Molecular mechanisms of econazole-induced toxicity on human colon cancer cells:G0/G1 cell cycle arrest and caspase 8-independent apoptotic signaling pathways.

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摘要

Abstract

Econazole (Eco), a potent broad-spectrum anti-fungal agent, has been used in the treatment of superficial mycosis. Eco is a store-operated Ca2+ channel antagonist which induces cytotoxic cell death of leukemia. However, little is known about its cytotoxic effect upon solid tumor cells. The purpose of this study is to investigate both the in vitro and in vivo molecular mechanisms of Eco-induced toxicity on colon cancer cells. We used COLO 205 cell line and nude mice xenograft model to investigate the cytotoxic effect of Eco. We demonstrated that lower doses Eco (5-20 μM) arrested human colon cancer cells at the G0/G1 phase of the cell cycle. The protein levels of p53, p21/Cipl, and p27/Kipl were significantly elevated while CDK2 and CDK4 kinase activity were significantly suppressed by Eco treatment in COLO 205 cells. At higher doses (40-60 μM), Eco induced COLO 205 cells apoptosis evidenced by ladder formation in DNA fragmentation assay and sub-Gl peak in flow cytometry analysis. Western blot analysis showed that caspases 3, 9 but not 8 were activated by high dose Eco treatment to the COLO 205 cells accompanied with cytochrome c and apoptosis-inducing factor (AIF) translocation. Significant anti-tumorigenesis effect was further demonstrated in vivo by treating nude mice bearing COLO 205 tumor xenografts with Eco 50 mg/kg intraperitoneally. Our findings highlight the molecular mechanisms underlying the Eco-induced toxicity on colon cancer cells.

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