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REVIEW

Role of OCT1 in hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is one of the most commonly diagnosed cancers causing death worldwide. It is difficult to detect at an early stage and most patients with advanced HCC rarely achieve satisfying therapeutic results. Accordingly, researchers have been trying to find new biomarkers for diagnosis and new methods of treatment. OCT1, a member of solute carrier super family, is highly expressed in normal liver tissues, and predominantly transports endogenous and exogenous substances, such as metabolites, drugs and toxins to hepatocytes. Studies have demonstrated that the expression of OCT1 is related to the progression and survival of HCC patients. Furthermore, sorafenib, which is regarded as the only effective molecular targeting drug for advanced HCC, is affected by OCT1 variants. In the current review, we summarized the reports about OCT1 and HCC in order to present a comprehensive overview of the relationship between OCT1 and HCC.

Keywords: hepatocellular carcinoma, organic cation transporters, solute carrier transporter family, sorafenib

Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related mortality worldwide, with about 841,000 new cases and 782,000 deaths annually.[1] HCC might be cured by surgical resection, liver transplantation or ablation at the early stage, and 5-year survival can be higher than 50%. Patients with a small single tumor and very good preserved liver function are optimal candidates for surgical resection. Liver transplantation is most beneficial for patients who are not good candidates for resection.[2]However, most patients are already at advanced stage when HCC is diagnosed. They have no opportunity to accept surgical treatment, and chemotherapy has obviously serious side effects. Therefore, new biomarkers for recognizing HCC at an early stage and novel treatments for advanced HCC are urgently needed.

The SLC22 transporter family comprises more than two dozen members, which are expressed in epithelial tissues of the kidney, liver, and other organs, and play a critical role in translocating small molecular endogenous metabolites, drugs, and toxins between tissues and interfacing body fluids.[3–6] Due to the significance in the field of various molecular metabolisms, plenty of attention has been focused on the SLC22 family. SLC22 family is divided into six subfamilies on the basis of substrates and mechanisms of transport, including OATs, OAT-like, OAT-related, OCTs, OCTNs, and OCT/OCTN-related subfamilies.[7]

OCTs contain three subtypes encoded by SLC22A1-3 genes and are plasma membrane carriers of organic cations, weak base, and some neutral compounds.[8]

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The three membrane transporter subtypes have amino identities about 50%–70%[9,10] and they facilitate their substrates to move bidirectionally across the plasma membrane as cation exchangers depending on the electrochemical gradient of the substrates.[9,11,12] Natural substrates and drugs transported by organic cation transporters are shown in Table 1. Even though organic cation transporters, OCT1, OCT2, and OCT3, have partly similar distribution in organs, overlapping substrate, and the same inhibitors, they are mainly expressed in different tissues.[10,13] OCT1 is mainly expressed in the liver, OCT2 is mainly expressed in the basolateral membrane of renal proximal tubules, and OCT3 is highly expressed in skeletal muscle.[14–16] All of them play important roles in absorption, excretion, and distribution of cationic drugs.

In the human body, almost 40% of drugs are organic cation in a physiological environment, therefore numerous drugs are potential substrates of OCTs.[17] More and more studies have demonstrated that OCTs, to a small or large extent, play a role in cellular uptake of multiple drugs and the development of drug resistance in various diseases, and also influence the progression and survival of cancers and the response to anti-cancer drugs in human malignant tumors. Especially, much attention has been paid to the role of OCT1 in HCC.

This review therefore aimed to show the expression of OCT1 in normal liver tissue and HCC tissue, and elucidate certain defined relationships between OCT1 and HCC, and summarize recent research progress regarding OCT1 and HCC. We believe that a comprehensive overview will contribute to a better understanding of the role of OCT1 in HCC and we aimed to further investigate characteristics of OCT1 in HCC and provide a new therapeutic approach for HCC treatment.

Structure and variant of OCT1

OCT1 was first cloned from a rat in 1994,[18] and first cloned from a human and described in detail in 1997.[19,20] The human OCT1 encoded by SLC22A1 gene is located on chromosome 6q25-q27 in a cluster and the gene contains eleven exons and ten introns, with a span of approximately 37.41 kb.[21–24] The OCT1 protein has 554 amino acids and consists of 12 α-helical transmembrane domains (TMDs) with N- and C-termini localized in intracellular position. The site of OCT1 protein in intracellular loop between TMD6 and TMD7 domains is phosphorylated post-translationally.[25,26] Additionally, residues of certain amino acids, including cysteine, glycine, and proline, are rather conserved in overall OCTs cloned hitherto, indicating that these residues play a pivotal role in the establishment of the secondary structure of these proteins.[27] When cation combines with OCT1, the conformation of transporter will be changed and finally OCT1 mediates the transposition across plasma membrane.[28]

Notably, there are many single nucleotide polymorphisms (SNPs) in SLC22A1 gene, which results in the presence of numerous SLC22A1 variants.[28,29] It has been confirmed that the existence of genetic variants in genes encoding proteins relating to the processes of drug detoxification is responsible for drug reaction, and sometimes contributes to serious consequences in regard to drug toxicity and therapeutic effect.[30] A broad range of drugs applied in clinical treatment are organic cations, therefore the genetic variant of SLC22A1 gene has important clinical significance for human pharmacology. For example, a variant of SLC22A1 gene inserted by an 8 bp in intron 7 between exons 7 and 8 brings about a truncated protein, which probably predisposes toward universality of adverse side effects in metformin-treated type 2 diabetes patients.[31] SLC22A1 gene has more than 1,000 site-mutations in the open reading frame, in the

Table 1 Natural substrates and drugs transported by organic cation transporters (OCTs)

OCTs	Natural substrates	Drugs
OCT1	TEA, MPP, ASP, acetylcholine, choline, corticosterone, epinephrine, histamine, guanidine, salsolinol serotonin, thiamine, progesterone, prostaglandin E_2/F_2.[9,22,96–101]	Acyclovir, atenolol, debrisoquine, furamidine, ganciclovir, lamivudine, lamotrigine, metformin, oxaliplatin, pentamidine, picoplatin, tropisetron, zalcitabine.[102–105]
OCT2	TEA, MPP, ASP, N-methylnicotinamide, aminoguanidine, acetylcholine, dopamine, epinephrine, norepinephrine, serotonin, histamine, cyclo (His-Pro), salsolinol, agmatinepolyamine, putrescine, choline.[22,100,101]	Amantadine, amiloride, atenolol, cimetidine, cisplatin, famotidine, ifosfamide, lamivudine, memantine, metformin, oxaliplatin, picoplatin.[102–103,106]
OCT3	epinephrine, norepinephrine, histamine, agmatine, cyclo (His-Pro), salsolinol.[101,]	Cisplatin, etilefrine, lamivudine, lidocaine, metformin, oxaliplatin, pramipexole, quinidine.[103,107]

Abbreviations: TEA, tetraethylammonium; MPP, 1-methyl-4-phenylpyridinium; ASP, 4-[4-(dimthylamino)-styryl]-Nmethylpyridinium.

promoter sequence, even in certain introns described in previous reports. However, we still have no complete understanding about the biological implication of numerous SNPs in the untranslated regions.[32–34] Except for the transcript variant hOCT1G/L554, most of OCT1 transcript variants will be translated into truncated proteins on account of the "skip" of certain exons and retention of several introns in variant mRNAs.[23,28] This is the reason why many previous reports show that OCT1 variant tends to be less functional or non-functional.[17,32,35–37] Regarding some less functional or non-functional OCT1 variants, the alterations of evolutionarily conserved glycine residues were observed, and the result indicates that these residues may play a key role in the function of OCT1.[35,36] Thus, amino acid variant has peculiar biological value for providing information about whether these residues mediate activity of protein and specificity of substrate.[25]

Some studies also demonstrated that several non-synonymous mutations exist on the SLC22A1 gene in each subject from different racial groups, such as L160F, P341L, and M408V. In addition, these variants still maintained transport ability own relatively high frequency in SLC22A1 gene.[38] However, not overall SLC22A1 gene mutations exhibit reduced function of transporters. For instance, patients suffering from chronic myeloid leukemia with the wild-type L160F variant have a worse response to imatinib than those with the mutation.[39]

Function of OCT1

OCT1, the poly-specific amphiphilic solute facilitator of transmembrane protein, transports organic cations electrogenically independent of Na^+ and H^+gradients.[19,40] Since OCT1 is mainly expressed in the liver, OCT1 predominates not only in the delivery of many endogenous substrates and cationic drugs into hepatocytes from sinusoids, but also in the release of organic cations from hepatocytes to sinusoids.[17,22,41] In hepatocytes, OCT1 mediates the detoxification of various endogenous or xenobiotic substrates in the first step.[25,42]

OCT1 is also involved in relevant transport of substances in other organs, such as the absorption and secretion of organic cations in the small intestine,[9,41] reabsorption of ultra-filtrated cations in the kidney and absorption of certain drugs in lungs.[41,43] Additionally, OCT1 promotes organic cations to traverse the blood–brain barrier in the brain and motivates the uptake of endogenous substrates and antiviral drugs in human immune cells.[44,45]

Expression and regulation of OCT1 in the liver

As described previously, OCT1 protein is expressed mainly in the liver, located in the basolateral sinusoidal membrane of normal hepatocytes and to a lesser degree in cholangiocytes. However, there are big differences in OCT1 protein and mRNA levels in different people. The high variation of OCT1 protein and mRNA levels (83- and 113-, respectively) was shown in 136 of 150 liver samples collected from Caucasian subjects. Similarly, this high variation (23.6- and 15.9-fold, respectively) was also detected in a Korean population. The correlation coefficient value of OCT1 protein and mRNA is just 0.53, which probably means very low post-transcriptional regulation of SLC22A1 gene expression.[17,46] The hepatic OCT1 mRNA possesses the highest expression in all human organs, but OCT1 transcripts have a pretty low expression in various other organs, such as the brain, testis, small intestine, spleen, mammary gland, eye, heart, kidney, lung, adipose tissue, skeletal muscles, and immune cells.[14,17,45,47–52] Similarly, OCT1 protein is also expressed in other tissues in low levels. OCT1 is localized to the lateral and basolateral membranes of enterocytes,[53,54] the luminal membrane of pulmonary epithelial cells,[43,55] and the endothelial cells of brain microvessels.[44]

Also, OCT1 expression in various tumor cells has been demonstrated, such as HCC cells, lung cancer cells, and lymphoma cells.[56–59] Significant down-regulation of OCT1 expression was detected in a variety of liver cancer tissues, such as HCC, cholangiocarcinoma (CCA), and hepatoblastoma, compared with adjacent non-tumor liver tissue.[37,60–62]

OCT1, predominating in hepatic uptake and excretion of cationic drugs and endogenous substances, is highly expressed only in hepatic parenchyma cells. Apparently, it implies that the expression of OCT1 is possibly regulated by certain liver-enriched transactivators. Saborowski et al found that HNF-4α can activate SLC22A1 gene to encode OCT1 protein via binding to two contiguous DNA-response elements contained by OCT1 promoter.[63] Some reports showed that HNF-4α also regulates the expression of many genes affecting most aspects of healthy hepatic function.[64–70] These functions refer to regulation of hepatic cell development, differentiation, bile acid synthesis, xenobiotic detoxification, serum protein production, and energy metabolism.[71] On the other hand, bile acid chenodeoxycholic acid (CDCA) is a typical ligand of farnesoid X receptor. The activation of HNF-4α to OCT1 tends to be

interrupted by CDCA via interference of small heterodimer partner (SHP) (Figure 1A).[63] Thus, when patients have cholestatic liver disease, OCT1 expression is down-regulated due to the increasing bile acid level which interferes with the promotion of OCT1 transcription by HNF-4α. Further studies demonstrated that upstream stimulating factors (USFs), USF1 and USF2, served as pivotal transcriptional regulators of the SLC22A1 gene via an E-box (CAGTG) which is located in the SLC22A1 core promoter region with abundant transcriptional factors, increasing the HNF-4α-mediated transactivation of SLC22A1 gene in another way.[72] In a hepatocyte-derived cell lines model, the HNF-4α-mediated transactivation of SLC22A1 gene was repressed by ligand-mediated activation of PXR via competing for SRC-1 with HNF-4α and USFs, for example, rifampicin, a ligand of PXR, can activate PXR to down-regulate SLC22A1 gene indirectly (Figure 1B).[73] This competition is called squelching.[74,75] In addition, Rulcova et al showed that glucocorticoids could transactivate SLC22A1 gene via up-regulating HNF-4α (Figure 1C).[76] Moreover, there are also additional transcription factors, such as CCAAT/C/EBP -α, -β, and -3γ, which generate a special effect on the transcription regulation of hepatic drug transporters.[77,78]

Ciarimboli et al established two different OCT1 expression systems, hOCT1-transfected Chinese hamster ovary cell line (CHO-K1) and human embryonic kidney cortex cells (HEK293-cells), to investigate the regulation mechanism of OCT1 protein function.[42] It has been shown that there are diverse intracellular signaling pathways which, together, regulate the function of OCT1. For example, OCT1 is negatively regulated by activation of PKA and endogenously positively regulated by the Ca^{2+}/CaM complex, the Ca^{2+}/CaM-dependent CaMKⅡ by PKA, and $p56^{lck}$ tyrosine kinase. Additionally, the result demonstrated that OCT1 defers in the same regulatory signaling pathway in different expression systems and also showed that the activation or inhibition of specific regulatory patterns and different expression systems collectively influences substrate affinities to a greater or lesser degree.[42,79]

OCT1 and development and progression of HCC

There are big discrepancies of OCT1 expression between hepatic tumor cell lines and healthy human hepatocytes. Heise et al first described the expression profiles of OCTs in a bigger series of human HCC, and the analysis of experimental data indicated that HCC patients with low expression of OCT1 usually progress to further advanced HCC stage and have worse survival than those with relatively high expression of OCT1.[62] Schaeffeler et al demonstrated that OCT1 expression in HCC is significantly inversely correlated with expression of the tumor proliferation marker MIB1/Ki-67,[56] indicating that OCT1 inhibits tumor proliferation via certain pathways. Previous studies also showed that MIB1/Ki-67 expression was decreased in diethylnitrosamine-treated $JNK1^{-/-}$ knockout mice[80] and that the high activation of JNK1 in HCC tissues is related to the reduction of OCT1 mRNA expression and worse prognosis.[81] In addition, the study from Lautem et al also found that the expression of OCT1 was down-regulated in patients with cholangiocellular carcinoma, which was closely related to larger tumor sizes or advanced tumor stage and a poorer overall patient survival.[82]

The fundamental mechanisms accounting for the reduced OCT1 expression in HCC tissues are still not understood completely. The study from Schaeffeler et al showed that DNA methylation of OCT1 is associated with down-regulation of OCT1 in HCC.[56] Several studies discussed the reasons of abnormal DNA methylation level in HCC. Lambert et al demonstrated that the methylation state in defined genes in HCC is affected by alcohol intake or viral infection, therefore inducing hepatocarcinogenesis.[83] Even though the understanding of the reduced expression of OCT1 in hepatic malignant cells is still not enough and the specific causes of aberrant DNA methylation may need to be elucidated further, undoubtedly, we can regard DNA methylation index of OCT1 as a novel molecular marker for diagnosing HCC at the early stage, and it may provide a new therapeutic method, such as pretreatment of demethylation, for patients with HCC.[56]

OCT1 and HCC treatment

Traditional chemotherapeutic drugs for HCC fail to obtain a relevant survival benefit because of marked chemo-resistance.[84,85] Sorafenib is one of the most effective drugs to conquer chemo-resistance in primary HCC.[37] Although sorafenib is a pretty effective antitumor drug in HCC treatment, it results in different effects in clinical therapy. Honestly, sorafenib treatment is far below optimal expectation by reason of a pronounced refractoriness that liver tumors possess originally to sorafenib.[86] Up to now, many studies have been conducted to investigate the fundamental mechanisms of the response to sorafenib and

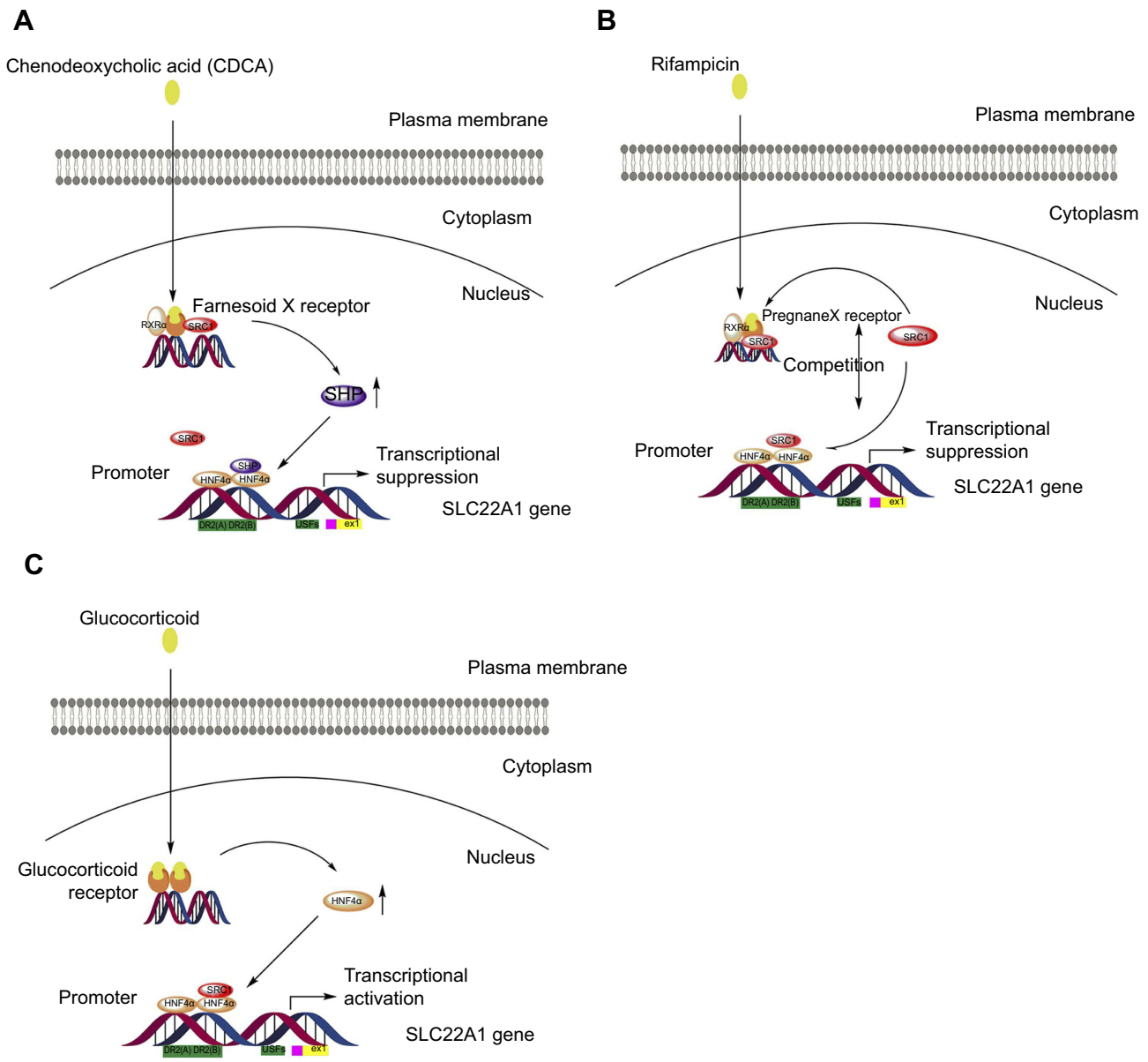

Figure 1 Schemes of pathways/processes affecting OCT1 expression.
Notes: (**A**) The SLC22A1 gene tends to be suppressed by CDCA via interference of small heterodimer partner (SHP), which can co-repress HNF-4α transactivation. (**B**) PXR is activated by rifampicin to compete for SRC-1 with HNF-4α, and thus represses the HNF-4α-mediated transactivation of SLC22A1 gene. (**C**) The HNF-4α-mediated transactivation of SLC22A1 gene is activated by glucocorticoids binding glucocorticoids receptor via up-regulating HNF-4α.
Abbreviation: CDCA, chenodeoxycholic acid.

trials have been carried out to surmount the obtainment of this drug resistance.

The heterogeneity of antitumoral efficacies of sarafenib in different patients, and the drug-related adverse side effects of sorafenib treatment make it essential to recognize biomarkers either in tumor tissue or peripheral blood to predict therapeutic outcomes of patients in individual treatment schemes.[87] Phorbolmyristate acetate-induced phosphorylation of ERK has been considered as a blood biomarker[88] and in addition, the level of pERK expression was identified as an ideal intratumoral marker of drug response.[89] Not only the presence of the molecular targets of sorafenib in hepatic tumors, but also the expression of various drug transporters displays a putative indicator of response to treatment. The specific mechanism of action of sorafenib is determined by access to intracellular targets, which may be affected by alteration of the expression and activity of transporters responsible for its uptake.[37,87] OCT1 plays a key role in the uptake of sorafenib in hepatic cells, which has encouraged numerous teams to

study the availability of OCT1 expression as a useful biomarker for response to sorafenib therapy for HCC.[25,37,90] Grimm et al reported that intratumoral OCT1 mRNA expression probably played a promising role as a prognostic biomarker for HCC patients receiving sorafenib treatment.[90]

Substrates mediated by OCT1 are endogenous and exogenous organic cations, involving drugs like metformin, anthracyclines, platinum derivatives, and tyrosine kinase inhibitors.[22,38,91,92] Generally, the drug-relevant transporter determines the response to the drug via affecting uptake of the drug in hepatocytes, for example, metformin is influenced by alterations in OCT1 expression and by the presence of impaired functional variants.[35] And there is a similar relationship between OCT1 genic mutations and a lower response to imatinib in patients with chronic myeloid leukemia.[93] Does this relationship still exist between OCT1 and sorafenib? Herraez et al reported that two novel identified variants of OCT1, R61S fs*10 and C88A fs*16, which encode truncated proteins unable to get to the plasma membrane, were expressed in HCC. Both the presence of less functional variants and down-regulated expression of OCT1 together, probably significantly affected the uptake and response of these tumors to sorafenib.[37] A further experiment from Geier et al found that there was no difference in sorafenib response in HCC tissues with and without OCT1 expression, but when considering OCT1 expression level at the plasma membrane of HCC cells, a pronounced better survival was presented in patients with high expression level at the plasma membrane.[87] They thus concluded that the expression of OCT1 at the plasma membrane is more significantly associated with a beneficial response in HCC patients treated with sorafenib rather than overall OCT1 expression. Thus, based on the views of Herraezetal and Geieretal, we easily see that variants and expression of OCT1 are possibly not the root reasons contributing to reduced sensitivity to sorafenib, and the effective expression of OCT1 at the plasma membrane may determine the response to sorafenib in patients with HCC. Considering that a large proportion of synthesized OCT1 mRNA is constituted by non-functional aberrant variants, Geieretal investigated the association between OCT1 and HCC at the level of proteins in order to reflect OCT1 function better.[87] And another surprising finding of this research was that expression of OCT1 protein at the plasma membrane did not correlate with tumor stage and previous treatment with transcatheter arterial chemoembolization or radiotherapy. Interestingly, Ruba et al recently showed that epigenetic factors and highly aberrant splicing, including miRNA-mediated mRNA decay and hypermethylation, can partly account for the low expression of OCT1 in HCC, and the down-regulated OCT1 triggers impaired sorafenib uptake and cytotoxic events.[94] Also, Lozano et al found a similar result in CCA, which showed that promoter hypermethylation, aberrant splicing, and miRNA-mediated degradation resulted in reduction of OCT1 mRNA and sorafenib uptake/response in CCA.[95] These discoveries also shed new light on the relationship among OCT1, sorafenib, and HCC. Based on these reports, OCT1 truly plays a critical role in response to sorafenib in HCC patients and is deeply involved in the development of sorafenib chemo-resistance.

Conclusion

In this review, we focused on research progress of OCT1 and the relationship between OCT1 and HCC in the last 2 decades. A number of achievements have been made in the field of regulatory mechanisms of OCT1 in healthy liver. The specific roles of OCT1 in the occurrence and progression of HCC are still elusive, and the precise molecular mechanisms of down-regulated OCT1 expression in HCC still need further investigation. However, we can confirm that OCT1-related functions are profound and novel targets for HCC research.

From existing studies of OCT1, it has been shown that OCT1 variant is an essential part of OCT1 subset, and we predict that perhaps a variant of OCT1 plays a critical role in many fields, including physiological and pathological conditions. There is still a great number of functions and presence of OCT1 variants to be found in the future, and further studies are urgently needed to comprehensively describe more mechanisms, epigenetic factors, transcriptional, and post-transcriptional factors regulating OCT1 expression and function in HCC.

OCT1 is involved in the formation of sorafenib resistance as well as in the uptake of sorafenib in HCC cells. Further studies are necessary to understand and solve this contradiction between OCT1 and sorafenib. On one hand, maybe we could look for the breakthrough at the level of amino acid residues of OCT1 variants, since the changes in these residues play a key role in the appearance of dysfunctional OCT1 variants, which dramatically affected the response of HCC patients to sorafenib. On the other hand, whether OCT1 has any connection with other various signaling pathways of developing sorafenib resistance, is also worth being considered.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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