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Contribution of the OATP1B Subfamily to Cancer Biology and Treatment

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Abstract

The organic anion transporter 1B (OATP1B) subfamily consists of OATP1B1 and OATP1B3.¹ These transporters have generally been considered liver-specific; however, recent evidence demonstrates that they are also expressed in extrahepatic tissues and in some tumors. This review discusses the potential influence of extrahepatic OATP1B expression on homeostasis and pathophysiology and its implications for pharmacotherapy in general.

OATP1B SUBSTRATES AND EXTRAHEPATIC EXPRESSION

Both organic anion transporter 1B1 (OATP1B1) and OATP1B3 are considered liver-specific transporters with ~70% sequence homology (reviewed in ref. 1). OATPs have overlapping substrate specificity toward molecules with steroid-like structures (e.g., several bile acids, estrone-3-sulfate, dehydroepiandrosterone-3-sulfate), peptide hormones and cyclic peptides (e.g., T3/ T4, microcystin, and CCK-8), fatty acids (e.g., leukotrienes), bilirubin, glucuronidated compounds (e.g., glucuronosyl-bilirubin, estradiol-17B-glucuronide), statins (e.g., fluvastatin, pitavastatin, rosuvastatin), and many small molecules (e.g., rifampicin, methotrexate, SN-38).¹ Several studies have demonstrated that OATP1Bs are important hepatic carriers involved in homeostatic physiology and drug absorption, distribution, metabolism, and excretion.¹

OATP1B expression in normal cells

Although OATP1B1 and OATP1B3 have been considered “liver-specific” transporters, more recent evidence demonstrates that the genes for these transporters are also transcribed in several extrahepatic tissues.¹ However, there is considerably less expression in these tissues than in the liver, and similar tissues taken from different healthy individuals do not always express OATP1Bs at detectable levels. Considerable research has been devoted to the role of OATP1Bs in liver homeostasis, but far fewer studies have focused on their expression in extrahepatic tissues and the physiologic consequences of carrier-mediated uptake of hormones and other endogenous substrates.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

For instance, OATPIBs are expressed in the thyroid and are involved in T4 uptake. However, to date, there have been no published studies investigating the role of OATPIBs in the normal thyroid. Further research needs to focus on characterizing OATPIB protein expression in various body tissues, the role of OATPIBs in extrahepatic physiology, and the mechanisms through which OATPs mediate extrahepatic cellular drug uptake and biodistribution. Moreover, OATPIBs should no longer be considered purely “liver-specific” transporters.

OATP1B3 expression in tumors

Although OATPIB expression has been observed in various nonhepatic cancer cell lines, Muto *et al.* were the first to observe that 50% of breast tumors are immunopositive for OATPIBs whereas OATPIBs are not expressed in normal breast epithelial. Several studies, published shortly thereafter, demonstrated that OATPIBs, or the genes encoding OATPIBs (*SLCO1B1* and *SLCO1B3*), are also expressed *de novo* in cancers of the prostate, colon, ovary, pancreas, and lung.^{1,2}

The precise molecular regulatory mechanism of *de novo* expression in tumors has not been elucidated. Nonetheless, initial data indicate that tumoral expression of OATPIBs has functional consequences. First, OATPs are involved in the cellular uptake of various endogenous hormones and bile acids; therefore, it is likely that OATPIB overexpression is involved in cancer etiology by concentrating intracellular hormones that fuel cancer progression. Second, OATPIBs influence the uptake of therapeutic agents, often in the very same tissues in which OATPIBs are overexpressed. It therefore appears that the transporters are expressed *de novo* as a function of tumor biology, and many effective anticancer therapies might be exploiting tumoral overexpression of the carrier function of OATPIBs in order to more specifically target tumor cells vs. normal cells. This scenario is observed in tumors treated with microcystin or paclitaxel.¹ However, overexpression of OATPIBs actually decreases the sensitivity to oxaliplatin therapy through an unknown mechanism whereby OATPIB3 uptake affects p53 pathways.¹

Therefore, studies should be undertaken to elucidate the role of OATPIBs in tumor biology and to investigate whether these carriers can be exploited through (i) taking advantage of their overexpression and using anticancer agents that are substrates of OATPs and/or (ii) inhibiting the uptake of hormones and other agents that fuel cancer progression. Both strategies may be useful, even in the same tumor type.

Tumor-specific *SLCO1B3*

Recently, Nagai *et al.* demonstrated that tumors express a tumor-specific OATP1B3 isoform (termed ct-OATP1B3) from a transcription start site that is different from that of the normal liver site.³ The new transcription start site exists in intron 2 and results in a protein that contains intronic DNA as the first exon that is spliced to exon 3 in the *SLCO1B3* gene. Therefore, ct-OATP1B3 is missing exons 1 and 2, a characteristic that may greatly change protein folding and alter substrate specificity. It is currently not known whether endogenous compounds and drugs that are substrates of liver OATP1B3 are also transported by ct-OATP1B3. Therefore, future studies on OATP1B3 in tumors must account for ct-OATP1B3 in drug and/or hormone uptake.

Diffusion of unconjugated testosterone

For years it was postulated that unconjugated steroid hormones diffuse through the membrane, bind to their receptors, and initiate the transcription of target genes. Specifically, it was postulated that testosterone enters tissues by simple diffusion. It was later suggested that passive diffusion could not completely account for the intracellular testosterone uptake rate.⁴ Recently, studies carried out in our laboratory showed that OATP1B3 concentrates unconjugated testosterone in cells.² In these studies, we showed that testosterone uptake is increased by more than twofold in Cos-7 cells transfected with OATP1B3. However, the precise kinetics of testosterone uptake has not yet been ascertained; therefore, it is unknown to what extent *de novo* OATP1B3 expression contributes to testosterone uptake and whether it is involved in the uptake of other unconjugated hormones. Moreover, it is likely that other OATPs are involved in the uptake of unconjugated steroid hormones.

OATP1B3 in prostate cancer

We studied polymorphic variations in the gene encoding OATP1B3 (*SLCO1B3*) in men who had advanced prostate cancer and were receiving docetaxel (an OATP1B3 substrate drug). We demonstrated that (i) OATP1B3 is expressed *de novo* in prostate tumor cells; (ii) OATP1B3 influences testosterone uptake into cells, where it is expressed differentially depending on a commonly inherited haplotype (i.e., 112S-233M associated with greater uptake and 112A-233I associated with lower uptake); (iii) polymorphic variations in *SLCO1B3* were related to progression-free survival in men receiving androgen deprivation therapy; and (iv) polymorphic variations in *SLCO1B3* were related to the duration of overall survival in men diagnosed with prostate cancer, regardless of docetaxel use.² We therefore concluded that *de novo* expression of OATP1B3 in prostate cancer may be a driver of resistance to androgen deprivation therapy through the mechanism of increasing the testosterone-uptake capability of prostate tumor cells starved of androgens (see Figure 1 for selected mechanisms of castration resistance). Subsequently, several studies have demonstrated results similar to ours, in prostate cancer as well as in other malignancies.¹ These findings suggest that OATPs are involved in disease pathogenesis as well as in disease progression and affect the response to treatment of these diseases with small molecules. Future studies in prostate cancer should focus on (i) the regulatory mechanism underlying *de novo* tumoral expression of OATP1B3 in prostate cancer, (ii) the functional kinetics of testosterone uptake, (iii) the potential for cancer-specific isoforms of OATP1B3, (iv) whether OATP1B3 inhibitors could be useful during or after androgen deprivation therapy, and (v) whether the considerable number of newly approved and upcoming prostate cancer therapies (e.g., abiraterone, MDV-3100, cabazitaxel) are themselves substrates of OATP1B3.

CONCLUSIONS

The extrahepatic and tumor-specific expressions of OATPIBs have only recently been demonstrated and have been very poorly investigated. Given the number of endogenous substrates and drugs associated with OATPIBs influx, it is likely that OATPIBs are more than mere liver-specific transporters, and that they regulate numerous physiologic and disease processes through mechanisms that require elucidation. Therefore, the subject of OATP1B transporters is fertile ground for further study. Future investigations should

establish how extrahepatic OATPIBs are regulated, which biological processes they regulate, and which drugs are influenced by tissue- or tumor-specific OATP1B3 expression, so that these transporters can be exploited for drug therapy. In theory, OATP1B inhibitors could cause symptoms similar to those of Rotor syndrome, a rare hereditary disease characterized by reduced liver uptake of several compounds.⁵

However, given that OATPIBs are expressed at levels several orders of magnitude higher in the liver, the risk of Rotor syndrome-like symptoms should not be considered an impediment to the development of therapeutics designed to inhibit OATPIBs. Studies of OATP1B3 in tumors must now account for ct-OATP1B3, which may confer “multidrug sensitivity” rather than multidrug resistance, as do certain efflux transporters such as P-glycoprotein.

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Figure 1.

Selected mechanisms of castration resistance in prostate tumors. **(a)** Under normal prostate homeostasis, testosterone diffuses through the membrane, is converted into dihydrotestosterone (DHT) by SRD5A2, and binds to the androgen receptor (AR), which translocates to the nucleus (nuc) and mediates signaling. During androgen-deprivation therapy, the intraprostatic testosterone concentration is significantly decreased by inhibiting production of testosterone by the testes. Prostate tumors become resistant to this therapy by **(b)** harboring AR mutations that result in promiscuous binding of multiple androgens; **(c)** increasing expression or copy number of the AR so that small concentrations of androgens result in more efficient signaling; **(d)** biosynthesizing intratumoral testosterone from androgen precursors (e.g., DHEA); and **(e)** scavenging testosterone into tumor cells through *de novo* synthesis of OATP1B3, complementing simple diffusion. These mechanisms are not mutually exclusive. ADT, androgen-depletion therapy; DHEA, dehydroepiandrosterone.