNA (2, 25, 46,

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83). Trx is released from cells, and has chemotactic activity extracellularly (7, 56), although the precise mechanism of Trx release is still unclear. Furthermore, the plasma level of Trx is regarded as a stress marker, which correlates with the stage of stress-related disease, including liver cirrhosis and autoimmune disease, as well as surgical stress (1, 53, 55, 76). On the other hand, in the GSH reducing system, glutaredoxin, which has the -Cys-Pro-Tyr-Cys- sequence in its active site, also operates as a protein disulfide/dithiol reducing system coupled with GSH, GSH reductase, and NADPH (28). Recently, an increasing number of molecules with disulfide/dithiol in their active sites are proposed to be designated as members of the "Trx superfamily" (62, 84).

SIGNALING PATHWAY OF APOPTOSIS

Apoptosis is one of the characteristic death modes that is different from conventional necrosis. This phenomenon was first described by Kerr *et al.* in 1972 (33), but it is not until the late 1980s that its molecular mechanism was becoming clear. Yonehara *et al.* discovered a phenomenon that an IgM class antibody induced cell death (92). Nagata *et al.* cloned the corresponding antigen on the cell surface, which is now known as Fas and belongs to the tumor necrosis factor (TNF) receptor family (31). They also cloned its physiological ligand, Fas ligand (75). In 1993, Horvitz *et al.* discovered that a *C. elegans* cell death gene, ced-3, has remarkable sequence similarity to mammalian ICE (IL-1β converting enzyme), which is responsible for maturation of pro-IL-1 (93). As these proteases have unique characteristics, they are now called caspases, proteases that have a cysteine residue (C) in the active site and cleave target molecules C-terminal to aspartate (Asp) residues (3, 81, 88). As caspase-1 (ICE) knockout mice did show deficiency in processing of pro-IL-1 and pro-IL-18 but little defects in apoptosis, this protease is now believed to function in immune regulation rather than in apoptosis signaling (36, 41). Once caspase is activated, an active caspase cleaves another procaspase to make active tetramers. The activation of caspases (especially caspase-3, 7, 8, and 9) is a very critical step for cells to execute apoptosis. Activated caspases cleave many nuclear and cytoskeletal structural proteins, such as lamins, NuMa, actin, fodrin, and gelsolin.

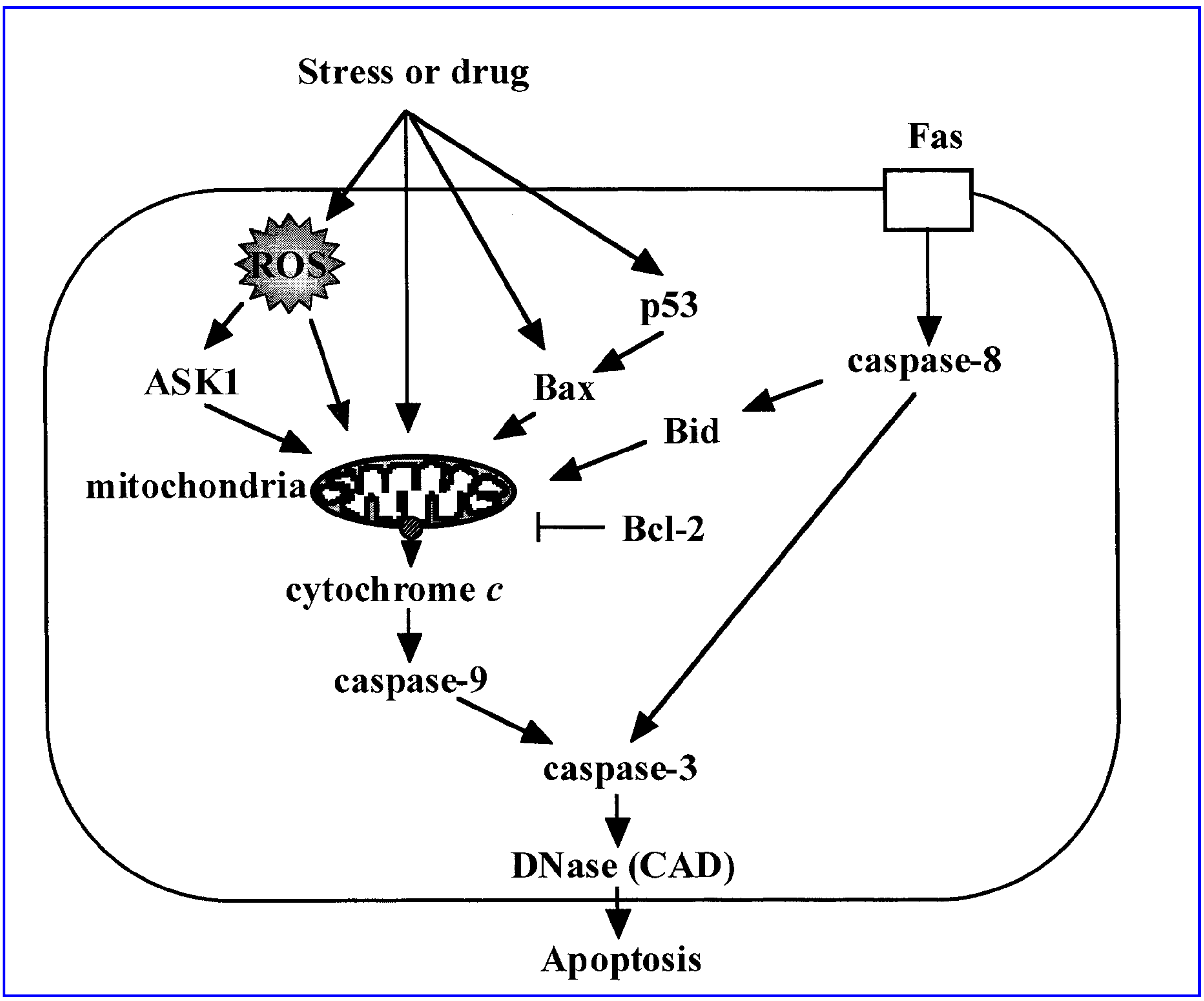

FIG. 1. Two pathways to induce caspase activation and apoptosis.

In the middle of the 1990s, it was considered that the main apoptosis pathway is a Fas-mediated one and stress-induced cell death is a bypass or an extraordinary pathway. When Fas ligand or anti-Fas antibody binds to cell-surface Fas, some adaptor molecules are recruited to this death receptor and activate caspase-8, which in turn activates caspase-3 (50). Hampton and Orrenius and we independently reported that oxidative stress also induces caspase-3 activation (19, 82). Caspase-3 is an especially important enzyme for executing apoptosis. Afterward, Nagata *et al.* discovered caspase-activated DNase (CAD) and its intrinsic inhibitor (ICAD), which binds CAD (15, 68). Caspase-3 cleaves ICAD and inactivates its inhibitory effect, leading to CAD-mediated DNA fragmentation and characteristic changes of nuclei.

It was reported in 1993 that antiapoptotic protein Bcl-2 is localized mainly in the mitochondrial outer membrane (51, 61). Kroemer *et al.* reported that mitochondria lose the transmembrane potential during apoptosis (94). Newmeyer *et al.* reported in 1994 that the mitochondria-enriched fraction enables the apoptotic changes of the nuclei in a cell free system (60). In late 1996, Wan *et al.* reported that cytochrome *c* is released from mitochondria, which was a surprising phenomenon (44), and mitochondria have been the focus of apoptosis research since.

Usually, mitochondria form the main ATP-generating system. However, once the apoptosis signal is turned on, cytochrome *c* is released and cells cannot refrain from activating caspases and apoptosis (66). Released cytochrome *c* makes a complex with Apaf-1/procaspase-9 (called "apoptosome"), which induces activation of caspase-9, followed by caspase-3 activation (42, 96). Thus, there are two pathways to induce caspase activation and apoptosis signal (Fig. 1). One is the death receptor-mediated pathway, in which caspase-8 and caspase-3 are activated sequentially. Another is stress-induced mitochondrial cytochrome *c* release, in which sequential activation of caspase-9 and caspase-3 occurs. Later, caspase-8 was reported to cleave Bid, one of the proapoptotic Bcl-2 family members, which is followed by cytochrome *c* release (40, 45). Kroemer *et al.* have reported that disruption of mitochondrial transmembrane potential ($\Delta\psi_m$) is also associated with apoptosis signaling (35, 94), and that apoptosis-inducing factor (AIF), another caspase-activating protein localized to the intermembrane space of unstimulated mitochondria, is released from mitochondria during apoptosis (35, 77). AIF, but not cytochrome *c*, also activates DNase directly without caspase activation (77). Now it is considered that mitochondria and cytochrome *c*, as well as caspases, play a crucial role in the process of apoptosis (16, 17).

REDOX CONTROL OF CASPASE AND APOPTOSIS/NECROSIS

We have been interested in oxidative stress-induced cellular events including apoptosis and have examined the mechanism of how Trx regulates cell death. In 1991, we reported that recombinant Trx inhibits Fas- or TNF-induced apoptosis in a monocyte cell line, U937 (48). We found the phenomenon that a thioloxidant, diamide, induces cell death in a T cell line, Jurkat cells. About 200 μ*M* diamide induced apoptosis, whereas at a concentration of >400 μ*M* diamide induced necrosis. Some intracellular redox state was suggested to regulate the morphologic changes, apoptosis or necrosis (70).

Next, we focused on caspases. Because each caspase has a cysteine residue in its active site and the activity of caspase-1 is lost when the active-site cysteine is replaced by other amino acids (86), it is possible that the activity of caspase is regulated by the redox state. We found that the enzymatic activity of caspase is regulated by the redox condition of the cysteine residue, and the protease is active in a reducing environment (82). Furthermore, we investigated the diamide-induced cell-death mechanism. Caspase-3 was activated when cells were cultured with 200 μ*M* diamide, which induced apoptosis, whereas no caspase-3 activation was detected with 500 μ*M* diamide, which induced necrosis (82). Hampton and Orrenius also reported that 50 μ*M* hydrogen peroxide induces apoptosis with caspase activation, and a higher concentration of hydrogen peroxide causes necrosis without caspase activity (19).

As ROS directly inhibits caspase activity *in vitro* (82), ROS cannot activate caspase directly. When apoptosis was induced in cells by exposure to 200 μ*M* diamide, cytochrome *c* was released, the intracellular Trx levels were maintained, and the intracellular generation of ROS was marginal (82). This result indicates that generated ROS may be buffered by intracellular reducing factors including Trx and GSH, although the intracellular GSH levels transiently decrease during diamide-induced apoptosis (70, 82). In contrast, when cells were exposed to 500 μ*M* diamide, intracellular ROS generation increased and processing of caspase-3 was not detected despite cytochrome *c* release, resulting in necrosis (82). Thus, cytochrome *c* is released into the cytosol after cells are exposed to oxidative stress regardless of whether it induces apoptosis or necrosis (Fig. 2).

The processing of caspase-3 is suppressed under the thiol-oxidized state (64). As caspase-9 activity was not detected during diamide-induced necrosis (S. Ueda *et al.,* unpublished observation), it is possible that excessively generated intracellular ROS also decrease caspase-9 activity after the step of procaspase-9 processing or interfere with the forming of the apoptosome complex. Disruption of caspase activity induced by oxidative stress seems to shift apoptosis to necrosis (26). It depends on the intracellular redox state and redox-sensitive caspase activity to regulate the morphological changes of cell death (Fig. 2). Other researchers reported that cellular ATP is required for induction of apoptosis, and its depletion results in necrosis (14, 38). Wang *et al.* reported that dATP or ATP is required to change the conformation of apoptosomes, leading to the activation of procaspase-9 (42, 44). Their results are consistent with ours, because mitochondria provide a proton to the Trx and GSH reducing systems during ATP synthesis. Thus, possibly after the step of caspase-9 activation together with dATP or ATP, reducing factors are required for the activation process and the activity of caspases (Fig. 2).

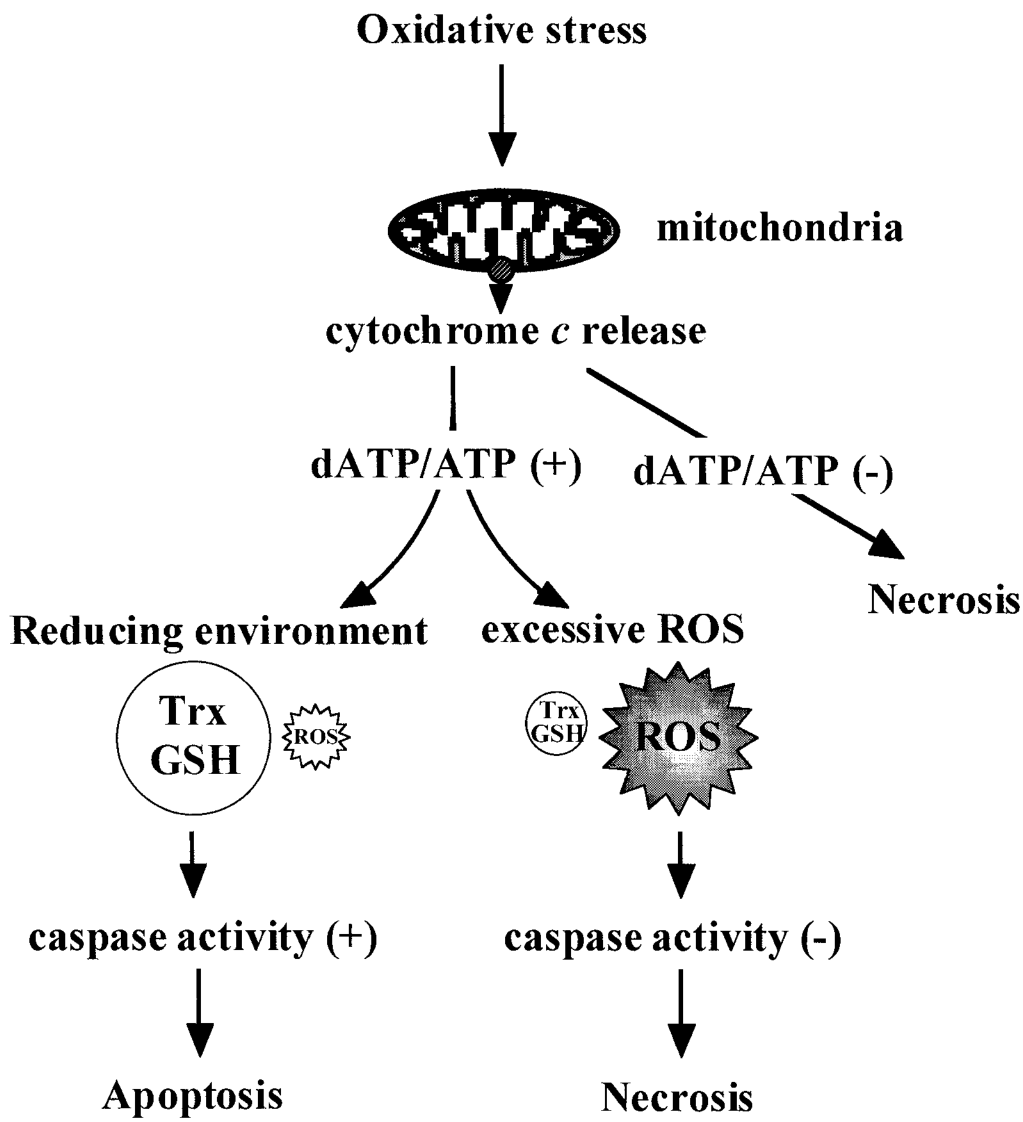

FIG. 2. Redox control of caspase activity and morphology; apoptosis or necrosis.

REDOX CONTROL IN MITOCHONDRIA, CELL DEATH-REGULATING ORGANELLE

There are many molecules in mitochondria that regulate the apoptosis pathway—Bcl-2 proapoptotic and antiapoptotic family members, cytochrome *c*, AIF, procaspase-2, 3, and 9, and antioxidant systems, such as manganese-superoxide dismutase, and the mitochondrial GSH- or Trx-dependent peroxidase system. A variety of signals converge on mitochondria to initiate or inhibit the apoptosis process.

Although releasing cytochrome *c* into the cytosol is a critical step in apoptosis signaling, the mechanism remains to be elucidated. One probable model is the formation of a mitochondrial megachannel called the permeability transition pore complex, which consists of voltage-dependent anion channel (VDAC), adenine nucleotide translocator (ANT), and cyclophilin D (85). ANT, one of the components of the permeability transition pore, is regulated by redox (12). Diamide-induced intermolecular crosslinking of ANT mediates membrane permeabilization. However, it is unlikely that cytochrome *c* (14.5 kDa) is released through ANT, because ANT is localized in the inner membrane and it can cause release of only molecules smaller than 1,500 Da (85). ANT may modulate cytochrome *c* release by affecting the function of the true target.

VDAC is localized in the outer membrane of mitochondria and regarded as the most probable candidate that regulates cytochrome *c* release. Tsujimoto *et al.* showed that proapoptotic Bax or Bak allowed cytochrome *c* to pass through VDAC reconstituted in liposomes, and that this passage was prevented by antiapoptotic Bcl-x_L through binding to VDAC directly (73).

It was reported that Trx peroxidases (peroxiredoxins; Prxs) inhibit oxidative stress-induced cytochrome *c* release and apoptosis by scavenging intracellular hydrogen peroxide (34, 95). Prxs reduce hydrogen peroxide coupled with Trx (59), and protect against cytochrome *c* release and apoptosis differently from Bcl-2 (95; Fig. 3).

We have reported that a thioloxidant can induce cytochrome *c* release from mitochondria and apoptosis, and that modulation of the intracellular thiol content influences the oxidative stress-induced apoptosis (70, 82). These data suggest that there may be a redox-sensitive molecule that is responsible for cytochrome *c* release and induction of apoptosis, and that intracellular reducing molecules are involved in the interaction with the target molecule in mitochondria to protect cells against oxidative stress. Recently, mitochondria-specific thioredoxin (Trx-2) was cloned (74). Trx-2 has a mitochondrial translocation signal at the N-terminus and conserved active disulfide/dithiol like other Trx family members. Trx-2 is more resistant to oxidative stress and scavenges ROS generated in mitochondria, which is a major physiological source of ROS during respiration. As we thought Trx-2 could modulate the apoptosis-inducing signal via mitochondria, we have generated a conditional Trx-2-deficient chicken B cell line, DT40 (80). Inhibition of the Trx-2 gene causes accumulation of intracellular ROS levels and induces cytochrome *c* release into the cytosol, followed by caspase-9 and caspase-3 activation. This result suggests that cytochrome *c* release is regulated by Trx-2 (Fig. 3).

It needs to be clarified whether the function of VDAC is modulated by redox directly or indirectly via redox-sensitive ANT. It is possible that diamide inactivates the reducing function of Trx-2 in mitochondria and induces cytochrome *c* release by modulating the function of VDAC or mitochondrial megachannel (80, 82). As AIF is a flavoprotein that shares sequence homology with bacterial oxidoreductases (77), we think redox possibly regulates the activity of AIF and also cytochrome *c* release via interaction between VDAC and ANT. Furthermore, the apoptosis-inducing function of cytochrome *c* itself may be regulated by redox, because it is a member of the mitochondrial electron transport system (20).

OXIDATIVE STRESS-INDUCED ACTIVATION AND REDOX CONTROL OF ASK1, JNK, AND P38 MAP KINASE

Oxidative stress induces activation of c-Jun N-terminal kinase (JNK; also referred to as stress-activated protein kinase or SAPK) and p38 mitogen-activated protein (MAP) kinase (30). Apoptosis signal-regulating kinase 1 (ASK1) was identified by Ichijo *et al.* as one of the MAP kinase kinase kinases that activates JNK and p38 MAP kinase and induces stress-mediated apoptosis signal (30). ASK1 is activated in cells treated with TNFα or *cis*-diamminedichloroplatinum (CDDP), and kinase-inactive ASK1 mutant inhibits TNFα- or CDDP-induced apoptosis, indicating that ASK1 is involved in the mechanism of stress- or cytokine-induced apoptosis (11, 30). Constitutively active mutant of ASK1 induces cytochrome *c* release and activation of caspase-9 and caspase-3, but not cas-

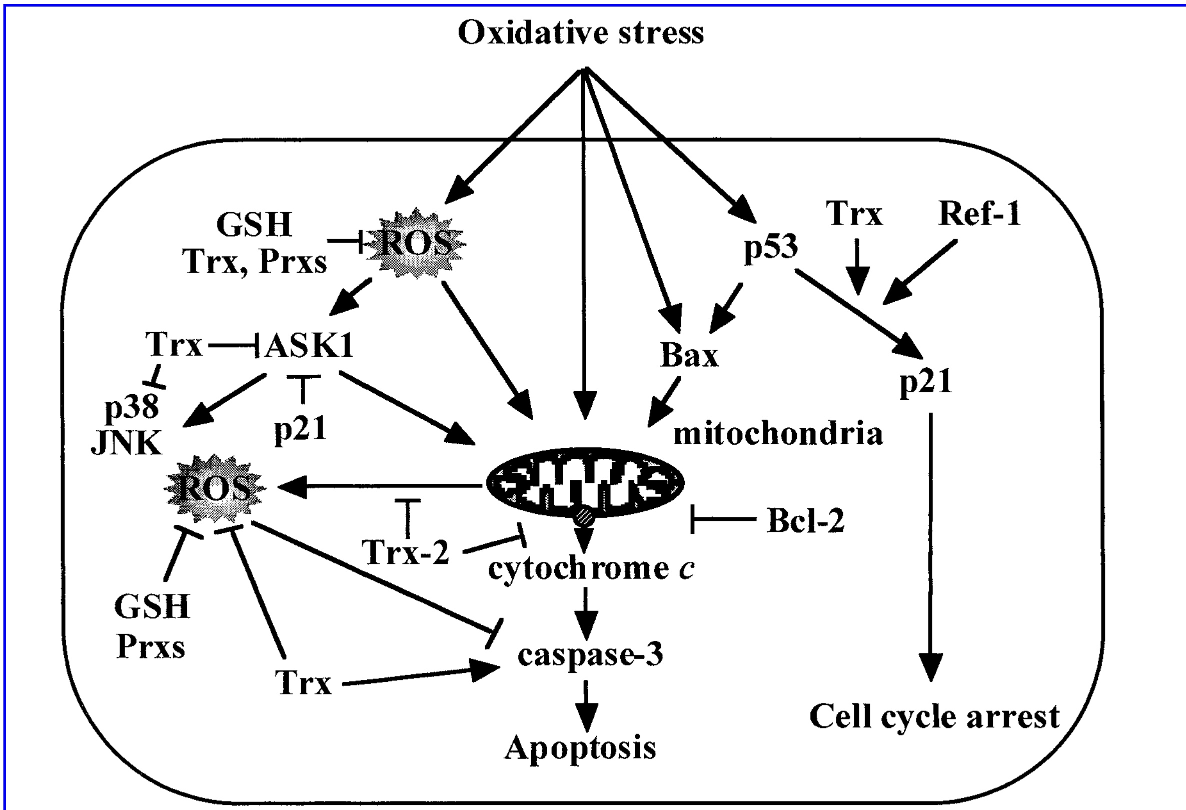

FIG. 3. Oxidative stress-induced signaling pathway and redox control.

pase-8, indicating that ASK1 executes apoptosis mainly by mitochondria-dependent caspase activation (24).

ASK1 directly binds to Trx and TNF receptor-associated factor 2 (TRAF2) (63, 67). Trx was identified as a negative regulator of ASK1 (67). Upon treatment of cells with TNF or ROS such as hydrogen peroxide, Trx is oxidized and dissociated from ASK1, resulting in activation of ASK1. Although ASK1 associates with TRAF2 transiently after the TNF treatment by which TNF activates both ASK1/JNK and ASK1/p38 axes, hydrogen peroxide cannot induce TRAF2–ASK1 interaction, suggesting that recruitment of ASK1 to TRAF2 is specific for TNF-mediated activation of ASK1 (29). However, overexpression of Trx also inhibits TRAF2–ASK1 interaction, suggesting that TNF-induced ASK1 activation requires ROS (43). As ASK1 also associates with Daxx, which is one of the adaptor molecules of the Fas system (10), it is possible that Trx regulates the downstream events of Fas-induced apoptosis by modulating the ASK1 signal. Trx also negatively regulates TNF-induced p38 activation (23). The cytoprotective effect of Trx can be partly explained by the regulation of the activity of ASK1 or p38 (Fig. 3).

Although many JNK/p38-activating stimuli are proapoptotic, the outcome of JNK or p38 activation strongly depends on the cell type and the cellular context (29, 39). Wisdom *et al.* reported that c-Jun-deficient fibroblasts are more sensitive to UV-induced apoptosis, suggesting that c-Jun acts as an antiapoptotic factor (87). Further study is necessary to clarify whether the JNK/p38 kinase pathway in addition to ASK1 is indispensable for stress-induced apoptosis signaling.

OXIDATIVE STRESS-INDUCED ACTIVATION AND REDOX CONTROL OF P53

Oxidative stress including UV or ionizing irradiation induces p53 activation, followed by cell-cycle arrest, presumably to allow an opportunity for DNA repair to occur before replication or mitosis (4, 22). One of the targets of p53 is $p21^{Cip1/WAF1}$, a G1 cyclin-dependent kinase inhibitor, through which p53 arrests the cell cycle (21). p53 protein is called "the guardian of the genome" because of its role in preventing the genomic alterations (37). Accumulation of p53 occurs without *de novo* transcription and protein synthesis (8, 65). Under normal cell growth conditions, p53 protein has a relatively short half life. MDM2 is regarded as a major intracellular regulator of p53 protein via the ubiquitin/proteasome system. Activation of p53 binding to target DNA is also regulated without increased protein levels of p53. Phosphorylation of p53 by ATM, the ataxia-teleangiectasia gene product, or DNA-dependent protein kinase is important for sequence-specific DNA binding of p53 in response to DNA damage (6, 9, 89). p53 has cysteine residues in the DNA-binding domain, and reducing factors, including redox factor-1 (Ref-1) and Trx, also enhance the DNA-binding activity (18, 32, 83). Ref-1 was originally identified as a DNA-repairing enzyme exhibiting apurinic/apyrimidinic endonuclease activity (13, 72). We showed that p53-dependent p21 transcriptional activity, as well as p21 protein expression, is augmented by the Trx/Ref-1 cascade and that CDDP induces translocation of Trx to the nucleus and activation of p53/p21, suggesting that Trx is involved in the p53-dependent repair mechanism (83; Fig. 3).

p53 also induces apoptosis to eliminate defective cells (*e.g.*, after UV or ionizing irradiation). p53 induces activation of Bax, which is a proapoptotic Bcl-2 family member, resulting in cytochrome *c* release, caspase activation, and apoptosis (49; Fig. 3). Interestingly, p21-deficient cancer cells increase susceptibility to p53-dependent apoptosis. Furthermore, p21 inhibits the activation of ASK1 and induction of apoptosis, suggesting that p21 switches p53-dependent signaling from apoptosis to cell cycle arrest (5). Whereas Trx can inhibit ASK1 activation only under reducing conditions, cytoplasmic p21 can inhibit ASK1 activation even in the presence of hydrogen peroxide (Fig. 3). p53 engages multiple signaling pathways, and has multiple functions by interacting with many molecules.

CONCLUDING REMARKS

A variety of cellular functions, including apoptosis signaling, are regulated by redox. Antioxidant systems usually protect cell death by scavenging ROS. ROS induce apoptosis as long as cells can maintain the intracellular reducing environment. Intracellular Trx is required to activate redox-sensitive caspases. When cells are exposed to too much stress, the capacity of the antioxidant system to scavenge generated intracellular ROS is exceeded, cells cannot maintain their intracellular reducing environment and caspase activity anymore, and they undergo necrosis (Fig. 2). Prxs or mitochondria-specific Trx-2 is suggested to modulate cytochrome *c* release from mitochondria during apoptosis. Some kinds of stress also induce cell-cycle arrest by activating the p53/p21 system that requires Trx and the intranuclear reducing environment to maintain its transcriptional activity (Fig. 3).

Now, an amazing number of articles continue to be published in the field of apoptosis and mitochondria. As mitochondria are indispensable for cells and are apparently the most redox-active organelle, it is exciting to dissect how redox or Trx-2 regulates cytochrome *c* release and the electron transport system in mitochondria that decide the fate of cells.

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ABBREVIATIONS

ADF, adult T-cell leukemia-derived factor; AIF, apoptosis-inducing factor; ANT, adenine nucleotide translocator; ASK1, apoptosis signal-regulating kinase 1; CAD, caspase-activated DNase; CDDP, *cis*-diamminedichloroplatinum; GSH, glutathione; ICAD, inhibitor of caspase-activated DNase; ICE, interleukin-1β converting enzyme; JNK, c-Jun N-terminal kinase; MAP, mitogen-activated protein; Prx, peroxiredoxin (thioredoxin peroxidase); Ref-1, redox factor-1; ROS, reactive oxygen species; TNF, tumor necrosis factor; TRAF2, tumor necrosis factor receptor-associated factor 2; Trx, thioredoxin; Trx-2, mitochondria-specific thioredoxin; UV, ultraviolet; VDAC, voltage-dependent anion channel.

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