J Cancer Sci Ther 2014, 6:10
http://dx.doi.org/10.4172/1948-5956.S1.035

OMICS Group Conferences
Accelerating Scientific Discovery

4th World Congress on
Cancer Science & Therapy
October 20-22, 2014 DoubleTree by Hilton Hotel Chicago-North Shore Conference Center, USA

Cytoplasmic p21 is a potential predictor for cisplatin sensitivity in ovarian cancer

Xia X, Ma Q, Li X, Ji T, Chen P, Xu H, Li K, Fang Y, Weng D, Weng Y, Liao S, Han Z, Liu R, Zhu T, Wang S, Xu G, Meng L, Zhou J and **Ma D**
Guangdong Medical College, P R China

Background: p21(WAF1/Cip1) binds to cyclin-dependent kinase complexes and inhibits their activities. It was originally described as an inhibitor of cancer cell proliferation. However, many recent studies have shown that p21 promotes tumor progression when accumulated in the cell cytoplasm. So far, little is known about the correlation between cytoplasmic p21 and drug resistance. This study was aimed to investigate the role of p21 in the cisplatin resistance of ovarian cancer.

Methods: RT-PCR, western blot and immunofluorescence were used to detect p21 expression and location in cisplatin-resistant ovarian cancer cell line C13* and its parental line OV2008. Regulation of cytoplasmic p21 was performed through transfection of p21 siRNA, Akt2 shRNA and Akt2 constitutively active vector in the two cell lines; their effects on cisplatin-induced apoptosis were evaluated by flow cytometry. Tumor tissue sections of clinical samples were analyzed by immunohistochemistry.

Results: p21 predominantly localizes to the cytoplasm in C13* compared to OV2008. Persistent exposure to low dose cisplatin in OV2008 leads to p21 translocation from nuclear to cytoplasm, while it had not impact on p21 localization in C13*. Knockdown of cytoplasmic p21 by p21 siRNA transfection in C13* notably increased cisplatin-induced apoptosis through activation of caspase 3. Inhibition of p21 translocation into the cytoplasm by transfection of Akt2 shRNA into C13* cells significantly increased cisplatin-induced apoptosis, while induction of p21 translocation into the cytoplasm by transfection of constitutively active Akt2 in OV2008 enhanced the resistance to cisplatin. Immunohistochemical analysis of clinical ovarian tumor tissues demonstrated that cytoplasmic p21 was negatively correlated with the response to cisplatin based treatment.

Conclusions: Cytoplasmic p21 is a novel biomarker of cisplatin resistance and it may represent a potential therapeutic target for ovarian tumors that are refractory to conventional treatment.

Myo-inositol trispyrophosphate-mediated hypoxia reversion controls pancreatic cancer in rodents and enhances gemcitabine efficacy

Zahary Raykov[1,2], Svitlana P Grekova[1,2], Gaetan Bour[1,2], Jean Marie Lehn[3], N A Giese[4], Claude Nicolau[5,6] and **Marc Aprahamian[1,2]**
[1]German Cancer Research Center (DKFZ), Germany
[2]Institut National pour la Sante et la Recherche Medicale, Germany
[3]Universite de Strasbourg, France
[4]University Hospital Heidelberg, Germany
[5]Normoxys Inc., USA
[6]Friedman School of Nutrition Science and Policy, USA

Hypoxia and dysfunctional tumor vessels represent a prominent feature of pancreatic cancer, being, at least in part, responsible for chemotherapy resistance and immune suppression in these tumors. We tested whether the increase of oxygen delivery induced *in vivo* by myo-inositol trispyrophosphate (ITPP) can reverse hypoxia, control tumor growth and improve chemotherapy response. Tumor size, metastatic development (microcomputed tomography scan follow-up) and the survival of rats and nude or NOD.SCID mice, (bearing syngenic rat and MiaPaCa2- or patient-derived pancreatic tumors), were determined on ITPP and/or gemcitabine treatment. Partial oxygen pressure, expression of angiogenic factors and tumor histology were evaluated. Infiltration and oxidative status of immune cells, as well as chemotherapy penetration in tumors, were determined by fluorescence-activated cell sorting, fluorometry, nitric oxide release assays, Western blot and confocal microscopy. Weekly intravenous ITPP application resulted in the inhibition of metastasis development and restricted primary tumor growth, showing a superior effect on the rats' survival compared with gemcitabine. ITPP treatment restored tumor normoxia and caused a reduction in hypoxia inducible factor-1a levels, with subsequent VEGF and Lox downregulation, resulting in improved vessel structure and decreased desmoplasia. The latter effects translated into elevated immune cells influx and improved susceptibility to gemcitabine treatment. Growth of human pancreatic tumor xenografts was strongly inhibited by administration of ITPP. ITPP exploits a two-stage mechanism causing rapid, early and sustainable late stage normoxia. This is due to the angiogenic factor modulation and vascular normalization, leading to enhanced chemotherapy delivery and synergistic life prolongation, on combination with low doses of gemcitabine.