

Enhanced Renal Clearance of Vancomycin in Rats with Carcinogen-Induced Osteosarcoma

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Abstract. Recently, it has been reported that total clearance (CL_{tot}) of vancomycin is significantly higher in patients with malignancies compared to those without malignancies. In the present study, to clarify the mechanism of this enhancement in malignancy, we adopted rat animal models, using chemical carcinogen-induced osteosarcoma, selected lung metastatic lesions (C-SLM), transplanted into thigh muscles. The CL_{tot} and renal clearance (CL_r) of vancomycin in the tumor-bearing rats were increased compared to the ones of the control rats without tumor. However, there was no difference in the glomerular filtration rate. The plasma concentrations of interleukin (IL)-1 β and IL-6, were elevated in the tumor-bearing rats. When renal proximal tubular epithelial cells (RPTEC) were exposed to IL-1 β , IL-6, and tumor necrosis factor (TNF)- α simultaneously, the excretory ratio increased significantly. These findings suggest that tubular excretion or re-absorption by cytokines might be associated with changes in the vancomycin CL_{tot} enhancement in the tumor-bearing rats.

Vancomycin is a glycopeptide antibiotic that is generally used for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) (1, 2). Its use requires effective therapeutic drug monitoring during the treatment period to keep the plasma concentration within the therapeutic range, thus, reducing the incidence of nephrotoxicity (3). Furthermore, in order to prevent the spread of resistant strains, it is necessary to maintain an adequate plasma concentration for a short period of time. It has been reported in other countries that clearance is significantly higher in elderly patients, infants, and children with malignancy compared to those without malignancies (4-6). Likewise, in Japan, we have reported that clearance of vancomycin was significantly higher in patients with malignancy than in those without malignancy (7). However, Omote *et al.* did not detect such relationships, suggesting little effect of the malignancy on the vancomycin clearance (8). More recently, other investigators (9) have reported higher values of vancomycin clearance for elderly patients with malignant tumors than in those without tumors, thus supporting our findings. Moreover, a similar phenomenon has been seen with aminoglycoside antibiotics, such as amikacin and gentamicin (10-13). However, the mechanisms are still unknown. Therefore, the aim of the current study was to confirm enhanced clearance of vancomycin in a tumor-bearing animal model and to try to clarify the mechanisms of this enhancement.

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Materials and Methods

Materials. Vancomycin hydrochloride was purchased from Shionogi (Osaka, Japan). Probenecid, quinidine sulfate and cimetidine were from Nacalai Tesque, Inc (Kyoto, Japan). Inulin was purchased from Wako Pure Chemical Co. (Osaka, Japan). Interleukin (IL)-1 β , IL-6,

and tumor necrosis factor (TNF)- α were purchased from PeproTech EC Ltd. (London, UK). All other chemicals were of reagent grade. Transwell-COL[®] cell culture chambers (pore size 0.4 μ m, diameter 12 mm, and surface area 1 cm²) were purchased from Costar (Bedford, MA, USA). Dulbecco's modified Eagle's medium/nutrient mixture F-12 (DMEM/F-12), fetal bovine serum (FBS), and other culture reagents were purchased from GIBCO (Grand Island, NY, USA). Epidermal growth factor (EGF), cholera toxin, hydrocortisone, and insulin-transferrin sodium selenite media supplement (ISL) were purchased from Sigma Chemicals (St. Louis, MO, USA). Penicillin G and streptomycin were purchased from Wako Pure Chemical Industries Ltd (Osaka, Japan). Human fibronectin was purchased from Boehringer Mannheim GmbH (Mannheim, Germany).

Animal model preparation. All animal experiments were carried out in accordance with the Declaration of Helsinki and with the Kanazawa University Guide for the Care and Use of Laboratory Animals. The chemical carcinogen-induced osteosarcoma, selected lung metastatic lesion (C-SLM) (14) tumor was kindly provided by Dr Mii (Nara Medical School, Japan) and maintained in male Fisher 344 rats by repeat inoculation with a tumor block (~10 mm³) subcutaneously on the back. In this experiment, we introduced C-SLM tumor into the hind limb thigh muscles in 7-week old rats. Sham operations were performed for the control group. When tumor size reached approximately 1000 mm³ (11-12 weeks old), vancomycin (5 mg/kg) was administered intravenously to the tumor-bearing rats and the control rats. Blood was collected from the jugular vein at 2, 5, 15, 30, 60, 90, 120, 150, and 180 min after vancomycin administration. Plasma was separated by centrifugation at 12,000 \times g for 10 min and stored at -30°C until analysis. The concentration of vancomycin in plasma was determined by high-performance liquid chromatography (HPLC). After plasma samples were deproteinized with acetonitrile, the supernatants were injected onto the HPLC. A chromatogram (model LC-9A; Shimadzu Corporation, Kyoto, Japan) was equipped with a variable wavelength UV detector (model SPD-6A; Shimadzu Corporation) and a 4.6 \times 150 mm stainless steel ODS Column (Shim-pack CLC-ODS (M); Shimadzu Corporation, Kyoto, Japan). The mobile phase was 8% acetonitrile in 0.05 M phosphate buffer (pH 5.5). The detection UV wavelength was 235 nm. A flow rate of 1.0 ml/min was used.

Biochemical laboratory data in plasma were measured by SRL Inc. (Tokyo, Japan). IL-1 β , IL-6 and TNF- α were measured using a rat IL-1 β immunoassay kit (IBL International Corp., Toronto, Canada), and IL-6 and TNF- α immunoassay kit (R&D Systems, Inc. Minnesota, USA), respectively.

Determination of plasma protein binding. The plasma protein binding of vancomycin was determined by an ultrafiltration technique with the MPS-3 Centrifree (Amicon Corporation, Denver, MA, USA) as described by Ichimura *et al.* (15). After equilibration at 37°C for 20 min, samples of the ultrafiltrate were obtained by centrifugation at 37°C for 5 min (1000 \times g). The unbound concentration of vancomycin in the filtrate was determined by HPLC.

Clearance study at steady state. The clearance study was conducted using the methods described in Nakamura *et al.* (16). A catheter was inserted into the femoral vein of the rats for blood sampling at designated stages. Urine was collected from a catheter inserted into the urinary bladder through a suprapubic incision. Vancomycin was

administered alone or with probenecid, cimetidine, or quinidine. The loading dose of vancomycin (2.0 mg), required to reach a steady state drug plasma concentration, was administered with inulin (10 mg) and mannitol (40 mg) through the femoral vein. A continuous infusion of vancomycin (1.36 mg/h) was started concomitantly with inulin (13.6 mg/h) and mannitol (68.2 mg/h) at 1.5 ml/h. Due to the rapid circulation of quinidine, the loading dose was omitted. After one-hour infusion for equilibration, urine samples were collected of three consecutive 20 min intervals. Blood was sampled at 70, 90 and 110 min after starting the infusion. In addition, we extracted infusion solution for 20 min after completion of the experiment. Plasma was separated by centrifugation at 12,000 \times g for 10 min and stored at -30°C until analysis. The concentration of vancomycin in plasma and urine was determined by HPLC. The inulin concentrations were also determined by using a cysteine/tryptophan reaction measured by photometry as described in Waugh *et al.* (17).

Cell culture. Human renal proximal tubular epithelial cells (RPTECs) (18), obtained from Bio-Whittaker (Walkersville, MD, USA), were cultured in Renal Epithelial Cell Basal Medium (REGM BulletKit[®]) from Takara Bio Inc. (Shiga, Japan) supplemented with addition factor set (0.5 mg/ml hydrocortisone, 10 μ g/ml hEGF, 10% FBS, 0.5 mg/ml epinephrine, 6.5 μ g/ml triiodothyronine, 10 mg/ml transferrin, 5 mg/ml insulin, GA-1000 (Gentamicin/Amphotericin-B)). Cells were passaged using standard trypsinization procedures and cultured in an atmosphere of 95% air and 5% CO₂ at 37°C.

Permeability study using RPTEC. RPTECs were seeded at a density of 3 \times 10⁴ cells/cm² on the filter membrane of a Transwell-COL insert and cultured in an atmosphere of 95% air and 5% CO₂ at 37°C for 7 to 9 days until confluence. In the permeability study, the RPTECs grown on a filter membrane were washed twice with Hank's balanced salt solution (HBSS) (1.3 mM CaCl₂, 5.0 mM KCl, 0.3 mM KH₂PO₄, 0.8 mM MgCl₂, 138 mM NaCl, 0.3 mM Na₂HPO₄, 5.6 mM D-glucose, and 10 mM HEPES, pH 7.4). HBSS was added to the apical side (200 μ l) and to the basal side (800 μ l) and preincubated for 30 min at 37°C.

In the permeability study with cytokines (IL-1 β , IL-6, TNF- α), the cell layer was preincubated with cytokines on both the apical and basal sides for 6 and 24 h. The concentrations of cytokines used were 0.1 and 10 ng/ml. In the assay of drug permeability from the apical to the basal side, the basal side contained vancomycin. A sample (80 μ l) was collected from the apical side and was subsequently replaced with an equal volume of HBSS at 37°C. In the assay of drug permeability from the basal to the apical side, the apical side contained vancomycin. A sample (200 μ l) was collected from the basal side and was subsequently replaced with an equal volume of HBSS at 37°C. The initial concentration of vancomycin was 5 μ g/ml on the apical side and 10 μ g/ml on the basal side. The collected samples were subsequently used for vancomycin determination with HPLC.

Pharmacokinetic analysis. The plasma concentration data after intravenous bolus administration of vancomycin were analyzed by a non-compartmental method. In the clearance study at steady state, total clearance (CL_{tot}) of vancomycin was calculated as the infusion rate divided by the steady-state plasma concentration (C_{ps}). The renal clearance (CL_r) was obtained as the urinary excretion rate divided by the C_{ps}.

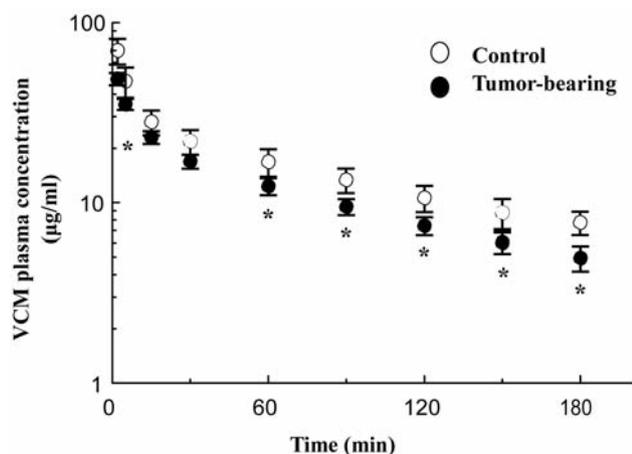


Figure 1. Vancomycin (VCM) plasma concentration versus time profiles for control and intramuscularly transplanted tumor-bearing rats after intravenous bolus injections with 5 mg/kg. Each point and vertical bar represents the mean \pm standard error of the mean (SEM) ($n=5$). *Significant difference between control and tumor-bearing rats at $p<0.05$.

Statistical analysis. Student's *t*-test was used to compare the unpaired mean values of two sets of data. The number of determinations is noted in each Table and Figure. A p -value <0.05 indicated a statistically significant difference between data sets.

Results

Tumor-bearing animal model and pharmacokinetics of vancomycin. Figure 1 shows the vancomycin concentration-time profiles in plasma of the control and tumor groups after intravenous bolus administration of 5 mg/kg vancomycin. Plasma vancomycin concentration of the tumor group decreased significantly compared to the one of the control group at 2, 60, 90, 120, 150, and 180 min. The laboratory data and estimated vancomycin pharmacokinetic parameters of the tumor group and the control group are presented in Table I. There was no difference in the volume of distribution at steady state (V_{ss}) between the control and tumor groups. On the contrary, the CL_{tot} value of the tumor group was increased compared to the one of the control group. There was no difference in the plasma creatinine, total bilirubin, aspartate amino transferase (AST), glucose and uric acid concentrations between the control and tumor groups and all were within normal ranges. IL-1 β and IL-6 plasma levels in the tumor group were higher than those of the control group. The plasma albumin level decreased in tumor-bearing rats but was within the normal range. The plasma protein binding of vancomycin was determined for control and tumor-bearing rats. The plasma protein binding behavior of vancomycin was constant under these experimental conditions. The values of plasma unbound

Table I. Estimated vancomycin pharmacokinetic parameters and laboratory data in plasma for control and tumor-bearing rats after 5 mg/kg intravenous bolus injection of vancomycin.

	Control	Tumor
Weight (kg)	0.231 \pm 0.023	0.254 \pm 0.022
V_{ss} (ml/kg)	190 \pm 71	232 \pm 32
CL_{tot} (ml/min/kg)	1.30 \pm 0.37	2.37 \pm 0.38*
Creatinine (mg/dl)	0.27 \pm 0.05	0.32 \pm 0.09
Albumin (g/dl)	4.41 \pm 0.38	3.78 \pm 0.50*
Total bilirubin (mg/dl)	0.65 \pm 0.34	0.49 \pm 0.31
AST (IU/l)	87 \pm 15	101 \pm 40
Glucose (mg/dl)	240 \pm 31	213 \pm 22
Uric acid (mg/dl)	2.29 \pm 1.37	1.95 \pm 0.85
IL-1 β (pg/ml)	<2.0	24.3 \pm 6.77*
IL-6 (pg/ml)	106 \pm 15	268 \pm 147*
TNF- α (pg/ml)	10.3 \pm 3.19	12.2 \pm 2.90

V_{ss} : Volume of distribution at steady state of vancomycin; CL : Total clearance of vancomycin; AST: Aspartate amino transferase; Each value is the mean \pm standard deviation (SD) ($n=5-13$). *Significant difference between control and tumor-bearing rats at $p<0.05$.

fraction of vancomycin (f_p) for control rats and tumor-bearing rats were estimated as 0.504 \pm 0.070 and 0.458 \pm 0.112, respectively.

Clearance study at steady state. Table II summarizes the effects of various drugs on the renal handling of vancomycin at an infusion rate of 1.5 mg/h for control and tumor-bearing rats. The CL_{tot} value of vancomycin was increased in the tumor group compared to the one of the control group as well as estimated CL_{tot} by plasma concentration profiles after intravenous bolus injection of 5 mg/kg vancomycin in Figure 1. Moreover, the CL_r of vancomycin was significantly increased in the tumor group. However, there was no difference in the glomerular filtration rate (GFR) between the control and tumor groups. The GFR was not affected by co-administration of drugs. The co-administered drugs, probenecid, cimetidine, or quinidine, inhibited the increase in CL_r in the tumor group compared with the control group. To clarify the contribution of renal tubular excretion and re-absorption, we compared the CL_r with the f_p GFR (Table I). The CL_r was greater than the f_p GFR in control rats. Therefore, net tubular excretion is suggested, as Nakamura *et al.* (16) reported previously. Among the control group, the level of suppression by co-administered drugs cimetidine and quinidine was slightly larger than the one of probenecid, but not significantly different. Among the rats of the tumor group, co-administration of drugs significantly inhibited vancomycin elimination compared with administration of vancomycin alone.

In addition, the GFR in the tumor group was normal in comparison with the control group, and only CL_r was increased in the tumor group. It is suggested that change of

Table II. Effect of co-administration of various drugs on the urinary excretion of vancomycin in drip infusion or control and tumor-bearing rats.

	Additional agent	CLtot (ml/min/kg)	GFR (ml/min/kg)	fpGFR (ml/min/kg)	CLr (ml/min/kg)
Control (n=3-6)	None	1.40±0.17	1.76±0.24	0.91±0.17	1.11±0.13
	Probenecid	1.00±0.17 [#]	1.60±0.17	0.83±0.13	0.90±0.32
	Cimetidine	1.03±0.31 [#]	1.54±0.71	0.80±0.38	0.77±0.13 [#]
	Quinidine	1.12±0.09 [#]	1.59±0.28	0.82±0.18	0.78±0.30
Tumor bearing (n=4-7)	None	1.78±0.32 [*]	1.73±0.38	0.81±0.26	1.41±0.14 [*]
	Probenecid	0.91±0.18 [#]	1.44±0.34	0.68±0.23	0.44±0.08 [#]
	Cimetidine	1.44±0.29 [#]	1.63±0.59	0.77±0.33	1.02±0.21 [#]
	Quinidine	1.57±0.19	1.60±0.59	0.75±0.33	0.72±0.14 [#]

CLtot: Total clearance of vancomycin; GFR: Glomerular filtration rate; fp: Plasma unbound fraction of vancomycin; CLr: Renal clearance of vancomycin; Each value is the mean±SD. Significant difference between ^{*}control and tumor-bearing rats at $p<0.05$. [#]with and without co-administration of drugs at $p<0.05$.

tubular excretion or re-absorption might be associated with enhancement of CLtot for vancomycin in the tumor group.

In vitro RPETC study. Vancomycin transport was measured for 2 h with confluent RPTEC. Permeability ratio proportionally increased over time and the ratio of apical to basal, and basal to apical fluxes for 1 h were 36.0±1.8, 6.4±0.5%, respectively. The effect of cytokines on vancomycin treatment in the RPTEC was examined for 1 h. Vancomycin apical to basal transport is shown in Figure 2. In the presence of TNF- α , vancomycin transport was significantly increased. However, other cytokine stimulation did not affect vancomycin transport. In the basal to apical flux, none of the cytokine stimulations had any significant effect on vancomycin transport, except for the use of mixed cytokines (IL-1 β , IL-6, and TNF- α), where vancomycin transport increased by 40%. The excretory ratios were calculated and are illustrated in Figure 3. The excretory ratio increased 60% when a mixture of cytokines were present.

Discussion

In this study, in order to aid in analyzing the mechanism of enhancement of CLtot of vancomycin in cancer patients as reported by Teramachi *et al.* (7), we developed an animal model. We succeeded in developing tumor-bearing animals that reproduced enhancement of CLtot of vancomycin by transplanted osteosarcoma cells in the thigh muscles.

Vancomycin is mainly eliminated through the kidneys and is usually not metabolized, and the fp is generally high (19, 20). Therefore, we focused on the elimination process in the kidney and carried out investigations into the mechanism of the enhanced clearance of vancomycin with tumor-bearing rats. There were no differences in the Vss and fp values between control and tumor-bearing rats after an intravenous bolus injection of vancomycin. In addition to CLtot, the CLr

was also increased in tumor-bearing rats, at steady state with drip infusion of vancomycin. Furthermore, the GFR did not change in tumor-bearing rats. However, quinidine, cimetidine, and probenecid inhibited the elevation of CLr of vancomycin in these rats. These results suggest that the enhancement of vancomycin clearance in tumor-bearing rats might be caused by changes in the tubular excretion or re-absorption processes. Because the structure of vancomycin includes a carboxyl group and a nitrogen radical, it is possible that it behaves as both an organic cation and an organic anion. There are only a few reports on the mechanism of vancomycin transport in the kidney. Through studies of rabbit renal basolateral and brush border membrane vesicles, Sokol (21) suggested that vancomycin crosses the basolateral membrane. Nakamura *et al.* (16) suggested the possible involvement of the organic cation transport system in renal excretion of vancomycin. Moreover, it is reported that organic cation transporters (OCT1, OCT2) and organic anion transporters (OAT1, OAT2, OAT3) were expressed at the basolateral membrane of proximal tubular cell (22, 23). In our present study, probenecid, a potent inhibitor of the renal OAT system, did not affect the renal handling of vancomycin in control rats. Quinidine and cimetidine, which are organic cations that can inhibit the renal OCT system, tend to reduce CLr of vancomycin. Therefore, as has already been reported, the OAT system may not be involved in the renal excretion of vancomycin. However, in the present study using tumor-bearing rats, probenecid, quinidine, and cimetidine inhibited enhancement of vancomycin CLr. Therefore, the mechanism of clearance enhancement of vancomycin in tumor-bearing rats might be associated with functional variations of the OCTs or OATs in the renal tubular membrane. Identification of the responsible transporters with an inhibition study is insufficient in clarifying the specific mechanism. Further studies are needed to clarify the mechanisms of enhancement of CLr in tumor-bearing rats.

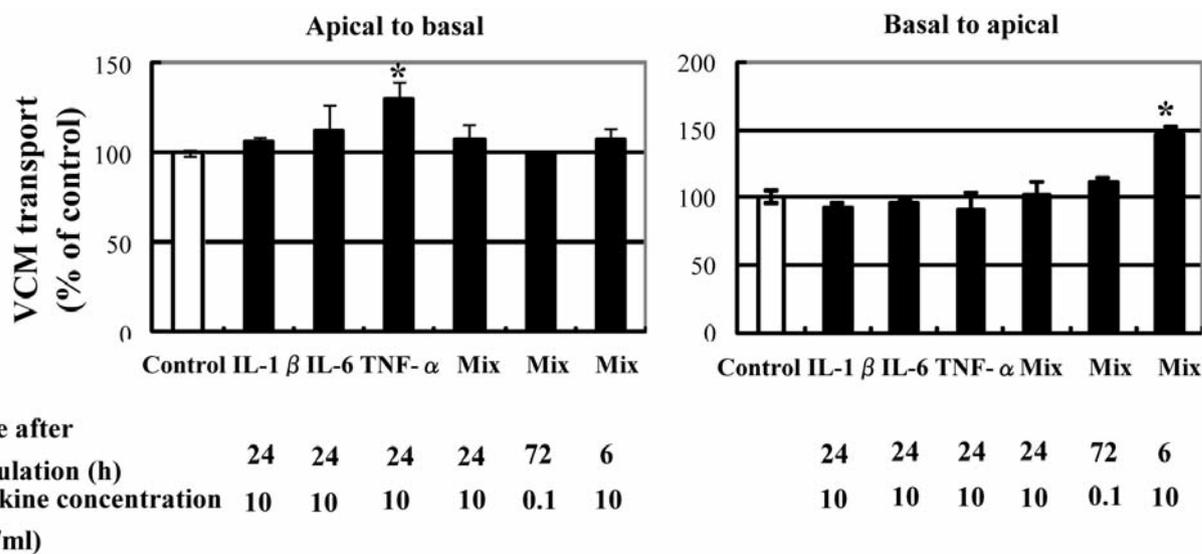


Figure 2. Vancomycin(VCM) transport (% of control) across RPTEC monolayers after exposure to several cytokines. Mix: IL-1 β , IL-6 and TNF- α were used simultaneously. Each value is the mean \pm SEM (n=3). *Significantly different from the control at p<0.05.

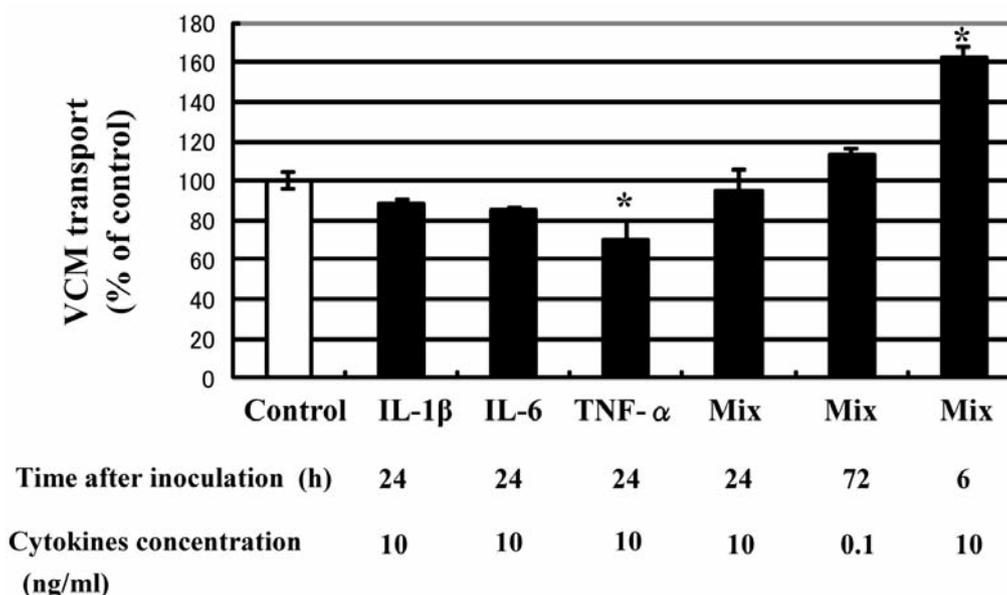


Figure 3. Excretory ratios of vancomycin(VCM) on RPTEC monolayers after exposure to several cytokines. Mix: IL-1 β , IL-6 and TNF- α were used simultaneously. Each value is the mean \pm SEM (n=3). *Significantly different from the control at p<0.05.

In the animal model used in this study, there were no notable changes in plasma laboratory data for creatinine, AST, total bilirubin, uric acid, and glucose with the exception of slightly low albumin levels in the tumor group. It was reported that streptozotocin-induced diabetic rats experienced decreased expression of both OCT1 and OCT2 proteins and also a decrease in *OCT2* mRNA accumulation (24). Habu *et al.* (25) showed decreased basolateral OAT

and OCT activity, accompanied by a specific decrease in OAT1, OAT3 and OCT2 expression in hyperuricemic rat kidney. However, in the current study, plasma glucose and uric acid concentrations did not increase in tumor-bearing rats. In this study, plasma levels of IL-1 β and IL-6 in tumor-bearing rats were significantly elevated compared with the control rats. We analyzed whether cytokines affect vancomycin transport in renal proximal tubular epithelial

cells. Since RPTEC is a normal cell type and easy to culture successively, these cells were adopted. According to our *in vitro* RPTEC studies, mixed cytokine exposure increased the excretory ratio of vancomycin. Therefore, it is suggested that cytokines might be candidates which mediate between tumor cells and the kidney. There are some reports of cytokines serving as key mediators in regulating hepatic expression of anion transporters in inflammatory cholestasis (26, 27). In these studies, murine Hepa 1-6 hepatoma cells were treated with different concentrations of cytokines (IL-1 β , IL-6, TNF- α ; 1 or 10 ng/ml in DMEM) and harvested at 6 and 24 h. Therefore, we followed the same protocol for the concentration of cytokines and duration of exposure as in their study. Since some synergistic relationships between IL-1 β , IL-6 and TNF- α have been reported in several tissues (28, 29), we exposed RPTEC to mixed cytokines. Although cytokine cross-talk might be associated with enhancement of vancomycin excretion, further studies are needed to clarify the relationship between cytokines and vancomycin transport in the kidney.

The present findings provide useful information for further studies of the mechanisms underlying the renal transport of vancomycin in the normal and the cancerous state.

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