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Long chain fatty acid analogs suppress breast tumorigenesis and progression.

Gluschnaider U[1], Hertz R[1], Ohayon S[1], Smeir E[1], Smets M[2], Pikarsky E[3], Bar-Tana J[4].

Author information

Abstract

Obesity and type 2 diabetes (T2D) are associated with increased breast **cancer** incidence and mortality, whereas carbohydrate-restricted **ketogenic** diets ameliorate T2D and suppress breast **cancer**. These observations suggest an inherent efficacy of nonesterified long-chain fatty acids (LCFA) in suppressing T2D and breast tumorigenesis. In this study, we investigated novel anti-diabetic MEDICA analogs consisting of methyl-substituted LCFA that are neither β-oxidized nor esterified to generate lipids, prompting interest in their potential efficacy as anti-tumor agents in the context of breast **cancer**. In the MMTV-PyMT oncomouse model of breast **cancer**, where we confirmed that tumor growth could be suppressed by a carbohydrate-restricted **ketogenic** diet, MEDICA treatment suppressed tumor growth and lung metastasis, promoting a differentiated phenotype while suppressing mesenchymal markers. In human breast **cancer** cells, MEDICA treatment attenuated signaling through the STAT3 and c-Src transduction pathways. Mechanistic investigations suggested that MEDICA suppressed c-Src transforming activity by elevating ROS production, resulting in c-Src oxidation and oligomerization. Our findings suggest that MEDICA analogs may offer therapeutic potential in breast **cancer** and overcome the poor compliance of patients to dietary carbohydrate restriction.

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