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Cytotoxicity of unsaturated fatty acids in fresh human tumor explants: concentration thresholds and implications for clinical efficacy.

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Abstract

BACKGROUND: Unsaturated fatty acids (UFAs) exhibit in vitro cytotoxicity against many malignant cell lines and yield decreased cancer incidence and reduced tumor growth in animal models. But clinical and animal studies to date have achieved response using only localized delivery methods such as intratumoral infusion. To explore possibilities for enhanced clinical efficacy, fresh surgical explants of tumors from 22 patients with five malignancies were exposed to gamma-linolenic acid (GLA) and alpha-linolenic acid (ALA) and analyzed with an in vitro chemosensitivity testing system, the Fluorescent Cytoprint Assay (FCA). A total of 282 micro-organ cultures derived from these malignant tumors were exposed to GLA and ALA at different concentrations.

RESULTS: GLA and ALA exhibited greater than 90% cytotoxicity at a sharp concentration threshold between 500 microM and 1 mM against all but two malignant micro-organ cultures tested in 5-10% serum. In tests using 30-40% serum, GLA and ALA killed tumor at concentrations of 2 mM and above.

CONCLUSIONS: The concentration threshold of 500 microM to 2 mM exhibited for antitumor activity by GLA and ALA is much higher than that observed in most previously reported cell culture studies but consistent with physiological concentrations found to kill tumor clinically and in animals. A mechanism of antitumor activity by unsaturated fatty acids through selective destabilization of the malignant plasma membrane is considered. An oral regimen is proposed for phase I clinical testing that could push the area under the curve for serum concentration of unbound unsaturated fatty acids over time to much higher levels than previously achieved for systemic administration and into the range that could yield antitumor response.

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