Inhibition of fatty acid synthase-dependent neoplastic lipogenesis as the mechanism of gamma-linolenic acid-induced toxicity to tumor cells: an extension to Nwankwo's hypothesis.

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Source

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Abstract >>> FAS = FASN

Gamma-linolenic acid (GLA), an essential omega-6 polyunsaturated fatty acid (FA) is an attractive concept as anticancer agent because it exerts selective cytotoxic on human breast cancer cells without affecting normal cells. This selective toxicity has been identified to be due, at least in part, to the production of lipid peroxides and free radicals. Interestingly, a novel hypothesis for GLA-induced tumor cell toxicity has recently been proposed. GLA, through a molecular mechanism involving the lipogenic enzyme fatty acid synthase (FAS), coordinately interrupts the pathways that replenish the pools of metabolic intermediates in the citric acid cycle (cellular anaplerosis). First, supraphysiological concentrations of GLA inhibit glycolysis, while a cytochrome P450-dependent epoxidation of GLA generates epoxides metabolites for GLA that would mimic the inhibitory action of standard FAS inhibitors such as cerulenin and C75. Second, GLA-epoxide inhibits FASN activity, thus resulting in the accumulation of cytosolic malonyl-CoA which, in turn, inhibits carnitine palmitoyl transferase I (CPT-I) and prevents FA oxidation. The recent characterization of GLA as a novel regulator of FASN expression in breast cancer cells supports and further expands this hypothesis, and directly involves FASN-dependent de novo fatty acid synthesis as the mechanism of GLA-induced toxicity to tumor cells. We hypothesize that, at low (physiological) concentrations, the inhibitory effect of GLA on FAS-regulated breast cancer cell survival is not specific and is due to cell toxicity caused by lipid peroxidation. Taking into account that the inhibitory effect of FAs on the expression of FASN in cultured
hepatocytes has been shown to be related to a non-specific peroxidative mechanism, a similar GLA-dependent FASN regulatory mechanism involving peroxidative products may occur in normal and neoplastic tissues. At high (supraphysiological) concentrations of GLA, the specific downregulation of FAS gene expression leads to accumulation of the substrate for FAS, malonyl-CoA, that, as a result of FAS blockade, continue to be generated by the rate-limiting enzyme of the fatty acid biosynthetic pathway acetyl-CoA carboxilase, which is not inhibited in the absence of FAS-catalyzed long chain endogenous fatty acids. Physiologically, the elevated levels of malonyl-CoA occurring during FA biosynthesis reduce FA oxidation to prevent a futile cycle of simultaneous FA synthesis and degradation. Paradoxically, high-dose GLA treatments of FAS-overexpressing breast cancer cells will promote malonyl-CoA-induced inhibition of CPT-I and FA oxidation, thus precipitating an energy crisis that triggers decreased proliferation or apoptotic cell death. In summary, this working model presents the concept that the breast cancer adaptation in FASN expression can be exploited to develop GLA-based dietary interventions aimed at altering the FASN synthesis pathway, which appears to be linked to neoplastic transformation and is associated with tumor virulence and adverse clinical outcome in a subset of human breast carcinomas.

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