S17-3 Organic cation transporters in platinum agent-induced cytotoxicity

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An anticancer agent cisplatin is commonly used in the many kinds of chemotherapy regimens, but its renal toxicity has been serious problem in patients receiving the drug with hydration more than 3,500 mL/day preventing renal impairment. We clarified that the renal distribution of cisplatin was mainly mediated by hOCT2/SLC22A2, but the luminal hMATE/SLC47A transporters never transport it, and therefore, accumulated cisplatin cause subsequent renal impairment. However, its derivative oxaliplatin does not affect renal function, because its tubular accumulation is considered to be decreased mainly by MATE2-K-mediated tubular secretion. Oxaliplatin is the third-generation platinum agent, and is used against colorectal cancers as a key drug of FOLFOX regimens. Its objective response rate for colorectal cancer is superior to cisplatin. We previously found that oxaliplatin, but not cisplatin, was transported by OCT3/SLC22A3. The cells with the high level of OCT3 mRNA showed high release of LDH and accumulation of platinum after the treatment with oxaliplatin. However, the amount of platinum accumulated following cisplatin-treatment did not differ among these cells. The expression of OCT3 mRNA in cancerous and normal colon derived from Japanese patients was also measured by real-time PCR. In conclusion, the organic cation transporters recognize the inorganic cations, platinum agents, as their substrate, and they play crucial roles in pharmacodynamic/toxicological effects of platinum drugs in cancer chemotherapy.