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γ -TOCOTRIENOL PROTECTS AGAINST HYDROGEN PEROXIDE-INDUCED REPLICATIVE SENESCENCE BY REGULATING APOPTOTIC PATHWAY AND MODULATING TELOMERASE ACTIVITY

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Background:

Oxidative stress has been shown to be associated with apoptosis (programmed cell death) in a number of cell systems. Apoptosis is controlled by a diverse range of intracellular signaling that regulates genes and proteins such as apoptotic and anti-apoptotic molecules. Besides, oxidative stress also resulted in telomere shortening and progressive reduction of telomerase activity leading to cellular senescence. Vitamin E has revealed many important molecular properties, such as scavenging free radicals, modulating signal transduction in antioxidant and non-antioxidant manners and plays a role in regulating apoptosis. In this study, we developed H₂O₂-induced premature senescence model of human skin fibroblasts to investigate the protection of γ -tocotrienol against cellular senescence.

Materials and Methods:

Primary human diploid fibroblasts derived from circumcision foreskins were cultured until passage 4 and were treated with 1 μ M γ -tocotrienol. Exposure to 20 μ M H₂O₂ was carried out for two weeks to induce replicative senescence. Real time RT-PCR was performed to determine the expression of pro-apoptotic genes (*Bax* and *Bid*) and anti-apoptotic genes (*Bcl-2* and *Bcl-xL*). Proteins expression of Bax and Bcl-2 was determined by Western blotting. Telomerase activity was detected using telomeric repeat amplification protocol (TRAP) while telomere length was determined by Southern Blotting.

Results:

Exposure to H₂O₂ up regulated *Bax* and increased its protein expression, decreased Bcl-2 protein expression, shortened telomere length and reduced telomerase activity in HDFs ($p < 0.05$). While, treatment with γ -tocotrienol was found to down regulate *Bax* and increased telomerase activity in H₂O₂-induced cells ($p < 0.05$).

Conclusion:

Our data suggested that γ -tocotrienol inhibited the progression of apoptosis as evidenced by inhibition of *Bax* expression. γ -Tocotrienol also showed protection against telomerase activity loss in H₂O₂-induced cells. This finding revealed the molecular mechanism of γ -tocotrienol in preventing H₂O₂-induced replicative senescence in human diploid fibroblasts.

Keywords:

γ -Tocotrienol, apoptosis, telomerase, fibroblasts, aging