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d-δ-Tocotrienol-mediated suppression of the proliferation of human PANC-1, MIA PaCa-2, and BxPC-3 pancreatic carcinoma cells.

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Abstract

OBJECTIVE:

The rate-limiting activity of the mevalonate pathway, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, provides intermediates essential for growth. Competitive inhibitors of HMG CoA reductase, such as the statins, and down-regulators of reductase, such as the tocotrienols, suppress tumor growth. We evaluated the impact of d-delta-tocotrienol, the most potent vitamin E isomer, on human MIA PaCa-2 and PANC-1 pancreatic carcinoma cells and BxPC-3 pancreatic ductal adenocarcinoma cells.

METHODS:

Cell proliferation was measured by using CellTiter 96 Aqueous One Solution (Promega, Madison, Wis). Cell cycle distribution was determined by flow cytometry. Apoptosis was evaluated by Annexin V staining and fluorescence microscopy after dual staining with acridine orange and ethidium bromide.

RESULTS:

d-delta-Tocotrienol induced concentration-dependent suppression of cell proliferation with 50% inhibitory concentrations of 28 (6) micromol/L (MIA PaCa-2), 35 (7) micromol/L (PANC-1), and 35 (8) microL (BxPC-3), respectively. These effects are attributable to cell cycle arrest at the G1 phase and apoptosis. Mevalonate attenuated d-delta-tocotrienol-mediated growth inhibition. A physiologically attainable blend of d-delta-tocotrienol and lovastatin synergistically suppressed the proliferation of MIA PaCa-2 cells.

CONCLUSIONS:

Suppression of mevalonate pathway activities, be it by modulators of HMG CoA reductase (statins, tocotrienols, and farnesol), farnesyl transferase (farnesyl transferase inhibitors),

and/or mevalonate pyrophosphate decarboxylase (phenylacetate) activity, may have a potential in pancreatic cancer chemotherapy.