murine orthologue of IL-8, rapidly dropped after pepducin treatment; the numbers of neutrophils in bronchioalveolar lavage fluid was reduced; and pepducins conferred protection from lung and liver damage. Importantly, the pepducin treatment did not suppress leukocyte migration towards other chemokines, and so its effects can be considered immunomodulatory rather than immunosuppressive.

These results indicate that blockade of IL-8 signalling with pepducins reverses several criteria of established systemic inflammatory response syndrome in septic mice, and suggest that this approach could prove to be a powerful tool to combat sepsis, even in the setting of advanced disease.

Alexandra Flemming

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LEAD DISCOVERY

Cell death by design

An NMR-based technique has been used to discover a potential new anticancer drug that targets interactions between the BCL2 family of apoptotic regulators. Oltersdorf *et al.* describe in *Nature* how they used 'SAR by NMR' (structure–activity relationship by NMR), to identify and optimize a potent small molecule that enhances pro-apoptotic signalling and induces cancer cell death *in vitro* and *in vivo*.

BCL2 family members BCL-X_L and BCL2 inhibit apoptosis and are upregulated in many cancers, making them attractive drug targets. However, blocking their activity has been challenging because it necessitates targeting protein–protein interactions. One possibility is to develop small molecules that mimic the activity of members of the 'BH3-only' subfamily of pro-apoptotic proteins, which inhibit BCL2 and BCL-X_L. BH3 proteins are so-called because they contain a conserved α-helix called the BH3 region that associates with the large hydrophobic BH3-binding groove in anti-apoptotic BCL2 family members. To find potential inhibitors of BCL2 and BCL-X_L, Oltersdorf and colleagues screened for compounds that bind to this BH3-binding groove and then optimized these to create a small-molecule inhibitor.

SAR by NMR is a method that can be used to identify and optimize low-affinity ligands. Small molecules that bind to the target are identified by mapping the NMR chemical shift that occurs after ligand binding. This structural information can then be used to guide the linkage of proximal molecular fragments to generate a molecule with improved binding affinity for the target.

Two compounds were identified that bind to distinct but proximal binding sites within the BH3-binding groove. Significantly, the two sites were the same as those occupied by amino-acid residues known to be crucial for the binding of a pro-apoptotic BH3 protein to BCL-X_L. The authors synthesized a molecule that spans both of these binding sites and further optimized this using structural information to produce a compound, ABT-737, which binds to and inhibits anti-apoptotic BCL2 family proteins at nanomolar concentrations.

In cytotoxicity assays, ABT-737 had an additive effect when used with chemotherapy and radiotherapy, enhancing the activity of several established anticancer drugs or regimens in a variety of tumour cell lines. Used alone, the inhibitor was particularly cytotoxic against cell lines representing lymphoid malignancies and small-cell lung carcinoma (SCLC).

Cancers of the lymphatic system are often a result of defective apoptosis, commonly through a chromosomal translocation that results in overexpression of the *BCL2* gene, so it is promising that when tested in a follicular lymphoma translocation-containing cell line, and patient-derived primary lymphoma and leukaemia cells, ABT-737 induced concentration-dependent apoptosis. The authors speculate that the activity of ABT-737 against SCLC cells might also show potential for treating solid tumours. To study this further they tested the compound on established SCLC tumour xenografts in mice and observed complete regression and a low incidence of tumour recurrence for the duration of the study.

For cancer patients, the discovery of ABT-737 as a novel drug candidate holds promise for the development of a new class of cancer treatments that target defective apoptosis. For drug discoverers, it is also a fine example of how NMR can be used to turn a low-affinity ligand for a difficult target into a potent, cytotoxic compound — literally performing drug discovery by design.

Joanna Owens

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