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FACILITATIVE TRANSPORT OF FLUOROQUINOLONES BY HUMAN MULTIDRUG AND TOXIN EXTRUSION PROTEINS
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We have recently found that rat multidrug and toxin extrusion protein 1 (rMATE1), which is abundantly expressed in the kidney, transports fluoroquinolones by a facilitative manner and indicated the possible role of MATE1 in their renal tubular secretion. To further examine the possibility in humans, we investigated into the transport of fluoroquinolones by human MATE1 (hMATE1) expressed in MDCKII cells. We also examined the transport of fluoroquinolones by a human-specific MATE (hMATE2-K). It was found that hMATE1 can transport fluoroquinolones such as ciprofloxacin (CPFX), enoxacin (ENX), levofloxacin (LVFX), norfloxacín (NFX) and several more. Although hMATE1 has been known as an apical organic cation/H⁺ antipporter, detailed investigation of hMATE1-mediated uptake of CPFX has revealed that it is not sensitive to intracellular acidification by treatments using NH₄Cl or nigericin, suggesting that trans-proton gradient is not involved in its transport as a driving force. However, it was dependent on extracellular pH, being greatest at pH 7.0 and smaller at both acidic and basic pH’s, in agreement with the profile of zwitterionization of CPFX. All these characteristics of hMATE1 for CPFX transport were similar to those of rMATE1. It was also found that hMATE2-K can transport CPFX with similar characteristics. It is notable, however, that hMATE1 has been suggested to have higher affinities for fluoroquinolones from kinetic analyses of the transport of CPFX, ENX, NFX and LVFX. These results suggest that hMATE1 and also hMATE2-K mediate the transport of fluoroquinolones by a facilitative manner and zwitterionic fluoroquinolones would be the transported molecular species. MATE1 and MATE2-K may play key roles in the renal tubular secretion of fluoroquinolones.

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CHARACTERIZATION OF HUMAN ORGANIC ANION TRANSPORTING POLYPEPTIDE 1B3 EXPRESSION IN CANCER CELLS
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Organic anion transporting polypeptide 1B3 (OATP1B3, gene symbol SLCO1B3) is specifically expressed in the liver under normal physiological condition and mediates the cellular transport of a wide range of amphiphatic compounds. To date, it has been reported that, in contrast to the normal tissues, OATP1B3 is also expressed in solid tumors including gastric, pancreatic, and colon cancers, where it might mediate the cellular uptake of some anticancer drugs. However, the mechanisms involved in expression of OATP1B3 mRNA in cancer cells have not been clarified. In this study, we examined mRNA expression of OATP1B3 and transcription factors (HNF1α, HNF3β and FXR), which are reported to be involved in the regulation of SLCO1B3 gene expression, in cancer cells by RT-PCR. Expression of OATP1B3 mRNA was detected in LS174T and LS180 cells (derived from colon cancer), KLM1 and PK45P cells (pancreatic cancer), but not in Caco2 cells (colon cancer). mRNA expression of transcription factors was not fully associated with expression of OATP1B3 mRNA. We next examined the effect of epigenetic modification on expression of OATP1B3 mRNA in cancer cells. Treatment of Caco2 cells with DNA methylation inhibitor, 5-aza-2'-deoxycytidine (5 μM), significantly increased the level of OATP1B3 mRNA expression. However, mRNA expression of transcription factors was virtually unchanged. Collectively, the results of the present study indicate that DNA methylation is involved in OATP1B3 mRNA expression and that HNF1α, HNF3β and FXR are not critical factors for OATP1B3 mRNA expression in cancer cells. Therefore, in addition to the epigenetic mechanisms, there seems to be some factors other than known regulators that are responsible for OATP1B3 mRNA expression in cancer cells. Further analyses are underway to determine the transcription factor and DNA methylation sites involved in the regulation of SLCO1B3 gene expression in cancer cells.