Cyclin-dependent kinase inhibitor p21 is a crucial molecular target for the potential antitumor efficacy of the dietary isothiocyanate erucin against prostate cancer

Short Title:
p21 upregulation by erucin

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Abstract:
It is becoming increasingly clear that many dietary agents, such as isothiocyanates (ITCs) from cruciferous vegetables, can retard or prevent the process of prostate carcinogenesis by multiple mechanisms \cite{1, 2}. Erucin (ER) is a dietary isothiocyanate present in cruciferous vegetables, which has been recently considered a new promising cancer chemopreventive phytochemical \cite{2}. In this study, the potential protective activity of ER against prostate cancer was investigated using two different human prostatic cell lines, normal prostate epithelium (PNT1A) and prostate adenocarcinoma cells (PC3), in order to analyze its effects on molecular pathways involved in cell growth regulation, such as the cyclin-dependent kinase (CDKs) inhibitor p21\textsuperscript{WAF1/CIP1} (p21) pathway \cite{3}. We have shown for the first time that the isothiocyanate ER may up-regulate significantly p21 protein expression in a dose-dependent manner to inhibit the proliferation of human adenocarcinoma prostate PC3 cells. Compared to the structurally related sulforaphane (SF), a well-studied broccoli-derived ITC, the isothiocyanate ER showed lower potency in inhibiting proliferation of PC3 cells, as well as in modulating p21 protein expression. Several studies have showed that the tumor suppressor protein p53 plays a key role in cellular response to DNA damage leading to apoptosis in case of unrepaired DNA damage, or indirectly to the block of cell cycle progression by transactivating p21 \cite{4}. Because PC3 cells do not express functional p53, our data suggest that the up-regulation of p21 by ER occurs through a p53-independent pathway. Moreover, our results showed that ER and SF did not affect p21 protein levels in normal prostate epithelium PNT1A cells at all concentrations tested (0-25 µM). These preliminary data demonstrate that the above structurally related ITCs exert a specific action on oncogenic signalling pathways, such as p53/p21 pathways, that could explain the stronger cytotoxicity observed in cancer cells compared to non malignant cells. Although these dietary bioactive compounds have exhibited selectivity for oncogenically transformed cell lines, ITCs selectivity is an area of great interest that warrants further investigation.

Reference