Editorial

Expression of Copper-transporting P-type Adenosine Triphosphatase (ATP7B) as a Chemoresistance Marker in Human Solid Carcinomas

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Introduction

The incidence and mortality of human solid carcinoma has not declined in the past decade. This is due to the lack of new effective therapy. The treatment with anticancer drug-based chemotherapy after reductive surgery has improved the prognosis of patients with several types of human solid carcinomas, however the complete pathologic response and 5-year survival rates have not improved. One of the most important problems in the treatment of human solid carcinoma is the intrinsic/acquired resistance to anticancer drug-based chemotherapy. Knowledge of the active mechanism of drug resistance may lead to new treatment strategies and allows the selection of those patients for specific treatment modalities.

Cisplatin is one of the active anticancer drug, widely used in clinic. Multidrug resistance (MDR) has been noted as an important mechanism of drug resistance. Several genes including MDR1, MRP and LRP have been identified.[1-4] MDR1 and MRP1 function as a drug efflux pump and are classified as ABC transporter gene family,[1,4] and are expressed in both human solid tumors and hematological malignancies.[5,6] The 110-kd LRP, the major vault protein, is frequently overexpressed in MDR cells, and has an important role(s) in transport of drugs from nuclei to cytoplasm and confers to MDR in vitro.[2] Recently, BCRP (MXR/ABCP) gene, another member of the ABC transporter family, has been described in breast, colon, gastric and fibrosarcoma cell lines.[7-10] However, no evidence(s) that these molecules are involved in cisplatin resistance in vitro and in clinic, has been reported. Therefore, the mechanism of cisplatin transport and its significance to drug-resistance in human solid carcinoma is unknown.

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Role of Copper-transporting P-type Adenosine Triphosphatase (ATP7B) in vitro

Recently, it has been shown that a copper-transporting P-type adenosine triphosphatase (ATP7B) is associated with cisplatin resistance in vitro.[10] The ATP7B gene was induced by exposure to cisplatin in human prostate cells and the ATP7B transfected cells showed dramatic decrease in cisplatin efflux.[11] Although an active efflux pump for cisplatin has yet to be identified, it is likely that ATP7B may function to efflux cisplatin from some carcinoma cells.

ATP7B is a member of a class of heavy metal-transporting P-type ATPases that pump copper, cadmium, zinc, silver or lead.[12-16] Copper is an essential trace element and is integrated into many enzymatic reactions. Excess level of copper is transported to the extracellular environment by an energy-dependent system[12] and alteration in copper homeostasis can cause severe problems. For example, Wilson disease (WND), an autosomal recessive disease of copper transport, is characterized by chronic liver and/or neurological disorder, sometimes accompanied by kidney damage.[17]

Overexpression of ATP7B in Human Solid Carcinoma

Detailed understanding of ATP7B is crucial in several diseases including cancer. The fact that such a transporter can also transport small molecule drugs is intriguing and could potentially have a significant value in the clinic. Therefore, we investigate the expression of ATP7B aim to determine whether its expression was predictive of re-

sponse to cisplatin-based chemotherapy and survival in patients with several types of human solid carcinomas by quantitative polymerase chain reaction (PCR) and immnohistochemical analysis in 353 human solid carcinomas.[18-23)]

ATP7B immunoreactivity in tissue was detected as granular cytoplasmic staining. In agreement with this observation, ATP7B has been reported to be abundant in the Golgi apparatus.[17)] In almost normal epithelial cell, ATP7B expression was not detected. Overexpression of cytoplasmic staining of carcinoma cells in several types of human solid carcinomas was observed in gastric carcinoma (41.2%, 21/51),[18)] breast carcinoma (22.0%, 9/41),[19)] esophageal carcinoma (76.5%, 13/17),[20)] ovarian carcinoma (34.6%, 36/104),[21)] hepatocellular carcinoma (5/10, 50.0%),[22)] colorectal carcinoma (64.3%, 18/28), oral squamous cell carcinoma (54.9%, 28/51)[23)] and uterine carcinoma (37.3%, 19/51).[24)]

Clinicopathologic and Prognostic Significance of ATP7B in Human Solid Carcinomas

ATP7B expression was significantly involved in degree of differentiation of tumor cells in gastric,[18)] breast,[19)] ovarian[21)] and uterine carcinomas.[24)] In esophageal carcinoma treated with cisplatin-based chemotherapy, ATP7B expression level might be a prognostic indicator.[20)] In uterine carcinoma, 27 patients were treated with cisplatin-based chemotherapy in this study. Interestingly, patients with ATP7B-positive tumors have an inferior response to chemotherapy [50.0% complete and partial response (6/12), and 50.0% no change and progress disease (6/12)] compared with the patients with ATP7B-negative tumors [86.7% complete and partial response (13/15), and 13.3% no response (2/15)]. Further, the patients with ATP7B-positive uterine carcinomas have poorer disease-free and overall survival than those with ATP7B-negative tumors.[24)] ATP7B positivity in poorly/moderately differentiated carcinoma was significantly higher than that in low malignant potential tumor/well-differentiated carcinoma (P=0.0276). Patients with ATP7B-positive tumors had a significantly inferior response to chemotherapy compared with the patients with ATP7B-negative tumors (P=0.025). The multivariate Cox regression analysis revealed that ATP7B expression (hazard ratio, 1.8; 95% confidence interval, 1.0-3.2, P=0.048), as well as International Federation of Gynecologists and Obstetricians stage (hazard ratio, 2.0; 95% confidence interval, 1.1-3.6, P=0.018), was prognostic for poor disease outcome after adjustment for p53 expression, grade, and residual tumor.[21)]

Conclusion

ATP7B, a transporter associated with chemoresistance, is expressed in several types of human solid carcinomas. Of special interest is the finding that the expression is more frequent in undifferentiated carcinomas that are usually more refractory to therapy. Therefore, analysis of ATP7B expression will be clinically relevant for the choice of therapy.

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