Bcl-x(L) retrotranslocates Bax from the mitochondria into the cytosol

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The Bcl-2 family member Bax translocates from the cytosol to mitochondria, where it oligomerizes and permeabilizes the mitochondrial outer membrane to promote apoptosis. Bax activity is counteracted by prosurvival Bcl-2 proteins, but how they inhibit Bax remains controversial because they neither colocalize nor form stable complexes with Bax. We constrained Bax in its native cytosolic conformation within cells using intramolecular disulfide tethers. Bax tethers disrupt interaction with Bcl-x(L) in detergents and cell-free MOMP activity but unexpectedly induce Bax accumulation on mitochondria. Fluorescence loss in photobleaching (FLIP) reveals constant retrotranslocation of WT Bax, but not tethered Bax, from the mitochondria into the cytoplasm of healthy cells. Bax retrotranslocation depends on prosurvival Bcl-2 family proteins, and inhibition of retrotranslocation correlates with Bax accumulation on the mitochondria. We propose that Bcl-x(L) inhibits and maintains Bax in the cytosol by constant retrotranslocation of mitochondrial Bax.
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