Relevance of CYP3A5 Expression on the Clinical Outcome of Patients With Renal Cell Carcinoma

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Abstract. Background/Aim: This study aimed to elucidate the detailed characteristics of CYP3A5 expression and the association between CYP3A5 expression and clinical outcomes in patients with renal cell carcinoma (RCC). Patients and Methods: This study retrospectively enrolled 124 Japanese patients with RCC treated at the Okayama University Hospital. The commonest CYP3A5 gene polymorphism, CYP3A5*3, and expression levels of CYP3A5 mRNA and protein in each tissue were examined. Results: Expression of CYP3A5 mRNA and protein in RCC tissues was significantly down-regulated compared to that in adjacent normal tissues. High level of CYP3A5 mRNA expression significantly extended cancer-specific survival (p=0.004) and overall survival (p=0.002). The CYP3A5 mRNA expression level was identified as a significant independent prognostic factor for both cancer-specific survival and overall survival. Conclusion: CYP3A5 could serve as a potential marker for prognostication and treatment planning for patients with RCC.

Renal cell carcinoma (RCC) is the commonest cancer of the kidney and comprises approximately 90% of all cases of kidney cancer (1). RCC is estimated to account for 2% of new cancer cases or cancer deaths worldwide (2, 3). Advances in cancer therapy have improved the 5-year survival rates for RCC, although the overall prognosis for RCC remains unsatisfactory, at approximately 65% of the current 5-year survival rates for RCC (4). Moreover, the global incidence of RCC has been gradually increasing (5).

Cytochrome P450 (CYP) 3A is the most abundant CYP subfamily that is responsible for the metabolism of a large number of substrates in humans. The major CYP3A isoform is CYP3A4; however, three minor isoforms, CYP3A5, CYP3A7, and CYP3A43, have been reported (6). Of these, CYP3A5 is the most abundantly expressed enzyme of the minor CYP3A isoforms in adults (6). The CYP3A5 gene is highly polymorphic, which causes individual variations in the expression of CYP3A5. The commonest allele responsible for the variable protein expression of CYP3A5 is CYP3A5*3 (rs776746, 6986 A>G) (7). Individuals who are homozygous for the CYP3A5*3 allele either express very low levels of CYP3A5 protein or lack CYP3A5 protein expression (7, 8). Interestingly, evidence from small cohort studies indicate that CYP3A5, but not CYP3A4, is markedly expressed in the normal kidney with a CYP3A5*1 allele (9, 10). Thus, CYP3A5 is considered to play a role in substrate metabolism in the kidney.

Most studies on the role of CYP3A5 in cancer have focused on the metabolism of exogenous agents, such as anticancer drugs, in the liver and small intestine. Many anticancer drugs are reported to be candidate substrates of CYP3A5 (11, 12). In addition, evidence has shown that CYP3A5 has several roles in cancer progression, via the metabolism of endogenous or carcinogenic substrates, that are independent of the metabolism of anticancer drugs (13).
Moreover, recent studies have suggested that CYP3A5 itself acts as a tumor suppressor by regulating cell signaling (14, 15). Thus, CYP3A5 expression has been proposed as a potential marker for cancer prevention and treatment. However, the potential role of CYP3A5 in promoting or inhibiting cancer progression may differ depending on the type of cancer. Thus far, the detailed characteristics of CYP3A5 expression in RCC and its clinical relevance in RCC patients remain unknown despite the fact that renal cells express CYP3A5. More information on CYP3A5 expression profiles in RCC may contribute to a better understanding of the underlying malignant behavior and metabolic capacity of RCC.

The aim of this study was to elucidate the detailed expression profiles of CYP3A5 and the association between CYP3A5 expression and clinical outcomes in RCC patients. Unlike most previously reported studies that focused on either the genotype or phenotype of CYP3A5 in cancer patients, this study has clarified both genotypic and phenotypic characteristics in RCC tissues. Moreover, to the best of our knowledge, this study includes the largest number of samples to directly elucidate the details of CYP3A5 expression profiles and its clinical relevance in RCC patients.

Patients and Methods

Patients. This study retrospectively enrolled 124 Japanese RCC patients who underwent surgery between March 2003 and December 2015 at the Okayama University Hospital and fulfilled the following criteria: 1) no neoadjuvant drug therapy or radiotherapy, 2) no history of other tumors, and 3) availability of detailed clinicopathological data. The collected RCC tissues and the corresponding adjacent normal kidney tissue specimens were stored at −80°C until analysis. Detailed information on patient characteristics is listed in the Table I. The nuclear grade values of participants were determined according to the General Rule for Clinical and Pathological Studies on Renal Carcinoma (16). In the samples with Fuhrman’s grading score, grades 1 to 3 corresponded to Fuhrman’s grading, and Fuhrman’s grade 4 corresponded to grade 3 disease scoring by the general rule. Cancer-specific survival (CSS), which is defined as death due to cancer-related problems, and the overall survival (OS) was ascertained from the records at Okayama University Hospital or the Okayama prefectural office or through a phone call to the patient, other hospitals, or the relevant general practitioner. This study was approved by the ethics committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences of Okayama University Hospital (approval number: 1802–033) and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Patients provided informed consent for study participation and were given the opportunity to freely opt out of this study at any time.

Preparation of DNA, RNA, and protein from each tissue specimen. RCC tissues or the adjacent normal tissues were sliced in half, and each part was used separately for genomic DNA/total RNA isolation and protein extraction, respectively. When the weight of tissue specimens was less than 30 mg, the tissues were not divided and only genomic DNA/total RNA was isolated without protein extraction. Genomic DNA and total RNA isolation were carried out using TRIzol® reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer’s instruction. Total proteins from each tissue were extracted by homogenizing with an extraction buffer comprising 20 mM Tris-HCl (pH 7.4), 150 mM sodium chloride, 10 mM EDTA, 0.5% Triton X-100, and 0.5% sodium cholate, followed by two cycles of freezing and thawing. After centrifugation for 15 min at 14,000 rpm at 4°C, the supernatant was used as the protein fraction.

CYP3A5*3 genotyping. CYP3A5*3 genotyping for each patient was carried out by the PCR-restriction fragment length polymorphism method with Dral (Takara, Shiga, Japan) and using specific primers (forward, 5'-CTAACCTATACCTTGTTTTTTAAAGGCTCTTITTGTTC TTAA-3'; reverse, 5'-AAGGTACTATGTTATGTAATCCA TAC-3') as described previously (17). Genomic DNA isolated from adjacent normal kidney tissues was used as the template for CYP3A5*3 genotyping.

Real-time PCR. Real-time reverse transcription PCR was carried out using ReverTra Ace® qPCR RT Master Mix with gDNA Remover (TOYOBIO, Osaka, Japan) and THUNDERBIRD® SYBR qPCR Mix (TOYOBIO) with specific primers (forward, 5'-AAGGTACTATGTTATGTAATCCA TAC-3'; reverse, 5'-CTAACCTATACCTTGTTTTTTAAAGGCTCTTITTGTTC TTAA-3'; forward, 5'-GAGGTACTATGTTATGTAATCCA TAC-3'; reverse, 5'-GAGGTACTATGTTATGTAATCCA TAC-3') according to the manufacturer’s instructions as described previously (17). GAPDH mRNA expression was used as an internal standard reference for CYP3A5 mRNA expression.

Western immunoblot analysis. Western immunoblot analysis was carried out as described previously (17). Polyclonal rabbit antibodies against CYP3A5 (Abcam, Cambridge, England) and GAPDH (ProteinTech, Rosemont, IL, USA) were used as the primary antibodies. Recombinant CYP3A5 (Corning Gentest, Woburn, MA, USA) was used as a positive control for the specific detection of CYP3A5. GAPDH protein expression was used as an internal standard reference for CYP3A5 protein expression.

Microarray dataset analysis. Microarray datasets from the Gene Expression Omnibus (GEO) database at the National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/geo/)
were used to determine the difference in the expression levels of CYP3A5 mRNA between normal kidney tissues and RCC tissues. The database included only two datasets from very small cohorts (GSE781 and GSE6344) that contained paired data for RCC tissues and adjacent normal tissues.

**Statistical analysis.** Statistical analyses were performed using GraphPad Prism 5 (GraphPad, San Diego, CA, USA) and JMP® 15 (SAS Institute Inc., Cary, NC, USA). Paired Student’s t-test or Mann–Whitney U-test test were used for the comparison of the means of the two groups. One-way ANOVA followed by Tukey’s post hoc test was used for multiple comparisons. The cutoff value for CYP3A5 mRNA expression was selected by using receiver operating characteristic curve analysis, and the highest value with both maximum sensitivity and specificity on the curve for survival of patients was applied. Associations between clinical characteristics and information on CYP3A5 expression were evaluated using the chi-square or Fisher’s exact test. Survival curves were produced using the Kaplan–Meier method, and differences in survival rates were compared using the log-rank test. Univariate and multivariate Cox analyses were performed to identify independent prognostic factors. All tests were two-tailed, and p<0.05 indicated statistical significance.

**Results**

**CYP3A5 expression profiles in RCC tissues and adjacent normal tissue specimens based on CYP3A5*3 genotype.** The expression of CYP3A5 protein was detected in RCC tissues and adjacent normal tissues (Figure 1A). To assess the details of CYP3A5 expression profiles, CYP3A5 mRNA and protein expression levels were analyzed based on the CYP3A5*3 genotypes (Figure 1B to E). In the adjacent normal tissues, CYP3A5 mRNA expression with the genotypes of *1/*1 and *1/*3 was significantly higher than that of the *3/*3 genotype. In RCC tissues, CYP3A5 mRNA expression with the genotypes *1/*1 and *1/*3 was significantly higher than that with the *3/*3 genotyped; moreover, a significant difference in CYP3A5 mRNA expression between *1/*1 and *1/*3 genotypes was observed. The results for CYP3A5 protein expression profiles were almost the same as those for CYP3A5 mRNA. In the adjacent normal tissues, the protein expression of CYP3A5 with genotypes *1/*1 and *1/*3 was significantly higher than that of the *3/*3 genotype. In RCC tissues, the protein expression of CYP3A5 was significantly higher in *1/*1 than in *1/*3 and *3/*3; however, there was no significant difference in CYP3A5 protein expression between the *1/*3 and *3/*3 genotypes. Significant correlations were observed among CYP3A5 mRNA expression level and its protein expression level in both adjacent normal tissues and RCC tissues (Table II). The allele frequency of CYP3A5*3 was 0.79, which was in the Hardy–Weinberg equilibrium. The concordance rates of the CYP3A5*1 genotype with the CYP3A5 protein expression in the adjacent normal tissues and RCC tissues were 86.4% (n=88) and 70.2% (n=104), respectively.

**Difference in the level of CYP3A5 expression between RCC tissues and the adjacent normal tissues.** In two datasets (GSE781, n=7; GSE6344, n=10) in the GEO database, the expression level of CYP3A5 mRNA in RCC tissues tended to be or was significantly lower than that in the adjacent normal tissues (Figure 2A and B). These results from the two datasets were in accordance with those from the cohort of this study. The expression level of CYP3A5 mRNA in RCC tissues was significantly lower than that in the adjacent normal tissues (Figure 2C). With regard to the level of CYP3A5 protein expression, there was a significant difference in the level of CYP3A5 protein expression between RCC tissues and adjacent normal tissues (Figure 2D). Frequent down-regulation of CYP3A5 protein expression was observed in RCC tissues compared with that in the adjacent normal tissues (Figure 2E).

**Correlation between CYP3A5 expression and clinicopathological parameters in RCC patients.** From results of the significant correlation between CYP3A5 mRNA and its protein expressions and low number of patients who expressed the CYP3A5 protein due to down-regulation of CYP3A5 protein expression, several clinicopathological parameters of RCC patients were assessed for correlation with the CYP3A5 mRNA levels (Table II). In the adjacent normal tissues, CYP3A5 mRNA was not correlated with any clinicopathological parameters. In RCC tissues, high levels of CYP3A5 mRNA expression were significantly correlated with lymph node status and histological types. With regard to the down-regulation of CYP3A5 mRNA expression in RCC tissues, decreased CYP3A5 mRNA expression in RCC tissues was significantly correlated with a higher TNM stage and histological types.

**Impact of CYP3A5 expression on clinical outcome in RCC patients.** The CYP3A5 mRNA level was evaluated to determine whether they correlated with clinical outcomes in RCC patients (Figure 3). In the adjacent normal tissues, there were no differences in CSS and OS with regard to the levels of CYP3A5 mRNA expression. On the other hand, patients with high CYP3A5 mRNA expression levels in RCC tissues exhibited significantly longer CSS and OS, indicating that the level of CYP3A5 expression possibly correlated with clinical outcome in RCC patients. With regard to changes in the levels of CYP3A5 mRNA expression, decreased CYP3A5 mRNA expression also significantly shortened CSS and OS.

Next, we investigated the prognostic value of the level of CYP3A5 mRNA expression in RCC tissues (Table III). Univariate Cox analysis identified TNM stage as a prognostic risk factor for CSS, whereas level of CYP3A5 mRNA expression tended to be a significant risk factor. On the other hand, TNM stage and the level of CYP3A5 mRNA expression were identified as significant prognostic risk factors. All tests were two-tailed, and p<0.05 indicated statistical significance.
factors for OS in univariate Cox analysis. Based on the results for univariate Cox analysis, the number of events in the present study, and the results from a previous paper from similar cohorts (18), we further analyzed two variables, TNM stage and level of CYP3A5 mRNA expression, in multivariate Cox analysis. The results showed that the level of CYP3A5 mRNA expression was an independent prognostic factor for CSS and OS in RCC patients.

Figure 1. CYP3A5 mRNA and protein expression based on CYP3A5*3 genotype in RCC tissues and the adjacent normal tissues. (A) Representative pattern of CYP3A5 protein expression in adjacent normal tissues (N) and RCC tissues (T). Proteins (20 µg) were analyzed by Western immunoblot analysis. PC, positive control (0.5 fmol). (B) and (C), the level of CYP3A5 mRNA expression in adjacent normal tissues (N; B) and RCC tissues (T; C). The expression level is presented as the ratio of the average value of CYP3A5 mRNA expression in the adjacent tissues. (D) and (E), the level of CYP3A5 protein expression in adjacent normal tissues (N; D) and RCC tissues (T; E). The expression levels are presented as mean±SD. ***, **, *, and “ns” indicate p<0.001, p<0.01, p<0.05, and not significant, respectively.
CYP3A isoform expressed in the kidney is CYP3A5, and not CYP3A5 in RCC tissues was valuable in this study. CYP3A4. Therefore, clarifying the detailed expression of protein expression in both RCC tissues and the adjacent expression of CYP3A5 in combination with the using the largest number of samples as compared with other (14, 15, 19-21). Herein, we first elucidated the detailed expression have been reported (6). However, most of these results, we did not find a detectable CYP3A4 (14, 15, 19-21). Matsumoto CYP3A5*3 mRNA in N, p-Value CYP3A5 mRNA in T, p-Value CYP3A5 mRNA, p-Value Total number 88 104 124 CYP3A5 genotype *1/*1 and *1/*3 30 (88.2) 4 (7.4) <0.001 33 (41.6) 5 (22.2) 0.060 - - - - *3/*3 4 (11.8) 50 (92.6) 47 (58.4) 19 (77.8) - - - - CYP3A5 protein expression Yes 20 (58.8) 2 (3.7) <0.001 11 (13.8) 0 (0.0) 0.001 - - - - No 14 (41.2) 52 (96.3) 69 (86.2) 24 (100.0) - - - - Age, years <65 18 (52.9) 23 (42.6) 0.343 36 (45.0) 12 (50.0) 0.667 22 (45.8) 35 (46.1) 0.981 ≥65 16 (47.1) 31 (57.4) - 44 (55.0) 12 (50.0) - 26 (54.2) 41 (53.9) - Gender Male 20 (58.8) 33 (61.1) 0.831 51 (63.8) 16 (66.7) 0.793 17 (35.4) 28 (36.8) 0.872 Female 14 (41.2) 21 (38.9) 29 (36.2) 8 (33.3) 31 (64.6) 48 (63.2) - - - - Tumor stage T1 21 (61.8) 34 (63.0) 0.910 50 (62.5) 13 (54.2) 0.148 34 (70.8) 43 (56.6) 0.111 T2+T3 13 (38.2) 20 (37.0) 30 (37.5) 11 (45.8) 14 (29.2) 33 (43.3) - - - - Lymph node status N0 32 (94.2) 51 (94.4) 1.000 76 (95.0) 19 (79.2) 0.029 47 (97.9) 68 (89.5) 0.152 N1+ N2 2 (5.8) 3 (5.6) 4 (5.0) 5 (20.8) 1 (2.1) 8 (10.5) - - - - Metastasis M0 29 (85.3) 46 (85.2) 1.000 69 (86.3) 17 (70.8) 0.095 43 (89.6) 61 (80.3) 0.169 M1 5 (14.7) 8 (14.8) 11 (13.7) 7 (29.2) 5 (10.4) 15 (19.7) - - - - TNM stage I+II 22 (64.7) 39 (72.2) 0.459 57 (71.3) 13 (54.2) 0.124 38 (79.2) 47 (61.8) 0.043 III+IV 12 (35.3) 15 (27.8) 23 (28.7) 11 (45.8) 10 (20.8) 29 (38.2) - - - - Nuclear grade 1+2 25 (73.5) 46 (85.2) 0.182 62 (77.5) 15 (62.5) 0.152 9 (18.4) 22 (28.9) 0.202 3 9 (26.5) 8 (14.8) 18 (22.5) 9 (37.5) 39 (81.6) 54 (71.1) - - - - Histological type Clear cell 27 (79.4) 39 (72.2) 0.444 67 (83.8) 12 (50.0) 0.001 43 (89.6) 55 (72.4) 0.022 Other 7 (20.6) 15 (27.8) 13 (16.2) 12 (50.0) 5 (10.4) 21 (27.6) - - - - The number of samples was 88 and 104, which corresponded to samples of CYP3A5*3 genotype, CYP3A5 mRNA, and CYP3A5 protein obtained from adjacent normal tissues and RCC tissues, respectively. CYP, Cytochrome P450; N, adjacent normal tissues; T, RCC tissues. Bold values indicate statistical significance.

Discussion

Currently, CYP3A5 expression in cancer is in the spotlight (14, 15, 19-21). Herein, we first elucidated the detailed expression of CYP3A5 in combination with the CYP3A5*3 genotypes and CYP3A5 mRNA expression in RCC tissues using the largest number of samples as compared with other papers. In many previous reports, there is no clear evidence of renal CYP3A4 expression (9, 22, 23). In concordance with those results, we did not find a detectable CYP3A4 protein expression in both RCC tissues and the adjacent normal tissues (n=20, data not shown). Thus, the main CYP3A isoform expressed in the kidney is CYP3A5, and not CYP3A4. Therefore, clarifying the detailed expression of CYP3A5 in RCC tissues was valuable in this study.

The allele frequency of CYP3A5*3 in this study was similar to that in previous reports from the Japanese population (24, 25). Nonetheless, CYP3A5 protein expression did not completely correspond to the CYP3A5*1 genotype in both the adjacent normal tissues and RCC tissues. The concordance rates of CYP3A5 protein expression with the CYP3A5*1 genotype in the kidney were lower than those in the liver and small intestine, where CYP3A5 protein expression was almost completely correlated with the CYP3A5*1 genotype (8). Several polymorphisms, such as CYP3A5*6 and *7, in the CYP3A5 gene that cause variations in the level of CYP3A5 protein expression have been reported (6). However, most of these polymorphisms were not observed or were rarely detected in the Japanese population (25, 26). CYP3A5 is expressed to a
Figure 2. Down-regulation of CYP3A5 expression levels in RCC tissues compared with that in the adjacent normal tissues. (A) and (B), difference in the level of CYP3A5 mRNA expression between adjacent normal tissues (N) and RCC tissues (T) in two datasets from the GEO database (A, GSE781; B, GSE6344). The expression level is presented as the ratio of the average value of CYP3A5 mRNA expression in the adjacent tissues. (C) and (D), differences in the expression levels of CYP3A5 mRNA (C, n=124) and protein (D, n=78) between adjacent normal tissues (N) and RCC tissues (T) in the cohort of this study. The expression levels are presented as mean±SE. (E), detailed expression changes of CYP3A5 protein from adjacent normal tissues to RCC tissues. The total protein fraction of the paired sample with RCC tissues and the adjacent normal tissues was 78. Down, Up, and ND indicate down-regulation, up-regulation, and not detected, respectively.
Figure 3. Impact of CYP3A5 mRNA expression on the survival of RCC patients. (A)–(D), Kaplan–Meier analysis of CSS and OS based on the CYP3A5 mRNA expression in normal adjacent tissues (A and B) and RCC tissues (C and D). (E) and (F), Kaplan–Meier analysis of CSS (E) and OS (F) based on changes in the expression levels of CYP3A5 mRNA. Incr. and Decr. indicate increasing and decreasing, respectively.
The down-regulation of CYP3A5 protein seems to be correlated with the expression of CYP3A5 mRNA and CYP3A5 protein. This may be partly explained by this down-regulation. A recent study has shown that there is no association between the expression of CYP3A5 genotype in the kidney and risk of ovarian cancer (30), indicating that the expression of these nuclear receptors might be involved in the regulation of CYP3A5 expression in RCC.

The difference in the level of CYP3A5 expression between normal tissues and cancer tissues has been determined in several types of cancer. The level of CYP3A5 expression in liver cancer and lung cancer tissues is lower than that in normal tissues (14, 15, 21). On the other hand, an increase in the level of CYP3A5 expression is observed in ovarian, colorectal, and breast cancers (27-29). A recent study has shown that there is no association between the CYP3A5 expression in RCC tissues. The transcriptional activity of CYP3A5 is possibly regulated by several nuclear receptors, such as pregnane X receptor (PXR; NR1I2), constitutive androstane receptor (CAR; NR1I3), hepatocyte nuclear factor 4α (HNF4α; NR2A1), and peroxisome proliferator-activated receptor alpha (PPARα; NR1C1), all of which are expressed in the kidney (31-34). These receptors activate the transcription of several targeted genes, including CYP3A5, after binding to ligands (35-37).

Using datasets from the GEO database (GSE781 or GSE6344), the mRNA expression levels of three of these receptors, NR1I3, NR2A1, and NR1C1, in RCC tissues were significantly lower than those in the adjacent normal tissues (p<0.001 for NR1I3, p=0.002 for NR2A1, and p=0.002 for NR1C1; data not shown), indicating that the expression of these nuclear receptors might be involved in the regulation of CYP3A5 expression in RCC.

The effects of down-regulation of CYP3A5 on cancer cells were examined in liver and lung cancers, both in vitro and in vivo. In liver cancer, elevated CYP3A5 expression in cancer cells inhibits cell migration and invasion via ROS/mTORC2/p-AKT signaling (14). CYP3A5-induced ROS accumulation inhibits AKT phosphorylation followed by a decrease in mTORC2 kinase activity, suggesting that CYP3A5 plays a protective role in cancer progression. In lung cancers, CYP3A5 represses the activation of Smad1 to inhibit lung cancer metastasis by interacting with ATOH8, which is a transcription factor that could increase the expression of CYP3A5.
phosphorylation of Smad1 (15). The interaction of CYP3A5 and ATOH8 results in a decrease in the Smad1 phosphorylation. The high CYP3A5 expression in these cancer tissues significantly increased the survival duration for these cancer patients, and CYP3A5 expression was identified as an independent prognostic factor in multivariate Cox analysis (14, 21). As our data were in accordance with these results, the high level of CYP3A5 mRNA expression significantly extended survival, and the level of CYP3A5 mRNA expression was identified as an independent prognostic factor for RCC patients. Indeed, the ROS/mTORC2/p-AKT signaling and Smad1 signaling pathways are reported to be important for RCC progression and for development of renal cells, respectively (38, 39). Although further investigation is needed, CYP3A5 might have a suppressive role in RCC by inducing ROS accumulation and decreasing Smad1 phosphorylation as well as in liver and lung cancers.

This study has two limitations, the number of events and the number of samples that expressed the CYP3A5 protein. Event numbers in RCC patients were low as the outcomes of RCC patients were relatively better than those of patients with other cancers, such as liver and lung cancers. Most of the patients included in this study were in relatively good condition because they could undergo surgery, which may also be related to the low number of events in this study. In addition, the number of patients who expressed the CYP3A5 protein was considerably lower than expected based on the allele frequency of CYP3A5*1 in the Japanese population, especially in RCC tissues, due to the discordance of CYP3A5 protein expression with the CYP3A5*1 genotype and down-regulation of CYP3A5 protein expression. Nonetheless, our results suggest that expression levels of CYP3A5 mRNA in RCC tissues significantly correlated with its protein expression and CYP3A5 protein expression is transcriptionally regulated in RCC tissues. Thus, CYP3A5 may be involved in RCC progression and may have a suppressive effect on RCC cells.

Conclusion

This study determined the detailed characteristics of CYP3A5 expression in RCC. The expression of CYP3A5 in RCC tissues was down-regulated compared to that in the adjacent normal tissues. The level of CYP3A5 mRNA expression in RCC correlated with several clinicopathological parameters and survival in RCC patients, suggesting that CYP3A5 may have a suppressive role in RCC. These findings provide basic information on CYP3A5 expression in the kidney, may facilitate better understanding of the importance of CYP3A5 in RCC, and may have implications for future prognostication and treatment planning for patients with RCC.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors’ Contributions

J. Matsumoto: Conceptualization, methodology, data curation, writing - original draft, and funding acquisition. Y. Koter: Formal analysis and data curation. K. Takeuchi: Formal analysis and data curation. S. Watari: Investigation and resources. H. Ueki: Investigation and resources. T. Koyama: Writing - review & editing and supervision. K. Wada: Writing - review & editing and supervision. M. Fujish: Writing - review & editing and supervision. Y. Nasu: Writing - review & editing and supervision. N. Ariyoshi: Writing - review & editing and supervision. All Authors have read and approved the final article.

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Matsumoto et al: CYP3A5 Expression in Patients With Renal Cell Carcinoma

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