

The Bcl-2 Family, Matters of Life and Death

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A central control point for the induction of apoptosis mitochondrial outer membrane permeabilization (MOMP), leading to the release of cytochrome c and other proteins residing in the mitochondrial intermembrane space. Within a short time, MOMP is followed by apoptosome formation and caspase activation resulting in apoptosis. Mitochondrial outer membrane permeabilization (MOMP) is controlled by the BCL-2 family of proteins, with proapoptotic Bax and/or Bak required for permeabilization. This is counteracted by antiapoptotic BCL-2 family members, mainly Bcl-2, Bcl-xL, and Mcl-1. Different proapoptotic BH3-only proteins such as Bim, Bid, Puma, and others, act to interfere with the function of the antiapoptotic Bcl-2 members and/or activate Bax and Bak.

I will discuss studies in cells and in cell-free systems that analyze the activation and regulation of Bax and Bak to effect MOMP. These observations present an emerging view, on how interactions among the Bcl-2 family and other proteins result in MOMP and apoptosis.

In addition to induction of cell growth and proliferation, growth factors maintain cell viability, as lack of appropriate growth factor stimulation will rapidly trigger apoptosis. Growth factor receptor engagement induces activation of the PI3K/AKT pathway, which prevents the release of cytochrome c. One way in which this occurs is through the inhibition of GSK3, which phosphorylates the anti-apoptotic Bcl-2 protein Mcl-1. This phospho-Mcl-1 is rapidly degraded by the proteasome. Therefore, upon growth factor withdrawal, Mcl-1 protein levels decline, thus reducing anti-apoptotic effects in the cell. Growth factor deprivation in lymphoid cells also results in upregulation of the Bax/Bak activator, Bim, via an independent pathway. As a result, MOMP and apoptosis ensues.

References

1. Muñoz-Pinedo, C., Guío-Carrión, A., Goldstein, J.C., Fitzgerald, P., Newmeyer, D.D., and Green, D.R. Different mitochondrial inter-membrane space proteins are released during apoptosis in a manner that is coordinately initiated but can vary in duration. *Proc. Natl. Acad. Sci. USA*, 103, 11573-11578, 2006.
2. Maurer, U., Charvet, C., Wagman, A.S., Dejardin, E., and Green, D.R. Glycogen synthase kinase-3 regulates mitochondrial outer membrane permeabilization and apoptosis by destabilization of Mcl-1. *Mol. Cell*, 21, 749-760, 2006.
3. Green, D.R. At the gates of death. *Cancer Cell*, 9, 328-330, 2006.
4. Spierings, D., McStay, G., Saleh, M., Bender, C., Chipuk, J., Maurer, U., and Green, D.R. Connected to death: the (unexpurgated) mitochondrial pathway of apoptosis. *Science*, 310, 66-67, 2005.
5. Kuwana, T., Bouchier-Hayes, L., Chipuk, J.E., Sullivan, B., Green, D.R., and Newmeyer, D.D. BH3 domains of BH3-only proteins differentially regulate Bax-mediated membrane permeabilization both directly and indirectly. *Mol. Cell*, 17, 525-535, 2005.
6. Chipuk, J.E., Bouchier-Hayes, L., Kuwana, T., Newmeyer, D.D., and Green, D.R. Puma couples the nuclear and cytoplasmic pro-apoptotic function of p53. *Science*, 309, 1732-1735, 2005.