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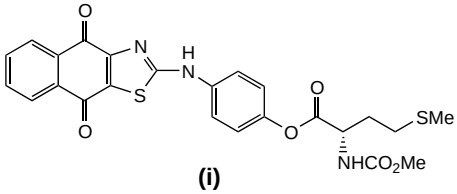
monitor

MOLECULES

Selective induction of apoptosis in Bcl-2-expressing breast cancer cells

Evasion of apoptosis is one of the fundamental 'hallmarks of cancer' [1], and aberrant regulation of apoptotic cell death is well-known to contribute to both tumour development and reduced sensitivity to chemotherapeutic agents. The Bcl-2 family, comprising both anti- and pro-apoptotic proteins, have important roles in caspase and apoptosis regulation, with high expression of the anti-apoptotic protein Bcl-2 being associated with a number of malignancies [2]. Inhibition of Bcl-2 or related anti-apoptotic proteins has been pursued as a strategy to either induce apoptosis in cancer cells or to sensitize these cells to chemotherapy; for example, the induction of apoptosis in a range of tumour cells has been demonstrated following administration of a Bcl-2 antisense oligonucleotide [3].

Structural analysis of the Bcl-2 protein [4] has facilitated the identification of small molecules that inhibit the interaction between the BH3 domain of pro-apoptotic proteins and the hydrophobic cleft of Bcl-2 or Bcl-x_L [5], and some of these compounds do have antitumour properties suggestive of therapeutic utility. However, the effect of Bcl-2-targeting agents on normal cells such as haematopoietic progenitors and epithelial cells has not previously been examined. Real *et al.* have recently reported the discovery of a new small molecule inhibitor of Bcl-2 [YC137; **(i)**] that induces apoptosis in breast cancer cell lines expressing high levels of Bcl-2 (e.g. MB435B and SUM159), by inhibiting the binding of Bid BH3 peptide to Bcl-2 [6]. Notably, the apoptotic response to YC137 was found to correlate with expression levels of Bcl-2 protein in a range of breast cancer cell lines. In contrast, various normal primary cells (e.g. $CD34^+$ progenitors, myoblasts and peripheral blood mononuclear cells) were found to be insensitive to YC137.



(i)

In vitro selection of cancer cells refractory to YC137 through generation of a YC137-resistant breast cancer cell line revealed reduced expression of Bcl-2, correlating with low activation of signal transducer and activator of transcription-3 (STAT3) and reduced expression of the human epidermal growth factor receptor-2 (HER2). Interestingly, YC137-resistant MB435B cells were found to be more sensitive to chemotherapy-induced apoptosis (paclitaxel or adriamycin). The elegance of this study lies in the selective killing of tumour cells expressing high levels of Bcl-2 through a small molecule Bcl-2 inhibitor, and in the enhanced susceptibility of resistant cells to conventional chemotherapy, suggesting a promising future avenue for rational combination treatments in the clinic.

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MOLECULAR BIOLOGY

The NMR structure of a DNA-quadruplex inhibitor of HIV-1 integrase

HIV-1 integrase catalyses the integration of viral DNA into the host's genome and is essential for the lifecycle of HIV, making it a

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