

## **Sulforaphane: a naturally occurring mammary carcinoma mitotic inhibitor which disrupts tubulin polymerization.**

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Sulforaphane (SUL), an isothiocyanate found in broccoli and other cruciferous vegetables, has been shown to induce phase II detoxification enzymes, inhibit chemically-induced mammary tumors in rats, and more recently to induce cell cycle arrest and apoptosis in cancer cells of the colon. Here, we provide evidence that SUL also acts as a breast cancer antiproliferative agent. The BALB/c mouse mammary carcinoma cell line F3II was treated with SUL at concentrations up to 15 micro M and examined for markers of cell cycle arrest and apoptosis. Treatment of asynchronous F3II cells with 15 micro M SUL resulted in G2/M cell cycle arrest, elevated p34(cdc2) (cdc2) kinase activity, Bcl-2 downregulation, evidence of caspase activation, and aggregation of condensed nuclear chromatin. Subsequent exposure of synchronized cells to 15 micro M SUL resulted in elevated numbers of prophase/prometaphase mitotic figures, indicating cell cycle progression beyond G2 and arrest early within mitosis. Moreover, cells treated with 15 micro M SUL displayed aberrant mitotic spindles, and higher doses of SUL inhibited tubulin polymerization in vitro. In addition, BALB/c mice injected s.c. with F3II cells and subsequently injected daily i.v. with SUL (15 nmol/day for 13 days) developed significantly smaller tumors (approximately 60% less in mass) than vehicle-treated controls. Western blot analysis of tumor proteins demonstrated significantly ( $P < 0.05$ ) reduced PCNA and elevated PARP fragmentation in samples from animals dosed with SUL. Taken together, these results indicate that SUL has mammary cancer suppressive actions both in cell culture and in the whole animal. Inhibition of mammary carcinogenesis appears in part to involve perturbation of mitotic microtubules and early M-phase block associated with cdc2 kinase activation, indicating that cells arrest prior to metaphase exit.