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Bcl-2 apoptosis proteins, mitochondrial membrane curvature, and cancer GHEE HWEE LAI, NATHAN SCHMIDT, Physics, UIUC, LORI SANDERS, Materials Science and Engineering, UIUC, ABHIJIT MISHRA, GERARD WONG, Bioengineering, UCLA, OLENA IVASHYNA, ERIC CHRISTENSON, PAUL SCHLESINGER, Cell Biology and Physiology, WUSTL Sch. of Medicine, KIYOTAKA AKABORI, CHRISTIAN SANTANGELO, Physics, U. of Massachusetts
— Critical interactions between Bcl-2 family proteins permeabilize the outer mitochondrial membrane, a common decision point early in the intrinsic apoptotic pathway that irreversibly commits the cell to death. However, a unified picture integrating the essential non-passive role of lipid membranes with the contested dynamics of Bcl-2 regulation remains unresolved. Correlating results between synchrotron x-ray diffraction and microscopy in cell-free assays, we report activation of pro-apoptotic Bax induces strong pure negative Gaussian membrane curvature topologically necessary for pore formation and membrane remodeling events. Strikingly, Bcl-xL suppresses not only Bax-induced pore formation, but also membrane remodeling by disparate systems including cell penetrating, antimicrobial or viral fusion peptides, and bacterial toxin, none of which have BH3 allosteric domains to mediate direct binding. We propose a parallel mode of Bcl-2 pore regulation in which Bax and Bcl-xL induce antagonistic and mutually interacting Gaussian membrane curvatures. The universal nature of curvature-mediated interactions allows synergy with direct binding mechanisms, and potentially accounts for the Bcl-2 family modulation of mitochondrial fission/fusion dynamics.

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