LETTER TO THE EDITOR

Nimbolide inhibits invasion of breast cancer

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Dear Editor,

With great interest I read the recent article in *Cell Proliferation* by Elumalai *et al.* (1). They showed that nimbolide inhibited invasion of breast cancer cells. Cancer chemo-preventative and therapeutic activities of nimbolide, a constituent of neem, have been extensively studied over the past few years in a variety of cancer cell lines and animal models (2).

For instance, nimbolide induces expression of Bax and Bad in breast cancer cells, while reducing the levels of Bcl-2 and Bcl-xL (3). A similar pattern of modulation of Bcl-2 family proteins has also been observed with nimbolide upon exposure to cervical cancer cells (4) and choriocarcinoma cells (5). Nimbolide also induces both G0/G1 and G2/M arrest in colon cancer cells accompanied by alterations in cyclins, CKIs and CDKs (6). In addition, nimbolide targets G2/M cell cycle checkpoint proteins, CHK2 and Rad17 (6). Although detailed mechanisms are unknown, nimbolide disrupts cell cycle progression, and thus inhibits proliferation of melanoma, leukaemia and lymphoma cells (7).

In addition to its anti-cancer properties as single agent, nimbolide has also been reported to possess additive or synergistic tumour killing activity in combination with different cytotoxic agents such as TNF- α , TRAIL and chemotherapeutic drugs. For example, cytotoxic and apoptotic inducing effects of TNF- α and chemotherapeutic drugs such as 5-FU and thalidomide have been shown to be enhanced by suppression of the IKK-induced NF- κ B pathway (8). More importantly, combined treatment of nimbolide with TRAIL has been indicated to synergize to induce apoptosis in different tumour cell lines, but not in normal breast cells, indicating tumour-specific cytotoxicity (9). As NF- κ B is a positive regulator of tumourigenic protein expression, NF- κ B suppression is associated with reduced transcription of Bcl-2, Bcl-xL, IAP-1, IAP-2, survivin, Mcl-1, c-Myc, cyclin D1, MMP 9, CXCR4, ICAM-1 and VEGF (8,10,11). Collectively, all these mediate effects of nimbolide on cell functions such as apoptosis, proliferation, cell migration and angiogenesis.

Consistent with these molecular events in cancer cell lines, nimbolide has also been proven to suppress tumour growth *in vivo* in animal studies. Nimbolide reduces growth of inoculated colon cancer xenografts (11), DMBA induced buccal pouch (12) and DMBA induced oral (13) carcinogenesis in the hamster, through mechanisms including induction of apoptosis, inhibition of angiogenesis, suppression of proliferation and reduction in oxidative stress.

The above examples clearly demonstrate the significant anti-neoplastic activity of nimbolide. Further research is required to completely explore its anti-tumour effects in other cancers and also further assess and evaluate its safety in humans.

Conflict of interest

None declared.

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