J Cancer Sci Ther 2013, 5:10
http://dx.doi.org/10.4172/1948-5956.S1.030

OMICS Group Conferences
Accelerating Scientific Discovery

3rd World Congress on
Cancer Science & Therapy

October 21-23, 2013 DoubleTree by Hilton Hotel San Francisco Airport, CA, USA

Investigation of the antitumor activity of cisplatin loaded long-circulating and pH-sensitive liposomes in a breast cancer animal model

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Recent experimental data suggest that cisplatin (CDDP) may have an important role on triple negative breast cancer (TNBC) treatment. Besides the great antitumor efficacy of this anticancer agent, severe side effects and the possibility of resistance development limit the therapy. Previous studies of our research group have shown that the encapsulation of CDDP into long-circulating and pH-sensitive liposomes (SpHL-CDDP) was able to overcome cell resistance, reduce acute toxicity and enhance antitumor efficacy on Ehrlich tumor-bearing mice. Therefore, the purpose of this work was to develop a TNBC xenograft animal model, and evaluate the antitumor activity after SpHL-CDDP administration .

Firstly, Balb/c nude mice were inoculated with MDA-MB-231 cell line and the animals were divided into three groups when the tumor reached approximately 50 mm^3. The animals were treated, intravenously, once a week for three weeks with 0.9% (w/v) saline, free CDDP (cumulative dose equal to 30 mg/kg) or SpHL-CDDP (cumulative dose equal to 12 mg/kg). Tumor volume was monitored twice a week using a caliper. Body weight of all animals were also monitored at the same time frame.

Control group presented an increase of the tumor volume (573%) during the entire experimental time. This increase was statistically higher from that observed for treated groups. No statistically difference on tumor growth was observed when treated groups (free CDDP or SpHL-CDDP) were compared. However, animals treated with free CDDP were the only ones to present loss of weight (~13%) at the end of the experiment, while animals treated with SpHL-CDDP or 0.9% (w/v) saline presented a slight gain of weight (~2%).

Results indicate that higher concentration of free CDDP is needed to reach the antitumor efficacy attained after SpHL-CDDP treatment. In addition, animals of the free CDDP treated group showed loss of weight indicating the appearance of toxicity. These findings demonstrate that the encapsulation allows administration of lower concentration of the drug leading to the same antitumor efficacy together with lesser side effects. In summary, these results suggest that SpHL-CDDP may be useful on TNBC treatment.

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Suppression of FOXM1 sensitizes human cancer cells to cell death induced by DNA-damage and oxidative stress

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The oncogenic transcription factor Forkhead Box M1 (FOXM1), which is over expressed in a wide range of human cancers, was reported to protect cancer cells from the adverse effects of oxidative stress (via trans-activation of ROS scavengers) and DNA-damage. Oxidative stress and DNA-damaging chemotherapeutic agents are commonly used in anticancer treatments. Following oxidative stress or DNA damage FOXM1 protein levels are often elevated. In this study, we sought to investigate the potential role of FOXM1 in programmed cell death induced by DNA-damage and ROS inducers. Human cancer cells after FOXM1 suppression were subjected to doxorubicin or γ-irradiation treatment. Our findings indicate that FOXM1 downregulation by stable or transient knockdown by RNAi or by treatment with proteasome inhibitors that target FOXM1 strongly sensitized human cancer cells of different origin to DNA-damage induced apoptosis. We also show that RNAi-mediated knockdown of FOXM1 or treatment with proteasome inhibitors further elevated intracellular ROS levels and increased sensitivity of cancer cells to ROS-mediated cell. In addition, we show evidence that FOXM1/proteasome inhibitor bortezomib in combination with ROS inducer PEITC efficiently inhibited the growth of breast tumor xenografts in nude mice. We demonstrated that FOXM1 partially inhibits apoptosis by suppression of the activation of pro-apoptotic JNK and activation anti-apoptotic Bcl-2. Since FOXM1 is widely over-expressed in human cancers, our data further support the notion that FOXM1 is a valid target for combinatorial anticancer therapy.

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