Organic cation transporter 6 directly confers resistance to anticancer platinum drugs

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Aim/Background: Organic cation transporters (OCTs) of the solute carrier family 22 have been identified as uptake transporters for the charge state of a substrate such as cationic drugs. The OCTs have an isoform of OCT1, OCT2, OCT3, and OCT6. Each OCT has a characteristic pattern of tissue expression and transport-specific substrates, and plays an important role in the cellular accumulation of antitumor platinum drugs. Previously we found that decreased OCT6 expression is associated with the resistance to cisplatin (CDDP) by decreased intracellular uptake of CDDP. In this study we examined whether OCT6 directly confers resistance to another platinum drug oxaliplatin (L-OHP).

Methods: We used lung cancer cell line PC-14, and SBC3 cells, and established the L-OHP-resistant lung cancer subline PC-14/L-OHP and SBC3/L-OHP cells. Further we used a forced expression of OCT6 cells by a transfection an OCT6 gene SLC22A16 using a forced expression vector. We examined the expression of OCT6 in relation with intracellular platinum drug concentration or platinum drug resistance using these cells.

Results: Both L-OHP resistant sublines showed cross resistance to CDDP and L-OHP, and decreased expression of OCT6. The intracellular accumulation of L-OHP in PC-14/L-OHP cells was reduced compared to their parental cells. These findings suggest that OCT6 expression confers platinum drug resistance in the sublines by enhancing the decreased uptake of platinum drugs into cancer cells. Further, we confirmed that intracellular L-OHP concentration are increased concomitant with decreased resistance to L-OHP in OCT6 overexpressed cells.

Conclusions: Taken together with our previous results, the present findings indicate that alteration of OCT6 expression is directly involved in platinum drug resistance according to platinum drug uptake into cancer cells.

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