Staying Alive: Defensive Strategies in the BCL-2 Family Playbook

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Many forms of apoptosis are initiated due to stress or damage that activates one or more members of the BH3-only subset of the BCL-2 family (Youle and Strasser, 2008). BH3-only proteins serve as pathway-specific damage or stress sensors that initiate apoptosis through promoting mitochondrial outer membrane permeabilization (MOMP) via a channel comprised of BAX and BAK (Chipuk et al., 2010). Opening of the BAX/BAK channel permits efflux of cytochrome c and other mitochondrial intermembrane space proteins into the cytosol, which seals the fate of the cell through instigation of a proteolytic cascade that coordinates cell death (Taylor et al., 2008). BAX/BAK channel opening is opposed by the prosurvival members of the BCL-2 family, which block cell death as a consequence. Precisely how the prosurvival BCL-2 family repress opening of the BAX/BAK channel to block apoptosis; in this issue Llambi et al. (2011) identify two modes of apoptosis inhibition that exhibit surprisingly different behavior upon repeat proapoptotic challenges by BH3-only proteins.

Much debate surrounds how prosurvival members of the BCL-2 family repress opening of the BAX/BAK channel to block apoptosis; in this issue Llambi et al. (2011) identify two modes of apoptosis inhibition that exhibit surprisingly different behavior upon repeat proapoptotic challenges by BH3-only proteins.
Where prosurvival BCL-2 proteins could engage simultaneously with BH3-only proteins as well as BAX/BAK (i.e., MODE 1 and 2) there was a progressive engagement of a MODE 1 at low concentrations of BH3-only protein, followed by engagement of MODE 2 where the ratio between BH3-only and prosurvival BCL-2 proteins approached 1:1.

But does it matter whether cells resist a proapoptotic challenge by blocking MOMP in MODE 1 or MODE 2? It seems that it does. Llambi et al. (2011) made the surprising observation that cells surviving a proapoptotic challenge in MODE 1 as a result of previous exposure to low doses of activated BH3-only proteins were paradoxically easier to derepress, using a small-molecule BH3 mimetic (ABT-737), than cells surviving a higher-intensity challenge of the same stress that engaged MODE 2 (Figure 1D). In other words, prior exposure to a low-intensity proapoptotic stress placed cells in a more vulnerable state (i.e., surviving in MODE 1) to a subsequent proapoptotic challenge than cells primed using a higher-intensity dose of the same stimulus (surviving in MODE 2). Because of the relative ease of derepression of MODE 1 versus MODE 2, the former was more readily overpowered than the latter in response to a repeat attack on cellular defenses.

Thus, the study by Llambi et al. suggests that not all defensive strategies within the BCL-2 family are equally robust. Some defensive positions (i.e., MODE 1) can leave cellular defenses compromised such that a repeat attack can lead to more rapid progression to apoptosis. This may have implications for therapeutic strategies aimed at manipulating the BCL-2 family network in diseases such as cancer where cells are often “primed for death” through previous encounters with stressors such as hypoxia or nutrient deprivation that trigger activation of BH3-only proteins to sublethal levels (Certo et al., 2006). A provocative implication of the MODE 1/MODE 2 scenario is that, in at least some therapeutic situations, lower drug doses may well produce more favorable therapeutic response rates in tumors primed for death in MODE 1 rather than MODE 2. In such situations, the old adage that “less is more” may be very apt.

Important questions remain. The precise composition of the BAX/BAK pore, whether it is capable of undergoing spontaneous assembly, and whether additional cellular cofactors are required remain unclear. Nonetheless, it is likely that BH3-only mimetic compounds capable of neutralizing prosurvival BCL-2 family defenses will have considerable utility as adjuncts to cancer therapy, serving to derepress the blocks to apoptosis found in many cancers. To minimize side effects on untransformed cells, the challenge will be to identify BH3-mimetics selective for individual prosurvival BCL-2 proteins that are elevated in particular malignancies. Hopefully, derepressing times for the BCL-2 family lie just around the corner.

**REFERENCES**


