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Anti-tumor activity of three ginsenoside derivatives in lung cancer is associated with Wnt/β-catenin signaling inhibition

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Numerous compounds isolated from Ginseng have been shown to exhibit various biological activities, including antioxidant, anti-carcinogenic, anti-mutagenic, and anti-tumor activities. Recent research has focused on the potential values of these compounds in the prevention and treatment of human cancers. The anti-tumor activity of 25-hydroxyprotopanaxadiol (25-OH-PPD), a natural compound isolated from Panax ginseng, has been established in previous study. In the current study, we investigated the anti-tumor activity of three derivatives of 25-OH-PPD, namely xl, 1c, and 8b with respect to lung cancer. All three compounds significantly inhibited the growth of the human lung cancer cells A549 and H460. Oral administration of these compounds significantly inhibited the growth of xenograft tumors in mice without affecting body weight. Further mechanistic study demonstrated that these compounds could decrease the expression levels of β-catenin and its downstream targets Cyclin D1, CDK4, and c-myc in lung cancer cells. Taken together, the results suggested that the anti-growth activity exerted by these 25-OH-PPD derivatives against lung cancer cells probably involved β-catenin-mediated signaling pathway, a finding that could have important implication for chemotherapeutic strategy aiming at the treatment of lung cancer.

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Pharmacological regulation of the tumor immuno environment

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The tumor microenvironment consist of a variable combination of tumor cells, stromal fibroblasts, endothelial cells and infiltrating leukocytes, such as macrophages, T lymphocytes, and Dendritic Cells (DC). Tumor progression is often associated with suppression or malfunction of the immune system, including the appearance of regulatory T cells and myeloid-derived suppressor cells, dysbalance of dendritic cell subsets and cytokine network, and polarization of Th1/Th2/Th3/Th17/Treg subsets and their balance. We have recently reported that antineoplastic chemotherapeutic agents could directly up-regulate development and functional activation of dendritic cells *in vitro* and *in vivo* if used in low nontoxic concentrations. Our new data revealed that low-dose nontoxic chemotherapy (or chemomodulation) increases resistance of dendritic cells to tumor-induced immunosuppression and converts suppressor dendritic cells into immunostimulatory cells. Furthermore, low-dose nontoxic chemotherapy down-regulated activity of myeloid-derived suppressor cells and regulatory T cells in the tumor microenvironment. Finally, antineoplastic chemotherapeutic agents in low, nontoxic concentrations blocked the ability of tumor cells to inhibit immune cell function. This effect was associated with increased expression of antigen-processing machinery components in tumor cells and, thus, increased immunogenicity of tumor cells. Together, these data suggest that the modulation of the tumor microenvironment by low-dose nontoxic chemotherapy – chemomodulation, - may serve as a powerful adjuvant for different immunotherapeutic modalities in cancer. In fact, application of low-dose chemotherapy prior to dendritic cell vaccines in the animal tumor models resulted in significant inhibition of primary and metastatic tumor growth *in vivo*. Thus, chemomodulation of the tumor environment with nontoxic doses of several common chemotherapeutic agents, including nanovehicle delivery of these agents, might target different cell populations, decrease tumor-induced immunosuppression, and improve the efficacy of modern vaccines for cancer therapy.

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