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Ketoconazole Induces Apoptosis through Induction of a Bax-signaling Pathway in Human Prostate Cancer Cell Lines

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ABSTRACT

Background. Ketoconazole (KT) has been registered in Taiwan for therapy of adults with dermatophyte infections of the skin and nails. Recent studies have demonstrated that KT can inhibit hepatic metastasis from a human pancreatic adenocarcinoma and reduce the incidence of pulmonary metastases in a nude mouse melanoma model. Our recent studies further demonstrated that KT induced apoptosis and arrested the cell cycle at the G0/G1 phase in various types of human cancer cells other than prostate cancer cells.

Aim. The specific aim of this study was to evaluate the molecular mechanisms and therapeutic potential of KT for prostate cancer. The apoptosis-associated protein levels were determined in KT- and mock-treated prostate cancer cells.

Methods. In this study, we determined whether KT, a widely used oral-antifungal agent, can inhibit proliferation of an androgen-dependent prostate cancer cell (LNCaP) and androgen-independent prostate cancer cell (PC-3) line. Both cell lines were used to investigate the mechanisms of KT-induced apoptosis.

Results. In androgen-dependent prostate cancer (LNCap) cells, DNA fragmentation analysis revealed that apoptosis was induced in a dose-dependent manner by ketoconazole treatment. Caspase 3 was activated, and its specific substrate, poly ADP-ribose polymerase, was degraded at 18-24 h after treatment with 40 μm M KT. Similar results were not found in androgen-independent prostate cancer (PC-3) cells. Dose-dependent experiments demonstrated that *Bax* gene expression was elevated in both of these cell lines.

Conclusions. Taken together, these results suggest that KT-induced cessation of prostate cancer cell proliferation may be due to the induction of apoptosis, which may be related to the existence of androgen receptors. Although the indirect effects of KT on hormone-dependent cancers have been investigated, our results indicate that additional mechanisms (induction of apoptosis and G0/G1 phase cell cycle arrest) are involved in the suppression of hormone-independent cancer cell growth. (N. Taipei J. Med. 2002;4:159-166)

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