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