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bcl-2: a convergence point for multiple signal transduction pathways that influence cell survival?

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Keywords

bcl-2, breast cancer, cell survival, mcl-1, signal transduction inhibitors

Context

Members of the bcl-2 family of proteins, such as bcl-2 and mcl-1, have been implicated in controlling cell survival in many normal and neoplastic cells in a tissue-specific manner. Delineating those family members of relevance to breast cancer and manipulation of their regulatory signalling pathways is therapeutically attractive. The aim of this study, performed in MCF-7 human breast cancer cells, was to determine whether inhibition of protein tyrosine kinase, protein kinase C, phosphatidylinositol 3-kinase or mitogen-activated protein kinase kinase (MEK) signal transduction influences expression of bcl-2 or mcl-1, monitoring cytotoxicity in parallel.

Significant findings

The authors observed that, while there were only limited changes in mcl-1, the examined signal transduction inhibitors (i.e. genistein, staurosporine, LY294002 and U0126) downregulated bcl-2 protein expression in a dose-dependent manner. In parallel, such agents were highly growth inhibitory, arresting cell cycle and increasing cell death. Synergistic cytotoxic activity was observed between the MEK inhibitor UO126 and other agents. The authors concluded that bcl-2, in contrast to mcl-1, plays a predominant role in the control of cell survival by diverse signal transduction pathways in MCF-7 cells.

Comments

This study has clearly demonstrated that bcl-2 downregulation results from inhibition of protein tyrosine kinase, protein kinase C, phosphatidylinositol 3-kinase and MEK signalling in MCF-7 breast cancer cells *in vitro*. These effects were not noted for mcl-1, and it is interesting that a lack of association between this protein and apoptosis has also recently been reported in clinical breast cancer (see Additional information). Changes in bcl-2 expression closely parallel the growth inhibitory effects of the examined signal transduction inhibitors; nevertheless, the data in the present study remain correlative since the authors do not address whether it is this modulation that is causative of the cytotoxicity. Antisense studies should clarify this issue. Moreover, it should be remembered that this study has addressed bcl-2 and mcl-1 in the MCF-7 cell line alone and results may not be entirely representative of breast cancer in general. Nevertheless, the data are certainly encouraging and indicate the likelihood that these signal transduction inhibitors will join the increasing battery of agents (including antihormones and chemotherapy) that induce cell death via their modulation of bcl-2 expression. Such data further confirm the pivotal role for the bcl-2 protein in the control of cell survival by multiple pathways in breast cancer, and moreover advocate its utility as a therapeutic target.

Methods

Cell culture, MTT assay, flow cytometry, annexin V-FITC, TUNEL, DAPI, western blot

Additional information

Rochaix P, Krajewski S, Reed JC, Bonnet F, Voigt JJ, Brousset P: ***In vivo* patterns of Bcl-2 family protein expression in breast carcinomas in relation to apoptosis.** *J Pathol* 1999 **187**:410-415.

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