Antiapoptotic Action of Mcl-1 and A-1(Bfl-1) via Interaction with the VDAC2/Bak complex

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Mitochondrial Outer Membrane (MOM) Permeabilization (MOMP) is a critical step in the intrinsic pathway of apoptosis and is dependent on the balance between the proapoptotic and antiapoptotic proteins of the Bcl-2 family. The proapoptotic proteins Bax and Bak are the main executors of MOMP in response to proapoptotic stimuli, allowing proteins in the mitochondrial intermembrane space, such as cytochrome c, to escape into the cytosol where they can induce caspase activation and cell death (1, 2). This process is actively opposed by the Bcl-2 family antiapoptotic members, such as Bcl-xL, Bcl-2, Bcl-w, Bcl-B, Mcl-1 and A-1 (Bfl-1), but the mechanisms are largely obscure. The predominant view is that antiapoptotic proteins act through direct interactions with Bax and BH3-only proteins in cytosol or with Bak integrated into the MOM. However, the interactions between the proteins in the cytosol in required orientation is highly inprobable thus suggesting that the cytosol case is unlikely and currently, it became clear that most of functional interactions between Bcl-2 family members occur at the MOM and that the membrane plays an active role in modulating the interactions between BCL2 proteins (3). Recently, the porin VDAC2 have been found to assist Bcl-2 family proteins Bax, Bak and tBid in MOMP by recruiting Bak to the MOM followed by the tBid-mediated Bak displacement from VDAC2 into a MOMP-competent state (4, 5). We suggested that Mcl-1 and A-1, known to interact with Bak, bind to VDAC2-bound Bak, thus preventing Bak proapoptotic activity. To test this we first predicted the 3D-structure of the complex VDAC2-Bak and then the interaction of VDAC2-Bak with Mcl-1 and A1 using computational structural biology methods. The combination of the global docking program Piper (4) with RosettaDock local refinement (5) was applied. We found that Bak binds to membrane-resident VDAC2 with high affinity (see Table 1). The high affinity binding took place for the binding of Mcl-1 and A1 to the VDAC2-Bak complex. The 3D-structures of the complexes is shown in Fig.1. The corresponding Piper/ RosettaDock scores are presented in Table 1.

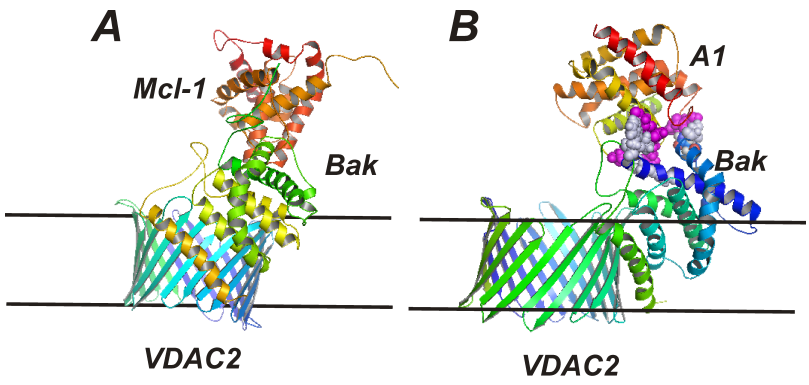

Fig.1. Structural models of the VDAC2-Bak-Mcl-1 (A) and VDAC2-Bak-A1 complexes.

Table 1**.** The Piper and RosettaDock for the highest- rank complexes VDAC2-Bak, VDAC2-Bak-Mcl-1 and VDAC2-Bak-Mcl-1

Protein complexes	The Piper weighted scores for the highest-ranked structures	The Rosetta scoring function values for refined structures
VDAC2-Bak	-1546.9	-465..95
VDAC2-Bak with Mcl-1	-1424.9	-407.95
VDAC2-Bak with A1	-1517.7	-427.87

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