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

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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.

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