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PHARMACOLOGY

Structure-based design for selective inhibition lowers toxicity

A compound that inhibits the growth of BCL-2–dependent tumours has been re-engineered to prevent the concurrent inhibition of the BCL-X_L protein that protects platelets, report Andrew Souers and colleagues in *Nature Medicine*.

Apoptosis is tightly controlled by pro-death and pro-survival proteins. Shifting the balance towards pro-survival proteins is one mechanism by which cancer cells are able to evade apoptosis. BCL-2 is a protein regulator of apoptosis that has a major role in the survival of a number of lymphoid malignancies. BCL-X_L is a related pro-survival protein that is associated with a number of haematological malignancies and solid–tumours, and is also is the primary pro-survival factor in platelets.

> “...higher concentrations of the drug can be administered without inducing toxicity”

The investigators had previously described navitoclax—a molecule with a high affinity for both BCL-2 and BCL-X_L. Navitoclax has antitumour activity in lymphoid malignancies that are dependent on BCL-2 for survival, but also reduces the number of circulating platelets, which limits the safe administrative dose of navitoclax in patients. “We wanted to engineer a compound that inhibits the BCL-2 protein that protects cancer cells, but does not inhibit the BCL-X_L protein that protects platelets” explains Souers, an Associate Director for AbbVie.

BCL-2 and BCL-X_L both contain similar BH3–binding domains that complicate the design of BCL-2–selective inhibitors. The team used X-ray crystallography to visualize protein interactions and noted that “an early and less potent analogue crystallized with the BCL-2 protein in such a way that a new means of interacting with the protein was discovered” says Souers, “the observation gave us significant insight into how a new compound could be made such that the activity against BCL-X_L would be substantially reduced.”

By removing and replacing key binding elements, the team were able to manipulate the structure of the molecule. The resulting compound, ABT-199, induced apoptosis in various cancer cell lines and resulted in tumour regression *in vivo* while sparing platelets, meaning that higher concentrations of the drug can be administered without inducing toxicity. Notably, administration of a single dose of ABT-199 in three patients with chronic lymphoid leukaemia resulted in rapid tumour lysis revealing the potential of this agent, and this structure-based design approach, in cancer therapy.

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Original article Souers, A. J. *et al*. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets *Nat. Med.* doi:10.1038/nm.3048