# Therapeutic efficacy and molecular mechanisms of snake (Walterinnesia aegyptia) venom-loaded silica nanoparticles in the treatment of breast cancer- and prostate cancer-bearing experimental mouse models.

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## Abstract:

The treatment of drug-resistant cancer is a clinical challenge, and thus screening for novel anticancer drugs is critically important. We recently demonstrated a strong enhancement of the antitumor activity of snake (Walterinnesia aegyptia) venom (WEV) in vitro in breast carcinoma, prostate cancer and multiple myeloma cell lines but not in normal cells when the venom was combined with silica nanoparticles (WEV+NP). In the present study, we investigated the in vivo therapeutic efficacy of WEV+NP in breast cancer- and prostate cancer-bearing experimental mouse models. Xenograft breast and prostate tumor mice models were randomized into 4 groups for each cancer model (10 mice per group) and were treated with vehicle (control), NP, WEV or WEV+NP daily for 28 days post tumor inoculation. The tumor volumes were monitored throughout the experiment. On day 28 post tumor inoculation, breast and prostate tumor cells were collected and either directly cultured for flow cytometry analysis or lysed for Western blot and ELISA analysis. Treatment with WEV+NP or WEV alone significantly reduced both breast and prostate tumor volumes compared to treatment with NP or vehicle alone. Compared to treatment with WEV alone, treatment of breast and prostate cancer cells with WEV+NP induced marked elevations in the levels of reactive oxygen species (ROS), hydroperoxide and nitric oxide; robust reductions in the levels of the chemokines CXCL9, CXCL10, CXCL12, CXCL13 and CXCL16 and decreased surface expression of their cognate chemokine receptors CXCR3, CXCR4, CXCR5 and CXCR6; and subsequent reductions in the chemokine-dependent migration of both breast and prostate cancer cells. Furthermore, we found that WEV+NP strongly inhibited insulin-like growth factor 1 (IGF-1)- and epidermal growth factor (EGF)-mediated proliferation of breast and prostate cancer cells, respectively, and enhanced the induction of apoptosis by increasing the activity of caspase-3,-8 and -9 in both breast and prostate cancer cells. In addition, treatment of breast and prostate cancer cells with WEV+NP or WEV alone revealed that the combination of WEV with NP robustly decreased the phosphorylation of AKT, ERK and I□B□; decreased the expression of cyclin D1, survivin and the anti-apoptotic Bcl-2 family members Bcl-2, Bcl-XL and Mcl-1; markedly increased the expression of cyclin B1 and the pro-apoptotic Bcl-2 family members Bak, Bax and Bim; altered the mitochondrial membrane potential; and subsequently sensitized tumor cells to growth arrest. Our data reveal the therapeutic potential of the nanoparticle-sustained delivery of snake venom against different cancer cell types.

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