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Bcl-2 Family Members Regulate Anoxia-Induced Cell Death

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ABSTRACT

The mechanisms underlying anoxia (0–0.5% oxygen)-induced cell death are not fully understood. Here we discuss the mechanisms by which cells undergo apoptosis in the absence of oxygen. Cell death during anoxia occurs *via* the intrinsic pathway of apoptosis. Key regulators of apoptosis during anoxia are the Bcl-2 family of proteins. The pathway is initiated by the loss of function of the prosurvival Bcl-2 family members Mcl-1 and Bcl-2/Bcl-X_L, resulting in Bax- or Bak-dependent release of cytochrome *c* and subsequent caspase-9–dependent cell death. *Antioxid. Redox Signal.* 9, 1405–1409.

INTRODUCTION

OXYGEN IS REQUIRED FOR SURVIVAL because it has a major role in energy production through the process of oxidative phosphorylation. Consequently, severe oxygen deprivation (anoxia; 0–0.5% oxygen), like that encountered in various pathologic conditions, including ischemic heart disease, stroke, renal dysfunctions, and cancer, is deleterious to cell survival (1, 10). Cells exposed to anoxia display morphologic characteristics of apoptosis, a process characterized by DNA fragmentation membrane blebbing, chromatin condensation breakdown of the cellular membrane, and exposure of phosphatidyl serines. The resulting apoptotic bodies are engulfed by macrophages and neighboring cells. Two apoptotic pathways have been identified, the extrinsic and intrinsic death pathways (7, 24). The extrinsic death pathway is triggered by ligands such as Fas or TNF binding to a death receptor on a cell surface. This leads to the formation of the death-inducing disc complex followed by the activation of a family of cysteine proteases termed caspases, which results in apoptosis by cleavage of various substrates. The intrinsic death pathway (or mitochondrial pathway) can be triggered by several stimuli, including DNA damage, growth-factor withdrawal, and oncogene activation (6). This pathway is controlled by the Bcl-2 family of proteins (discussed in more detail later) and results in the permeabilization of the mitochondrial outer membrane and redistribution of cytochrome *c*, Smac/DIABLO, and apoptosis-inducing factor (AIF) from the mitochondria into the cytosol. These apoptogenic proteins can then lead to the downstream activation of caspases. This review provides an update of events leading to apoptosis in anoxic conditions and highlights the Bcl-2 family of proteins (4, 16, 23).

Bcl-2 FAMILY MEMBERS REGULATE INTRINSIC PATHWAY OF APOPTOSIS

The Bcl-2 family of proteins are key regulators of the intrinsic pathway of apoptosis and are divided into three groups based on their conserved Bcl-2 homology (BH) domains (8). They are divided into either the prosurvival members, which include Bcl-2, Bcl-Xl, Bcl-w, Mcl-1, and A1, which contain BH1-4 domains, or the proapoptotic members. The proapoptotic members are further divided into two groups: those that contain only one BH3 domain (BH3-only proteins) and others containing multiple BH3 domains. The BH3-only proteins include Bad, Bid, Bik, Bmf, Bim, Hrk, Noxa, and Puma, and act as sensors of apoptosis, whereas the multi-BH3 domains (Bak, Bax, and Box) act as executioner of apoptosis. Bax and Bak are critical in initiating the mitochondrial outer membrane permeability (MOMP), although the exact mechanism of this process remains to be elucidated. Activation of MOMP leads to cytochrome *c* release, which can then interact with the apop-

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totic protease activating factor (Apaf-1) to form a macromolecular complex, the apoptosome, in an ATP-dependent reaction. The apoptosome subsequently recruits and activates procaspase 9, the *bona fide* initiator caspase of the intrinsic pathway. The activated caspase 9 then cleaves effector caspases 3 and 7, thus initiating the death cascade.

Currently several models propose the mechanism by which Bax and Bak are activated to induce MOMP. One model states that Bax and Bak proapoptotic activity is kept in check by the prosurvival proteins at all times until an apoptotic signal causes activation of other proapoptotic proteins, which can then negate the role of the prosurvival proteins (5). This allows the release of Bax and Bak from the prosurvival proteins to activate MOMP. Alternatively, another mechanism states that only certain BH3-only proteins can activate Bax and Bak (12, 13). These BH3-only proteins, such as Bim, tBid, and Puma, act as direct "activators" of Bax and Bak, and can function in this manner only when "sensitizer" proteins, such as Bad and Noxa, neutralize the function of the prosurvival proteins. In this model, the action of the sensitizer proteins is critical to free the activator proteins.

ANOXIA INDUCES APOPTOSIS THROUGH THE INTRINSIC PATHWAY

Evidence indicating that anoxia induces the mitochondrial pathway of apoptosis started to emerge with studies demonstrating that antiapoptotic Bcl-2 protein could protect cells from dying when exposed to oxygen deprivation (23). Additionally, cells lacking the Bcl-2 members Bax and Bak also do not undergo cell death when exposed to anoxic conditions for several days (16). Under normal oxygen conditions, Bak resides on the mitochondrial membrane, whereas Bax mostly localizes in the cytosol and gets recruited to the mitochondrial membrane upon a death signal. Bax translocation from the cytosol to the mitochondrial outer membrane has been observed during anoxia-induced cell death (19). The release of cytochrome *c* and activation of caspase 9 are also observed in wild-type cells undergoing anoxic cell death, whereas mouse embryonic fibroblasts deficient for caspase 9 and Apaf-1 are resistant to death when exposed to anoxia, thus further confirming the requirement of the intrinsic pathway (14). Apoptosis during anoxia primarily occurs through the intrinsic pathway and not the extrinsic pathway of apoptosis, because Bid-null fibroblasts can still undergo cell death when exposed to anoxic conditions (4). Bid is the BH3-only protein that links the extrinsic pathway to the intrinsic pathway.

LOSS OF ANTIAPOPTOTIC PROTEINS FUNCTION IS REQUIRED FOR ANOXIA-INDUCED CELL DEATH

BH3-only proteins are upstream regulators of Bax and Bak and are counteracted by the antiapoptotic proteins. A key step in initiating the intrinsic death pathway is to negate the prosurvival function of antiapoptotic proteins Mcl-1 and Bcl-2/Bcl-X_L to initiate Bax- or Bak-dependent release of cytochrome *c*. In most cells, the negation of either Mcl-1 or Bcl-2/Bcl-X_L is not sufficient to induce cell death (15, 25). Anoxia induces the degradation of the Mcl-1 protein but not Bcl-2/Bcl-X_L (4). The decrease in Mcl-1 protein levels observed under anoxia is mediated *via* the proteasomal pathway and occurs in cells devoid of both Bax and Bak, confirming the loss of this prosurvival factor as an early event upstream of Bax and Bak activation. Despite the decrease in protein levels, the mRNA levels of Mcl-1 do not decrease under anoxic conditions, but rather increase (4). The increase in mRNA levels under anoxia is not surprising, because the Mcl-1 protein was previously demonstrated to have a hypoxia-inducible factor 1 (HIF-1) response element (HRE) site within its promoter region (18). Interestingly, the decrease in Mcl-1 protein levels does not occur under mild oxygen deprivation (hypoxia; 1–3% oxygen), which also does not induce cell death.

Mcl-1 protein degradation has previously been demonstrated to be involved in apoptotic cell death, resulting from DNA damage, adenoviral infection, and growth-factor withdrawal (15, 25). The degradation of Mcl-1 is dependent on five critical lysine residues at positions 5, 40, 136, 194, and 197 that undergo polyubiquitination by the E3 ligase identified as Mule/ARF-BP1 (26). Under DNA damage, the BH3-only protein Noxa binds to Mcl-1 and promotes the degradation of Mcl-1 protein *via* the proteasomal pathway. However, anoxia induced degradation of the Mcl-1 protein in cells deficient of Noxa (4). The dispensability of Noxa during anoxic cell death suggests that other possible binding partners of Mcl-1 mediate its degradation, or an alternate mechanism distinct from that of UV-induced Mcl-1 protein degradation. Besides Noxa binding, Mcl-1 protein can also be targeted for proteasomal degradation by phosphorylation (15). One example is GSK-3 phosphorylation of Mcl-1 at serine 159 (15). This form of Mcl-1 regulation has been shown to be important under conditions of growth-factor withdrawal, in which the decrease in Mcl-1 protein levels is a requirement for cytochrome *c* release, and, consequently, cell death. Whether phosphorylation of Mcl-1 plays a role in its degradation under anoxia is still unknown.

A second class of antiapoptotic proteins that would have to be inhibited under anoxia to execute the intrinsic death pathway is the prosurvival function of Bcl-2/Bcl-X_L. The BH3-only protein Bad has been shown to negate the prosurvival function of Bcl-X_L, Bcl-2, and Bcl-w (12, 13). However, Bad-null cells still undergo anoxia-induced cell death (4). Additionally, the individual loss of Puma, Bid, Bim, a class of BH3-only proteins that can inhibit all antiapoptotic proteins, does not protect against cell death under anoxia. Thus, the individual loss of BH3-only proteins fails to protect cells under conditions of oxygen deprivation. In light of the recent findings that the combination of Bim and Puma can also elicit death (11), it is unknown whether under anoxia, combinational loss of these two proapoptotic proteins will provide protection from anoxic cell death. A fundamental question that remains unanswered is how the prosurvival activity of Bcl-2, Bcl-XL, and Bcl-w is inhibited to allow Bax and Bak to induce the loss of the outer mitochondrial membrane integrity.

MITOCHONDRIAL ELECTRON-TRANSPORT CHAIN IS REQUIRED FOR ANOXIA-INDUCED CELL DEATH

The mitochondria provide cells with energy through the production of adenosine-5'-triphosphate (ATP). ATP is produced from adenosine-5'-diphosphate (ADP) and inorganic phosphate (Pi) through the process of oxidative phosphorylation. Key enzymes that allow this process are encoded from the mitochondrial DNA. In total, the mitochondria encoded 13 polypeptides, including key components of the electron transport chain (ETC): complex I (NADH dehydrogenase), complex III (bc1 complex) complex IV (cytochrome *c* oxidase), and the complex V. Electrons are shuttled through the complexes of the ETC, generating a proton gradient across the inner mitochondrial membrane. Oxygen is the final electron acceptor, and cytochrome *c* oxidase reduces it to water. ATP production occurs at ATP synthase, which is powered by the proton gradient. Thus, oxygen limitation results in electron-transport inhibition. Cells depleted of their mitochondrial DNA, ρ°-cells, lack a functional mitochondrial electron-transport chain. These cells are resistant to anoxia-induced cell death. However, these cells can obtain energy through the process of glycolysis and can still undergo apoptosis in response to other stimuli such as growth-factor withdrawal, DNA damage, and staurosporine treatment, indicating that they still have an intact intrinsic death pathway (9). Adaptation to glycolysis is not the explanation for survival of the ρ°-cells during anoxia, because cells deficient in cytochrome *b* can still undergo apoptosis induced by anoxia (14). The cytochrome *b* null cells lack complex III activity and also rely on anaerobic glycolysis as an ATP source. Unlike ρ° cells, cytochrome *b* null cells, despite being incompetent for oxidative phosphorylation, still posses some residual electron transfer capacity that might signal to Bax/Bak activation.

How the electron-transport chain links to the negation of antiapoptotic Bcl-2 family members to activate Bax/Bak remains unknown. A functional ETC is not required for the decrease in Mcl-1 protein levels during anoxia, because ρ° cells still display a decrease in Mcl-1 protein levels during anoxia. This also indicates that the decrease in Mcl-1 protein levels is not sufficient to induce apoptosis due to residual prosurvival Bcl-2/Bcl-X_L. The administration of the Bad BH3 peptide, which inhibits the activity of Bcl-2/Bcl-X_L, induces cell death in ρ° cells under anoxia, implying that the negating Bcl-2/Bcl-X_L coupled with the degradation of Mcl-1 proteins during anoxia is sufficient to induce cell death (4). Collectively these data indicate that the degradation of Mcl-1 protein during anoxia is independent of electron-transport-chain inhibition, whereas the negation of Bcl-2/Bcl-X_L is likely dependent on electron-transport inhibition (Fig. 1).

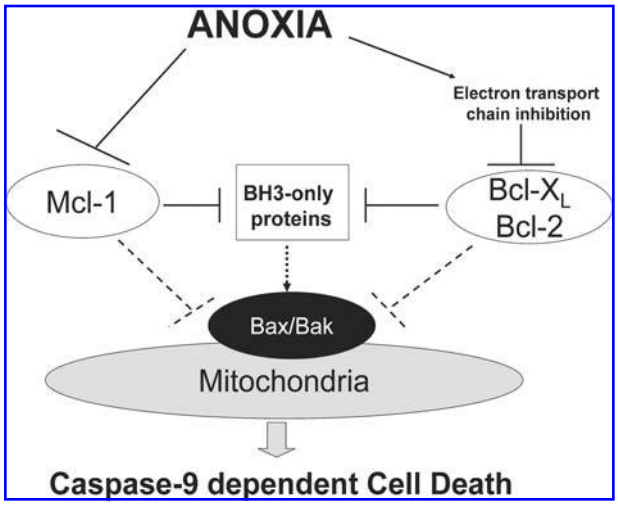

FIG. 1. Anoxia induces cell death through the intrinsic apoptotic pathway. Anoxia initiates cell death by degrading Mcl-1 protein levels coupled with the inhibition of the electron-transport chain to diminish the prosurvival activity of Bcl-X_L/Bcl-2. These two critical events release BH3-only proteins to initiate Bax/Bak-dependent release of cytochrome *c*, resulting in caspase-9–dependent cell death.

ENDOPLASMIC RETICULUM (ER) STRESS AND ANOXIA-INDUCED CELL DEATH

The endoplasmic reticulum (ER) ensures that proteins are matured, folded, and transported at a highly efficient rate to different locations in the cell. Consequently, if this process is perturbed, the ER has evolved a highly specific signaling-response pathway called the unfolded protein response (UPR) (20, 22). Two outcomes exist for UPR. The first is a less-severe response, which results in a decrease in global protein synthesis. This allows the cells to conserve energy while undergoing repair or adaptation to the stress. The second signaling response occurs when protein misfolding is persistent or excessive. Under this circumstance, the cell cannot adapt, and apoptosis occurs. Anoxia has been demonstrated to be one of the several stresses that can trigger the UPR. Under anoxia-induced ER stress, the stress-inducible transcription factor ATF4 is upregulated in a PERK-dependent manner (3). PERK is the ER-resident kinase that senses a change in the levels of misfolded proteins and triggers downstream signaling (3). ATF4 can then bind to the CHOP promoter region and trigger CHOP expression. Expression of CHOP is reported to induce apoptosis, perhaps through Puma (14, 27). Cells deficient in PERK are more sensitive to anoxia, indicating that the PERK-ATF4 pathway provides a survival advantage under anoxia (2). It is not fully understood how the PERK provides a survival advantage. The prediction based on other cell-death stimuli would have been that anoxia triggers the PERK-ATF4-CHOP pathway to promote cell death, as opposed to prevent death.

Another ER-residing protein implicated in regulation of anoxia-induced cell death is oxygen-regulating protein (ORP-150), a member of the heat-shock proteins (17). ORP-150 is expressed under conditions of oxygen deprivation and has been demonstrated to have a protective function, as cells overexpressing ORP-150 were protected from apoptosis when deprived of oxygen. In neuronal cells, ORP-150 was demonstrated to inhibit the release of cytochrome *c* and cell death when cells were deprived of oxygen. HEK cells in which ORP-150 expression was silenced un-

derwent cell death with morphologic features as seen in cells undergoing apoptosis. The exact mechanism by which ORP-150 plays a protective function is still not known. Interestingly, the localization of Bax and Bak at the ER has been demonstrated to be important in mediating stress-induced release of calcium from the ER (21, 28). Thus, how the ER proteins cross-talk to the intrinsic apoptotic pathway remains unknown.

CONCLUSIONS

In the past decade, much progress has been made in understanding the role of programmed cell death during anoxia. Cell death under anoxia is executed *via* the mitochondrial pathway, and commitment to apoptosis occurs on the release of cytochrome *c* and activation of caspase 9. The levels of Mcl-1, a prosurvival member of the Bcl-2 family that acts upstream of Bax and Bak, decreases in a Noxa-independent manner. This decrease is the result of degradation *via* the proteasomal pathway. Although this decrease appears to be important in anoxia-induced apoptosis, it is not sufficient to induce cell death. Other prosurvival factors (Bcl-xL, Bcl-2, and Bcl-w) must be inhibited for death to occur under anoxia. The mechanism and intracellular events that inhibit the remaining prosurvival factors Bcl-xl, Bcl-2, and Bcl-w are still not fully understood. The electron-transport chain also plays a key role, and current data propose a model in which oxygen deprivation inhibits the electron transport. The link between the inhibition of the electron-transport chain and negation of the remaining prosurvival factors still remains to be investigated.

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ABBREVIATIONS

AIF, apoptosis-inducing factor; Apaf-1, apoptotic protease-activating factor; ATF-4, activating transcription factor-4; BH, Bcl-2 homology; CHOP, C/EBP homologous protein; DIABLO, direct inhibitor of apoptosis-binding protein with low pI; ER, endoplasmic reticulum; GSK-3, glycogen synthase kinase 3; HIF-1, hypoxia-inducible factor 1; HRE, HIF-1 response element; MOMP, mitochondrial outer membrane permeabilization; Mule/ARF-BP1, *M*cl-1 *u*biquitin *l*igase *E*3/ARF-binding protein 1; PERK, endoplasmic reticulum resident kinase; TNF, tumor necrosis factor; UPR, unfolded protein response.

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