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CypB was associated with mitochondrial permeabilization and cytochrome c release, with similar kinetics to other pro-apoptotic stimuli. CypB induced apoptosis in a Bax-independent manner and by a mechanism distinct from that of Bax or BH3-only proteins. CypB-mediated apoptosis was partially inhibited by truncation mutants of Bax, indicating that distinct regions of Bax could be independently required for its induction of apoptosis and mitochondrial permeabilization. Molecular replacement experiments mapped the critical residues of CypB in the cyclophilin domain and the N-terminal peptide-binding groove to be essential for apoptosis induction. Partial replacement of the N-terminal peptide-binding groove with a short peptide mimicking the class D peptide-binding determinant of CypA blunted Bax-dependent apoptosis, suggesting the specific effects of CypA on Bax function in the cytosol in this context. Our results demonstrate a novel role for CypB as a potent proapoptotic stimulus, further supporting a critical role for CypB in apoptosis induction. Generalized synchrony in d0c515b9f4

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