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第一篇(已刊出)

Curcumin Enhances Cytotoxicity of Chemotherapeutic Agents in Prostate Cancer Cells by Inducing $p21^{WAF1/CIP1}$ and C/EBPβ Expressions and Suppressing NF-κB Activation

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BACKGROUND. The modulatory effects and molecular mechanisms of curcumin (CCM) on the cytotoxicity of chemotherapeutic agents to prostate cancer cells were explored.
METHODS. The combined effects of CCM and chemotherapeutic agents were examined by three different administration schedules (one concurrent and two sequential treatments) in two androgen-independent prostate cancer (AIPC) cells (PC-3 and DU145). Alteration of cell cycle progression, protein levels, and transcriptional activation in PC-3 cells were assayed by flow cytometry, Western blotting, and gel shift assay, respectively.
RESULTS. The combined effects of CCM → chemotherapeutic agent schedule showed the greatest synergistic cytotoxicity when compared to the other two schedules in both cells. CCM induced a significant G1 arrest in PC-3, which may be mediated by the induction of $p21^{WAF1/CIP1}$ and C/EBPβ. Moreover, CCM was able to inhibit both the constitutional and TNF-α-induced NF-κB activation in a time-dependent manner.
CONCLUSIONS. The incorporation of CCM into cytotoxic therapies may be a promising strategy for the treatment of AIPC. *Prostate 51: 211–218, 2002.* © 2002 Wiley-Liss, Inc.

KEY WORDS: **drug therapy; drug synergism; drug administration schedule; cell cycle; protein p53**

INTRODUCTION

Prostate cancer is one of the major life-threatening diseases in most Western countries. The incidence and mortality rates of prostate cancer have also rapidly increased in the past decade in Taiwan [1]. Although patients with metastatic prostate cancer can benefit from androgen-ablation therapy at the initial stage, most patients die of hormone-refractory prostate cancer (HRPC) in only few years. Salvage cytotoxic therapy has been notoriously related to significant morbidity with little, if any, survival benefit.

To improve treatment effects, many lines of research have focused on how to modulate various phenotypes of cancer cells. Recent studies have demonstrated that several factors may be responsible for uncontrolled progression of prostate cancer cells, such as activation of NF-κB [2], upregulation of IL-6-related signaling pathways [3], and protein kinase C activation [4]. Agents that are able to modulate these

Abbreviations: HRPC, hormone-refractory prostate cancer; CCM, curcumin; 5-FU, 5-fluorouracil; C/EBPβ, CCAAT/enhancer binding protein β; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor B; Fa, fraction affected; CI, combination index

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第二篇(已接受)

Enhanced suppression of prostate tumor growth by combining C-CAM1 gene therapy and angiogenesis inhibitor TNP-470

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Abbreviated title: Combining C-CAM1 and TNP-470 for Prostate Cancer

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ABSTRACT

We have previously shown that C-CAM1-based gene therapy effectively suppressed prostate tumor growth in nude mice xenograft models. In this study, we examined the effects of combining C-CAM1-based therapy and TNP-470, a potent angiogenesis inhibitor, on prostate cancer in a xenografted tumor model. The direct cytotoxic effects of Ad-C-CAM1 (recombinant adenovirus containing C-CAM1 cDNA) and TNP-470 on DU145 cells *in vitro* were determined by microculture tetrazolium assay. The *in vivo* anti-tumor effects of either agent alone were studied in a DU145 xenografted tumor model. Cells were infected with Ad-C-CAM1 or the control virus at multiplicities of infection (MOI) of 5 or 10 and then inoculated onto nude mice 48 h later. TNP-470 (0, 17 or 35 mg/kg) was given 15, 17, and 19 days after inoculation. Combined treatments *in vivo* were carried out to determine whether there were synergistic anti-tumor effects. Both Ad-C-CAM1 and the control virus were minimally toxic to DU145 *in vitro*. There was evident dose-dependent suppression of xenografted tumor growth by either Ad-C-CAM1 or TNP-470. By the median-effect analysis, combination of the two agents generated strong synergistic anti-tumor effects as shown by marked tumor suppression as compared to either treatment alone. The novel strategy may have clinical implications for the treatment of prostate cancer.

Key words: cell adhesion molecule; tumor suppressor; gene therapy; xenograft; prostatic neoplasms

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Interleukin-6 is Responsible for Drug Resistance and Anti-apoptotic Effects in Prostatic Cancer Cells

預投稿至"Prostate"

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ABSTRACT

BACKGROUND. We investigate the role of IL-6-meadiated anti-apoptotic behavior in human prostate cancer cells.

METHODS. ELISA, Western blot, DNA fragmentation assay, ELISA-based cell death assay, IL-6-specific antisense reaction, RT-PCR and cell transfection assay were used to explore the IL-6 levels, anti-cancer drug-mediated apoptosis, protein levels and mRNA levels in prostate cancer cells respectively.

RESULTS. We have demonstrated that exogenous IL-6 conferred serum-starved PC-3 cells resistance to apoptosis induced by anti-cancer drugs and IL-6 specific antisense oligonucleotide treatment. Closely examining the levels of Bcl-2 family members in serum-starved PC-3 cells revealed that Bcl-xL protein is increased by IL-6 stimulation. The abolishing endogenous STAT3 activity by dominant-negative mutants of STAT3 in PC-3 cells partially blocked IL-6-mediated anti-apoptotic effect.

CONCLUSIONS. This study is first to demonstrate IL-6 is as an anti-apoptotic effect for anti-cancer drugs-mediated apoptosis in human prostate cancer cells through up-regulation of *bcl-xL* in a STAT3-independent pathway.

Key Words: **anti-cancer drugs; apoptosis; prostatic neoplasms; Bcl-xL; STAT3**