AS4-1

Cancer chemopreventive effects of diallyl trisulfide derived from garlic

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Garlic has been widely used as a therapeutic agent as well as a spice for more than 2000 years. Besides its well-known cardioprotective effects, garlic is also considered to possess potential cancer preventive properties. Chemopreventive effects of garlic have been attributed to its oil-soluble sulfur ingredients, such as diallyl sulfide, diallyl disulfide, and diallyl trisulfide (DATS), but their underlying molecular mechanisms remain largely unresolved. In the present study, we have compared the effects of aforementioned allyl sulfides on the growth of cultured human breast carcinoma (MCF-7) cells. DATS inhibited the growth of MCF-7 cells to a greater extent than did the other allyl sulfides as determined by the MTT assay. DATS also induced apoptosis in MCF-7 cells, which was mediated through accumulation of reactive oxygen species with subsequent activation of JNK that catalyzes phosphorylation of Bcl-2 at Ser70. In another experiment, DATS prevented tumor formation in a mouse xenograft model. Aberrant upregulation of cyclooxygenase-2 (COX-2) has been frequently observed in several types of cancer cells and is considered as a molecular target for cancer chemoprevention. Topically applied DATS inhibited the 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced COX-2 expression in dorsal skin of female ICR mice. DATS inhibited the DNA binding activity of AP-1 which is one of key transcription factors regulating the inflammation and expression of COX-2. DATS inhibited TPA-induced phosphorylation of Akt and JNK, which are major MAPKs regulating AP-1. A pharmacologic Akt inhibitor LY294002 and a JNK inhibitor SP600125 abrogated the TPA-induced COX-2 expression, suggesting that suppression of COX-2 expression by DATS in TPA stimulated mouse skin is mediated by blocking the PI3K-Akt and JNK signaling. Topical application of DATS protected against mouse skin carcinogenesis induced by 7,12-dimethylbenz[a]anthracene plus TPA. In addition, DATS strongly inhibited DNA binding activity of NF-κB compared with other allyl sulfides in human mammary epithelial (MCF10A) cells treated with TPA. DATS inhibited the transcriptional activity of NF-κB, phosphorylation of IkBα, and activity of IKKβ. Inhibition of NF-κB DNA binding activity and IKKβ activity by DATS were blunted by addition of the antioxidant N-acetyl-L-cysteine (NAC) and the reducing agent dithiothreitol. Therefore, anti-inflammatory activity of DATS may be associated with oxidation or covalent modification of thiol groups contained in IKKβ.

AS4-2

The anti-cancer effects of pterostilbene in sensitive and nicotine-induced chemoresistant bladder cancer cells

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Cigarette smoke is a major risk factor for bladder cancer and contributes to chemoresistance in bladder cancer patients who continue to smoke while receiving chemotherapy. Nicotine has been implicated as a co-carcinogen that promotes lung cancer development through pro-survival pathways and is known to induce chemoresistance in some cancer cells through anti-apoptosis mechanisms. The aims of our study were to investigate the role of nicotine in inducing bladder cancer cells proliferation and chemoresistance. We found that transient nicotine stimulation activates Stat3/ERK1/2 leading to induction of Stat3 and NF-κB DNA binding activity, which is associated with cyclin D1 expression and cell proliferation in bladder cancer cell line T24 cells. Chronic nicotine exposure strongly activated Stat3 leading to cyclin D1 overexpression, cell cycle perturbations, and chemoresistance. Nicotine mobilized cell proliferation/chemoresistance is mainly mediated by Stat3 and its downstream signals via nicotinic acetylcholine receptor. We further found that pterostilbene effectively inhibits the growth of sensitive and nicotine-induced chemoresistant human bladder cancer cells by inducing necrosis, cell cycle arrest, autophagy and apoptosis. Pterostilbene-induced autophagy was triggered by the inhibition of AKT/mTOR/p70S6K pathway and activation of ERK1/2 pathway.

Key words: pterostilbene, bladder cancer, nicotine, chemoresistant, autophagy