Non-Tumorigenic Melanocyte Cell Death Induced by Fatty Acid Synthase Inhibitors

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Fatty acid synthase (FASN) is the anabolic enzyme responsible for the endogenous synthesis of saturated fatty acid palmitate from acetyl-CoA and malonyl-CoA. In contrast to most normal cells, malignant cells depend on FASN activity for growth and survival. FASN is overexpressed in a variety of human cancers including cutaneous melanoma, in which its levels of expression are associated with a poor prognosis and depth of invasion. We have previously shown that the specific inhibition of FASN activity by orlistat significantly reduces proliferation and promotes apoptosis in the mouse metastatic melanoma cell line B16-F10. However, the toxicity of FASN inhibitors in normal cells are not well known. Here we investigated the effects of FASN inhibitors in non-tumorigenic melanocytes, melan-a. FASN inhibitors cerulenin or orlistat induced cell death mainly by apoptosis, which was preceded by caspase-3 activation. These effects were attained with cerulenin and orlistat concentrations 50% and 10%, respectively, of those necessary to induce apoptosis in tumor cells. Cerulenin, but not orlistat, significantly reduced melan-a cell proliferation as evidenced by a decreased number of cells in S phase. In contrast to the mechanism of tumor cells death mediated by oxidative stress no redox changes were observed either in mitochondria or cytosol from melan-a cells. In addition, apoptosis in melan-a cells did not require the involvement of the tumor suppressor protein p53, as observed in melanoma cells. Together these findings suggest that non-tumorigenic cells are more sensitive to FASN inhibitors and show different apoptotic pathways than tumor cells.

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