APOPTOSIS

New strategies to tip the BCL-2 balance

IMAGE SOURCE

The BCL-2 family, which is composed of pro- and anti-apoptotic proteins that regulate the mitochondrial pathway of programmed cell death, is a hotly pursued target for anti-cancer drugs. Most therapeutic approaches focus on inhibiting the function of the pro-survival protein BCL-2, thereby shifting the balance towards cell death. Now, two papers present new ways to tweak the BCL-2 family equilibrium. Reporting in *Cancer Cell*, Zhang and colleagues describe a peptide that can convert BCL-2 from a protector into a potent killer, and reporting in *Nature*, Walensky and colleagues identify the previously unknown activation site of the pro-apoptotic protein BAX.

The central players of the BCL-2 family are the pro-survival proteins such as BCL-2 and BCL-X_L, the apoptotic effector proteins BAX and BAK, and the BH3-domain only proteins, which transmit pro-death signals from various stimuli. Once deployed, the BH3-only proteins are either neutralized by pro-survival family members such as BCL-2 — which contain an anti-apoptotic binding groove that can bind and sequester BH3-only proteins — or delivered to the mitochondrial executioners BAK and BAX.

BCL-2 is a particularly attractive anticancer target, as it is frequently overexpressed in cancer cells, and can confer resistance to chemotherapy and radiotherapy. Identifying compounds that bind to its anti-apoptotic binding groove, thereby neutralizing its ability to sequester BH3-only proteins, is a popular therapeutic strategy. In their paper, Zhang and colleagues describe an alternative approach, based on previous findings from the group showing that the nuclear receptor NUR77 can induce a phenotypic conversion that turns BCL-2 into a pro-apoptotic protein, by binding to a large unstructured loop between the BCL-2 BH3 and BH4 domains.

Taking the opportunity to develop a drug that may be particularly active in cancer cells with high levels of BCL-2, peptides from a subregion of NUR77 were synthesized and conjugated to a cell-penetrating peptide. The NUR77 activity on BCL-2 was found to reside in a 9 amino-acid peptide, termed NuBCP-9. Encouragingly, the proteolytically stable D-peptide enantiomer showed similar activity, efficiently inducing cell death in cell lines, and in animal models when directly injected into solid tumours. The peptide was shown to induce a conformational change in BCL-2 that interfered with the binding and sequestering of BH3-only proteins, turning it into a 'BH3-like' protein that subsequently inhibits its pro-survival relative BCL-X_L, and induces BAX/BAK-dependent apoptosis.

Another attractive way to induce apoptosis in cells expressing high levels of BCL-2 would be to bypass the BCL-2-family-mediated regulation of BAX/BAK, and to directly activate these cell-death inducers. However, although there is evidence that at least two BH3 proteins — BID and BIM — can do so, deciphering this interaction has been a major challenge in apoptosis research.

Using a combination of structural techniques, and a previously described death-inducing BIM-derived peptide that was chemically 'stapled' into its α-helical conformation, Walensky and colleagues have now succeeded in shedding light on the mechanism that initiates BAX activation. In relation to the anti-apoptotic binding groove, the peptide appeared to 'stab BAX in the back', revealing an unforeseen activation site at a novel structural location that could provide a new target for intervention in the apoptotic cascade.

Overall, the two papers have provided new mechanistic insights into apoptosis induction, and efforts are underway to develop potential drug candidates on the basis of the peptides identified.

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ORIGINAL RESEARCH PAPERS Kolluri, S. K. *et al.* A short Nur77-derived peptide converts Bcl-2 from a protector to a killer. *Cancer Cell* **14**, 285–298 (2008) | Gavathiotis, E. *et al.* BAX activation is initiated at a novel interaction site. *Nature* **455**, 1076–1081 (2008)