

Abstract

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Gamma-tocotrienol induced apoptosis is associated with unfolded protein response in human breast cancer cells.

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BACKGROUND: Gamma-tocotrienol (γ -T3) is a member of the vitamin E family. Tocotrienols (T3s) are powerful antioxidants and possess anticancer, neuroprotective and cholesterol-lowering properties. Tocotrienols inhibit the growth of various cancer cell lines without affecting normal cells. Less is known about the exact mechanisms of action of T3s on cell death and other growth inhibitory pathways.

OBJECTIVE AND METHODS: In the present study, we demonstrate that γ -T3 induces apoptosis in MDA-MB 231 and MCF-7 breast cancer cells as evident by PARP cleavage and caspase-7 activation.

RESULTS: Gene expression analysis of MCF-7 cells treated with γ -T3 revealed alterations in the expression of multiple genes involved in cell growth and proliferation, cell death, cell cycle, cellular development, cellular movement and gene expression. Further analysis of differentially modulated genes using Ingenuity Pathway Analysis software suggested modulation of canonical signal transduction or metabolic pathways such as NRF-2-mediated oxidative stress response, TGF- β signaling and endoplasmic reticulum (ER) stress response. Analysis of ER-stress-related proteins in MCF-7 and MDA-MB 231 cells treated with γ -T3 demonstrated activation of PERK and pIRE1 α pathway to induce ER stress. Activating transcription factor 3 (ATF3) was identified as the most up-regulated gene (16.8-fold) in response to γ -T3. Activating transcription factor 3 knockdown using siRNA suggested an essential role of ATF3 in γ -T3-induced apoptosis.

CONCLUSION: In summary, we demonstrate that γ -T3 modulates ER stress signaling and have identified ATF3 as a molecular target for γ -T3 in breast cancer cells.

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