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Vitamin E gamma-tocotrienol induces death of cancer cells by altering sphingolipids via inhibition of dihydroceramide desaturase

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Gamma-tocotrienol (γTE) is a vitamin E form rich in palm oil. Gamma-tocotrienol has been shown to be stronger than vitamin E tocopherols in inducing death of cancer cells, and therefore proposed to be a potentially useful chemopreventive agent. However, mechanisms underlying these actions are not clear. Here using liquid chromatography tandem mass spectrometry, we show that γTE induced marked changes of sphingolipids including rapid elevation of dihydrosphingosine and dihydroceramides (dhCers) in various types of cancer cells. The elevation of dihydrosphingolipids coincided with increased cellular stress, as indicated by JNK phosphorylation, and was prior to any sign of induction of apoptosis. Chemically blocking *de novo* synthesis of sphingolipids partially counteracted γTE-induced apoptosis and autophagy. Experiments using $^{13}C_3$, ^{15}N-labeled L-serine together with enzyme assays indicate that γTE inhibited cellular dihydroceramide desaturase (DEGS) activity without affecting its protein expression or *de novo synthesis* of sphingolipids. Unlike the effect on dhCers, γTE decreased ceramides (Cers) after 8 h treatment, but increased $C_{18:0}$-Cer and $C_{16:0}$-Cer after 16 and 24 h, respectively. The increase of Cers coincides with γTE-induced apoptosis and autophagy. Since γTE inhibits DEGS and decreases *de novo* Cer synthesis, elevation of Cers during prolonged γTE treatment is likely caused by sphingomeylinase-mediated hydrolysis of sphingomyelin. This idea is supported by the observation that an acid sphingomeylinase inhibitor partially reversed γTE-induced cell death. Our study demonstrates that γTE altered sphingolipid metabolism by inhibiting DEGS activity and possibly by activating SM hydrolysis during prolonged treatment in cancer cells.

Biography

Dr. Jiang is a Professor in the Department of Nutrition Science at Purdue University. Her research has focused on different forms of vitamin E and novel vitamin E metabolites, long-chain carboxychromanols, with respect to their anti-inflammatory and anticancer activities. Her lab has identified new vitamin E metabolites and novel bioactivities, and developed various analytical methods for quantifying vitamin E metabolites. Dr. Jiang has authored in 48 publications and obtained three patents. She is a member of the editorial board of Journal of Nutritional Biochemistry. She has served as a reviewer in study sections of NIH and USDA as well as numerous scientific journals. She is a recipient of E.L.R. Stokstad Award for outstanding fundamental research in nutrition from American Society for Nutrition and University Faculty Scholar Award from Purdue University.

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