Bcl-x\(_L\) Promotes the Open Configuration of the Voltage-dependent Anion Channel and Metabolite Passage through the Outer Mitochondrial Membrane*

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The diffusion of metabolites across the outer mitochondrial membrane is essential for coupled cellular respiration. The outer membrane of mitochondria isolated from growth factor-deprived cells is impaired in its ability to exchange metabolic anions. When added to mitochondria, recombinant Bcl-x\(_L\) restores metabolite exchange across the outer membrane without inducing the loss of cytochrome \(c\) from the intermembrane space. Restoration of outer membrane permeability to anionic metabolites does not occur directly through Bcl-x\(_L\) ion channels. Instead, recombinant Bcl-x\(_L\) maintains the outer mitochondrial membrane channel, VDAC, in an open configuration. Consistent with these findings, when ADP-induced oxidative phosphorylation is limited by exogenous \(\beta\)-NADH, recombinant Bcl-x\(_L\) can sustain outer mitochondrial membrane permeability to ADP. \(\beta\)-NADH limits respiration by promoting the closed configuration of VDAC. Together these results demonstrate that following an apoptotic signal, Bcl-x\(_L\) can maintain metabolite exchange across the outer mitochondrial membrane by inhibiting VDAC closure.

The primary pathway for metabolite diffusion across the outer mitochondrial membrane (OMM)\(^1\) is through the voltage-dependent anion channel (VDAC), a large conductance channel that in its open configuration is permeable to molecules of up to \(\sim 5000\) daltons (1, 2). However, a conserved property of the primary VDAC isoform from all organisms tested is its ability to adopt multiple conductance states (3, 4). Treatment of isolated mitochondria with agents that favor VDAC closure, such as \(\beta\)-NADH, limits metabolite flux across the outer membrane and inhibits mitochondrial function (5–9). This ability of VDAC to adopt a closed configuration and inhibit ADP-coupled respiration has been suggested to contribute to the Crabtree effect (9), a paradoxical response in which treatment of respiring cells with glucose leads to inhibition of oxidative phosphorylation (10).

OMM permeability has also been reported to play an important role in apoptosis. Failure of the OMM to sequester cytochrome \(c\) in the intermembrane space can induce apoptosis (11). The pro- and anti-apoptotic members of the Bcl-2 family of proteins have been shown to exert their activity by regulating mitochondrial functions (12, 13). Interestingly, some members of the Bcl-2 family (such as Bcl-2 and Bcl-x\(_L\)) are permanent residents of the OMM whereas many pro-apoptotic members of the family (such as Bax, Bad, and Bid) can be translocated from the cytosol to the OMM following an apoptotic signal. The anti-apoptotic protein Bcl-x\(_L\) exhibits both structural and functional similarity to prokaryotic pore-forming proteins. Both, Bcl-2 and Bcl-x\(_L\), inhibit cytochrome \(c\) release by regulating OMM integrity or permeability (12, 13). It has been proposed that VDAC may have a role in regulating cytochrome \(c\) release by forming together with Bax, a high conductivity channel that can release cytochrome \(c\) from the intermembrane space to the cytosol (14).

Recently we have found that early in apoptosis, prior to the loss of OMM integrity and the release of cytochrome \(c\), the OMM becomes impermeable to small metabolites (15). This impermeability might lead to further disruptions of mitochondrial homeostasis and ultimately to the loss of OMM integrity. Following growth factor withdrawal, both the loss of OMM permeability and cell death are inhibited in Bcl-x\(_L\)-expressing cells (15). However, the mechanism by which Bcl-x\(_L\) maintains OMM permeability remains controversial. In this study, we describe a direct biochemical activity of Bcl-x\(_L\) protein in regulating the conductivity of VDAC. We demonstrate that Bcl-x\(_L\) can increase the probability of VDAC to be in an open configuration under conditions that favor VDAC closure. Therefore, it is suggested that in response to an apoptotic signal that would result in VDAC closure, Bcl-x\(_L\) promotes the open configuration of VDAC and maintains metabolite exchange between the mitochondria and the cytosol.

**EXPERIMENTAL PROCEDURES**

**Cell Culture—**FL5.12 cells were maintained at 37 °C and 5% CO\(_2\) in RPMI 1640 medium supplemented with 10% fetal bovine serum, 50 \(\mu\)M 2-mercaptoethanol, and 300 pg/ml recombinant mouse interleukin-3 (IL-3) (PharMingen). For growth factor withdrawal, cells were washed three times in serum-free medium and resuspended in full medium with (control) or without IL-3.

Recombinant Bcl-x\(_L\), Protein Production and Analysis—Full-length human Bcl-x\(_L\) was cloned into the pET-16b bacterial expression vector (Novagen), and recombinant protein was purified from BL21 (DE3)pLysS \(E\). coli on a Ni\(^{2+}\) column using a standard commercial kit (Novagen). Following elution of the protein with increas-...
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A. mitochondria were isolated from FL5.12 cells cultured in the presence (+IL-3) or absence (−IL-3) of IL-3 for 12 h, and the amount of phosphocreatine was determined by HPLC. The phosphocreatine peak was confirmed by co-injection of purified phosphocreatine. The average phosphocreatine peak area, normalized to mitochondrial protein, is shown for each treatment. The data presented are the mean ± S.E. from four independent experiments. The increase in phosphocreatine observed upon growth factor withdrawal was statistically significant by Student's t test (p < 0.05). B, mitochondria were isolated from growth factor-deprived cells and incubated in the absence (Control) or presence (+Bcl-xL) of recombinant Bcl-x<sub>L</sub> (3 μg/ml) or subjected to hypotonic shock as indicated. The amount of Bcl-x<sub>L</sub> present after 30 min of treatment was determined by Western blot analysis as shown. C, the amount of phosphocreatine present in mitochondria isolated from growth factor-deprived cells incubated for 30 min in the absence (Control) or presence (+Bcl-xL) of recombinant Bcl-x<sub>L</sub> (3 μg/ml) was determined by HPLC. The average phosphocreatine peak area, normalized to mitochondrial protein, is shown for each condition. The data presented are the mean ± S.E. from four independent experiments. The decrease in phosphocreatine observed upon Bcl-x<sub>L</sub> addition was statistically significant by Student's t test (p < 0.05). D, mitochondria were isolated from growth factor-deprived cells and incubated for 30 min in the absence (Control) or presence (+Bcl-xL) of recombinant Bcl-x<sub>L</sub> (3 μg/ml) or were subjected to hypotonic shock as indicated. Following treatment, the mitochondria were pelleted by centrifugation, and the amount of cytochrome c present in the supernatant was determined by Western blot analysis.

**FIG. 1.** Bcl-x<sub>L</sub> can increase OMM permeability to phosphocreatine without disrupting membrane integrity. A, mitochondria were isolated from FL5.12 cells cultured in the presence (+IL-3) or absence (−IL-3) of IL-3 for 12 h, and the amount of phosphocreatine was determined by HPLC. The phosphocreatine peak was confirmed by co-injection of purified phosphocreatine. The average phosphocreatine peak area, normalized to mitochondrial protein, is shown for each treatment. The data presented are the mean ± S.E. from four independent experiments. The increase in phosphocreatine observed upon growth factor withdrawal was statistically significant by Student's t test (p < 0.05). B, mitochondria were isolated from growth factor-deprived cells and incubated in the absence (Control) or presence (+Bcl-xL) of recombinant Bcl-x<sub>L</sub> (3 μg/ml) or subjected to hypotonic shock as indicated. The amount of Bcl-x<sub>L</sub> present after 30 min of treatment was determined by Western blot analysis as shown. C, the amount of phosphocreatine present in mitochondria isolated from growth factor-deprived cells incubated for 30 min in the absence (Control) or presence (+Bcl-xL) of recombinant Bcl-x<sub>L</sub> (3 μg/ml) was determined by HPLC. The average phosphocreatine peak area, normalized to mitochondrial protein, is shown for each condition. The data presented are the mean ± S.E. from four independent experiments. The decrease in phosphocreatine observed upon Bcl-x<sub>L</sub> addition was statistically significant by Student's t test (p < 0.05). D, mitochondria were isolated from growth factor-deprived cells and incubated for 30 min in the absence (Control) or presence (+Bcl-xL) of recombinant Bcl-x<sub>L</sub> (3 μg/ml) or were subjected to hypotonic shock as indicated. Following treatment, the mitochondria were pelleted by centrifugation, and the amount of cytochrome c present in the supernatant was determined by Western blot analysis.

**RESULTS**

**Recombinant Bcl-x<sub>L</sub> Protein Restores Outer Membrane Permeability to Phosphocreatine in Mitochondria of Survival Factor-deprived Cells**—Mitochondria isolated from growth factor-deprived cells have lost the ability to exchange organic metabolites such as ATP, ADP, and phosphocreatine with the cytosol (15). It was previously suggested that this is because of a decrease in OMM permeability to small anionic metabolites. In IL-3-dependent FL5.12 cells, changes in OMM permeability following IL-3 withdrawal can be detected by measuring phosphocreatine levels in the intermembrane space of mitochondria (15) (Fig. 1A). To determine whether Bcl-x<sub>L</sub> can restore outer membrane anion permeability when added directly to mitochondria impaired in phosphocreatine exchange, recombinant Bcl-x<sub>L</sub> was generated. Recombinant Bcl-x<sub>L</sub> efficiently incorporated into mitochondria isolated from growth factor-deprived cells in the absence (Control) or presence (+Bcl-xL) of recombinant Bcl-x<sub>L</sub> (3 μg/ml) was determined by HPLC. The average phosphocreatine peak area, normalized to mitochondrial protein, is shown for each condition. The data presented are the mean ± S.E. from four independent experiments. The decrease in phosphocreatine observed upon Bcl-x<sub>L</sub> addition was statistically significant by Student's t test (p < 0.05). D, mitochondria were isolated from growth factor-deprived cells and incubated for 30 min in the absence (Control) or presence (+Bcl-xL) of recombinant Bcl-x<sub>L</sub> (3 μg/ml) or were subjected to hypotonic shock as indicated. Following treatment, the mitochondria were pelleted by centrifugation, and the amount of cytochrome c present in the supernatant was determined by Western blot analysis.

**Mouse liver mitochondria were isolated by tight dounce homogenization and differential centrifugation in 10 mM Hepes buffer, pH 7.4, containing 200 mM mannitol, 70 mM sucrose, 1 mM EGTA, 1 mg/ml bovine serum albumin. Where indicated, recombinant Bcl-x<sub>L</sub> was incubated with mitochondria at the specified concentration for 10 min at room temperature. Immediately prior to use in respiration studies, mitochondria were diluted into 20 mM Hepes buffer, pH 7.4 containing 250 mM sucrose, 10 mM KCl, 5 mM succinate, 3 mM KH<sub>2</sub>PO<sub>4</sub>, 1.5 mM MgCl<sub>2</sub>, 1 mM EGTA, 1 mg/ml bovine serum albumin. β-NADH and ADP were added at concentrations of 100 μM. Oxygen consumption was measured in a functionally airtight water-jacketed chamber at room temperature using a polarographic oxygen electrode.

**Electrophysiological Analysis—**Membranes were made from monolayers of diphtyanylophosphatidylcholine by the method of Montal and Mueller (19) and as modified (20). Recordings were made under voltage-clamp conditions using calomel electrodes with saturated KCl bridges. Current was filtered at 90 Hz using a Butterworth filter.
Bcl-x<sub>L</sub> Is Not a Phosphocreatine Channel—Bcl-x<sub>L</sub> forms ion channels in vitro (22, 23), suggesting that a channel activity of Bcl-x<sub>L</sub> may be directly responsible for the equilibration of phosphocreatine across the outer membrane. To test this possibility, the ability of Bcl-x<sub>L</sub> channels to pass phosphocreatine was examined by reconstitution into planar phospholipid membranes. Recombinant Bcl-x<sub>L</sub> was inserted into an uncharged phospholipid membrane in the presence of a 2-fold chemical solution of Na<sub>2</sub>C<sub>6</sub>H<sub>5</sub>N<sub>3</sub> (phosphocreatine<sup>−</sup>), and current was recorded before and after addition of recombinant Bcl-x<sub>L</sub> (1.4 μg/ml) as indicated. The reversal potential measured after Bcl-x<sub>L</sub> addition demonstrates that the resultant channels are permeable to sodium but not to phosphocreatine. The arrow denotes the reversal potential expected for a channel with ideal selectivity for Na<sup>+</sup>. The data presented are representative of three independent experiments.

Bcl-x<sub>L</sub> Regulates VDAC Properties—The major outer membrane channel, VDAC, is permeable to anionic metabolites in the open state, but exhibits a large reduction in permeability to anions such as phosphocreatine when the channel adopts closed configurations (15, 25). Thus, VDAC must be closed for phosphocreatine to be retained in isolated mitochondria. In vitro, the presence of a membrane potential closes VDAC and has been shown to favor Bcl-x<sub>L</sub> channel formation (22). To determine whether Bcl-x<sub>L</sub> can alter OMM permeability via an effect on VDAC when residing in the same membrane, the ability of recombinant Bcl-x<sub>L</sub> to alter VDAC channel properties was examined. Purified rat liver VDAC reconstituted into a planar phospholipid membrane exhibits decreased channel conductance (closed states) when a voltage is applied across the membrane. In results from a typical experiment, average conductance through VDAC channels is illustrated before and after Bcl-x<sub>L</sub> addition (Fig. 3A). Bcl-x<sub>L</sub> caused an increase in conductance (channel opening) at potentials between −25 mV and +25 mV. This increase correlates with the amount of Bcl-x<sub>L</sub> added in a dose-dependent manner. The increase in membrane conductance reflects an increase in VDAC channel conductance rather than an additive effect of independent Bcl-x<sub>L</sub> and VDAC channels because the conductance of Bcl-x<sub>L</sub> channels is much lower than that of VDAC channels. The failure of Bcl-x<sub>L</sub> addition to increase conductance through VDAC at potentials greater than +25 mV or less than −25 mV define a limit past which Bcl-x<sub>L</sub> does not influence VDAC closure.

To further explore the effect of Bcl-x<sub>L</sub> on VDAC channel properties, single-channel experiments that determine the conductance of each state and transitions between states were performed. Sample traces from one such experiment show the conductance (slope of trace) and transitions between states (vertical connecting lines) as voltage was varied between ±50 mV (Fig. 3B). The probabilistic nature of single-molecule behavior does not allow one to observe differences merely by examining one trace. From analysis of many such traces, the probability of observing the channel in its highest conducting state (the open probability) was determined (Fig. 3C). VDAC channels have two gating processes working at opposite potentials (26). Bcl-x<sub>L</sub> increased the open probability primarily for the gating process that occurs at positive potentials, indicating an asymmetric effect. Because this effect was observed when Bcl-x<sub>L</sub> was added to both sides of the membrane, the asymmetry is likely a property of VDAC. A second-order effect on VDAC conductance was also observed. The single-channel conductance of VDAC in both the open and closed states was reduced by about 5% when Bcl-x<sub>L</sub> was added. This may reflect an interaction between the proteins or may be attributed to a physical interference with VDAC conductance caused by the close proximity of the proteins in the membrane.

Recombinant Bcl-x<sub>L</sub> Maintains VDAC Open in Isolated Mitochondria under Conditions That Promote VDAC Closure—The single-channel experiments indicate that Bcl-x<sub>L</sub> increases the conductance of VDAC by increasing the probability of the channel to be open. This also explains the ability of Bcl-x<sub>L</sub> to increase the permeability of the OMM. To explore this property further, the ability of Bcl-x<sub>L</sub> to maintain outer membrane permeability to relevant anions such as ADP was tested under...
conditions that are known to close VDAC. β-NADH favors VDAC closure in planar phospholipid membranes (8) and decreases the permeability of the outer membrane to ADP in isolated mitochondria (9). Addition of recombinant Bcl-xL to mitochondria isolated from mouse liver resulted in a dose-dependent incorporation of Bcl-xL at the indicated amounts. The average conductance through VDAC in response to triangular voltage waves is shown before and after Bcl-xL addition. The data presented are the average conductances measured from 14 and 16 waves respectively and are representative of six independent experiments. B, triangular voltage waves were applied to a planar phospholipid membrane containing a single VDAC channel. Representative current records of the VDAC channel are shown before (Control) and after (+Bcl-xL) addition of recombinant Bcl-xL (15 μg/ml). C, multiple current records were analyzed to determine the likelihood that a single VDAC channel was in the highest conducting state (open configuration) as a function of voltage. This open probability is graphed in the absence (Control) and presence (+Bcl-xL) of recombinant Bcl-xL as indicated.

**Fig. 3. Bcl-xL promotes the maintenance of VDAC in an open configuration.** A, the current through isolated rat liver VDAC incorporated into a planar phospholipid membrane was recorded during the application of successive triangular waves (4 mHz, ±100 mV) before and after the addition of recombinant Bcl-xL at the indicated amounts. The average conductance through VDAC in response to triangular voltage waves is shown before and after Bcl-xL addition. The data presented are the average conductances measured from 14 and 16 waves respectively and are representative of six independent experiments. B, triangular voltage waves were applied to a planar phospholipid membrane containing a single VDAC channel. Representative current records of the VDAC channel are shown before (Control) and after (+Bcl-xL) addition of recombinant Bcl-xL (15 μg/ml). C, multiple current records were analyzed to determine the likelihood that a single VDAC channel was in the highest conducting state (open configuration) as a function of voltage. This open probability is graphed in the absence (Control) and presence (+Bcl-xL) of recombinant Bcl-xL as indicated.

outer membrane permeability expected when VDAC is open, the addition of recombinant Bcl-xL had no measurable effect on ADP-dependent respiration in the absence of β-NADH (data not shown). However, recombinant Bcl-xL prevented β-NADH addition from prolonging the time it takes the mitochondria to complete the respiratory burst induced by a defined amount of ADP (Fig. 4B). ADP-dependent respiration requires both the diffusion of ADP across the outer membrane and the facilitated transport of ADP across the inner membrane by the adenine
nucleotide transporter (ANT). A steady-state level of ADP is maintained in the intermembrane space resulting in equal fluxes across both membranes. At physiological levels of ADP, the diffusion-based flux through the outer membrane can become rate-limiting. This is manifested as a delay in the time that the change in PO₂, which corresponds to the conversion of a given bolus of ADP to ATP, is achieved.

The delay in the transition between state III (ADP present) and state IV (ADP converted to ATP) was used to calculate the change in outer membrane permeability by using the method of Lee et al. (9, 27). The respiration data were fitted to a theoretical expression that accounts for the diffusion through VDAC in a planar phospholipid membrane. This results in an increase in respiration rate as would be expected if either Bcl-2 or Bcl-xL is present in the intermembrane space resulting in equal fluxes across both membranes. At physiological levels of ADP, the diffusion-based flux through the outer membrane can become rate-limiting. This is manifested as a delay in the time that the change in PO₂, which corresponds to the conversion of a given bolus of ADP to ATP, is achieved.

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Bcl-xL were to close VDAC, and it seems unlikely that under normal conditions Bcl-xL closes VDAC. It is possible though that under some conditions Bcl-2/Bcl-xL stabilize VDAC and prevent formation of a cytochrome c-releasing pore (13, 29). The data presented in this study support the hypothesis that Bcl-xL functions to maintain VDAC in an open configuration under conditions that favor VDAC closure. This open configuration of VDAC does not enable the passage of cytochrome c, but maintains free metabolite exchange across the OMM, supporting oxidative phosphorylation. Whereas VDAC appears to close following growth factor withdrawal (15), the signal that induces VDAC closure is not known. It is possible that the translocation of pro-apoptotic proteins such as Bax to mitochondria might directly or indirectly result in VDAC closure. Alternatively, VDAC closure may result as a consequence of changes in cellular metabolism. For instance, an early cellular response to growth factor withdrawal is a decrease in both the mitochondrial membrane potential and the rate of electron transport (30). This decrease in mitochondrial function may result in NADH accumulation because oxidative phosphorylation is required to efficiently regenerate NAD from NADH. Alternatively, changes in metabolite flux across the OMM may be responsible for inducing a potential across the outer membrane (31).

There are several possible ways by which Bcl-xL could maintain the open configuration of VDAC. Bcl-xL may alter the gating properties of VDAC by physically interacting with it. Based upon co-immunoprecipitation studies of detergent-solubilized membranes, it has been reported that Bcl-xL can interact with VDAC (28). However, it remains unclear whether this reflects an actual physical association of the proteins within the membrane, or the innate properties of hydrophobic proteins following membrane dissolution. Alternatively, Bcl-xL may insert into the membrane and alter the local electrical or lipid environment of the membrane and inhibit VDAC closure indirectly. If the action is indirect, it must be exerted in close proximity to VDAC. In any event, the action of Bcl-xL is to favor the open configuration of VDAC. Factors favoring the closed state, such as high electric fields, can overcome the effects of Bcl-xL.

Recombinant Bcl-xL can regulate metabolic anion exchange across the OMM. This demonstrates for the first time a direct function for an anti-apoptotic Bcl-2 protein in an organelle to which it is targeted. The regulation of VDAC gating properties may at least partially explain the ability of Bcl-xL to promote cell survival. By facilitating the continued exchange of metabolites across the OMM during periods of cellular stress, Bcl-xL protects against a disruption in mitochondrial physiology that results in the release of cytochrome c from mitochondria (30). Furthermore, the demonstration that metabolite flux through VDAC can be regulated by Bcl-xL may explain how Bcl-2 proteins impact on both the redox state and pH of the cell (32, 33). Maintaining ADP-coupled oxidative phosphorylation should limit lactate production, reduce the amount of glucose consumed by glycolysis, and preserve greater substrate availability for the production of reducing equivalents through the pentose phosphate shunt. Changes in both pH and redox state have been associated with apoptosis. Thus, the ability of Bcl-2 proteins to regulate transport across mitochondrial membranes could account for their ability to affect a wide variety of apoptotic pathways.

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