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**Id1, inhibitor of differentiation, is a key protein mediating anti-tumor responses of gamma-tocotrienol in breast cancer cells**

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**Background:** Gamma-tocotrienol has demonstrated anti-proliferative effect on breast cancer (BCa) cells, but mechanisms involved are largely unknown. This study aimed at deciphering the molecular pathways responsible for its activity.

**Methods:** MTT cell proliferation, DNA fragmentation and flow cytometry were performed to investigate gamma-tocotrienol induced cell cytotoxicity and cell cycle arrest. Western blotting was used for characterizing multiple-signaling pathways of  $\gamma$ -tocotrienol treated breast cancer cells. Docetaxel, the compound that able to provide a significant survival advantage in metastatic BCa, was used in the chemosensitization studies.

**Results:** Our results showed that treatment of BCa cells with gamma-tocotrienol resulted in induction of apoptosis as evidenced by activation of pro-caspases (cleaved caspase-3, -7, -8, -9 and cleaved PARP), accumulation of sub-G1 cells and DNA fragmentations. Examination of the pro-survival genes revealed that the gamma-tocotrienol-induced cell death was associated with suppression of Id1 and NF- $\kappa$ B through modulation of their upstream regulators (Src, Smad1/5/8, Fak and LOX). Meanwhile, gamma-tocotrienol treatment also resulted in the induction of JNK signaling pathway and inhibition of JNK activity by specific inhibitor partially blocked the effect of gamma-tocotrienol. Furthermore, synergistic effect was observed when cells were co-treated with gamma-tocotrienol and Docetaxel. Interestingly, in cells that treated with gamma-tocotrienol, alpha-tocopherol or  $\beta$ -aminopropionitrile were found to partially restore Id1 expression. Meanwhile, this restoration of Id1 was found to protect the cells from gamma-tocotrienol induced apoptosis. Consistent outcome was observed in cells ectopically transfected with the Id-1 gene.

**Conclusion:** Our results suggested that the anti-proliferative and chemosensitization effect of gamma-tocotrienol on BCa cells may be mediated through downregulation of Id1 protein.