Chinese Journal of Physiology 57(4): 220-226, 2014
DOI: 10.4077/CJP.2014.BAC213

Association of *Caveolin-1* Genotypes with Renal Cell Carcinoma Risk in Taiwan

Wen-Shin Chang[1, 2, *], Chia-Wen Tsai[2, 3, *], Shu-Ming Wang[2], Shyi-Wu Wang[4], Hsi-Chin Wu[2], Hong-Xue Ji[2], Chih-Hsueh Lin[2, 5], Zhi-Hong Wang[5], Jou-Chun Chou[5], Da-Tian Bau[1, 2, 3], and Paulus S. Wang[3, 5, 6]

[1]*Graduate Institute of Clinical Medical Science, China Medical University, Taichung 40402*
[2]*Terry Fox Cancer Research Laboratory, China Medical University Hospital, Taichung 40447*
[3]*Graduate Institute of Basic Medical Science, China Medical University, Taichung 40402*
[4]*Department of Physiology and Pharmaclogy, College of Medicine, Chang-Gung University, Kwei-San, Taoyuan 33302*
[5]*Medical Center of Aging Research, China Medical University Hospital, Taichung 40402*
and
[6]*Department of Biotechnology, Asia University, Taichung 41354, Taiwan, Republic of China*

Abstract

The alteration of caveolin-1 (Cav-1) during carcinogenesis is of great interest and its over-expression in the tumor cell cytoplasm can predict a poor prognosis of renal cell carcinoma (RCC). However, whether the over-expression in RCC is associated with inherited polymorphism is not clear. In this hospital-based case-control study, the association of *Cav-1* genotypes with RCC risk in a central Taiwanese population was investigated. Ninety-two patients with RCC and five hundred and eighty of age/gender-matched healthy controls were recruited and genotyped for six polymorphic sites at *Cav-1*, C521A (rs1997623), G14713A (rs3807987), G21985A (rs12672038), T28608A (rs3757733), T29107A (rs7804372), and G32124A (rs3807992). The results showed that there were statistically different distributions of the genotypic (P = 0.0170 and 0.0011) and allelic (P = 0.0033 and 0.0352) frequencies for the *Cav-1* G14713A and T29107A polymorphisms among RCC patients and control subjects, respectively. As for the haplotype analysis, subjects carrying "GG/AT or GG/AA" at *Cav-1* G14713A/T29107A showed a 2.06-fold increased odds ratio of RCC compared to those with GG/TT, while those of any other combinations were of unaltered odds ratios. In conclusion, this is the first report providing evidence showing that *Cav-1* genotype is associated with RCC. The results showed that the G allele of the *Cav-1* G14713A and the A allele of the *Cav-1* T29107A are risky genetic factors for RCC susceptibility and the combinative GG/AT or GG/AA haplotype at *Cav-1* G14713A/T29107A can serve as one of the RCC predictors for Taiwanese.

Key Words: caveolin-1, genotype, renal cell carcinoma, single nucleotide polymorphisms

Introduction

Renal cell carcinoma (RCC) is the predominant form of tumor of the kidney (> 80%), and accounts for about 3% of all human malignancies (9, 13). A significant increase in its incidence has been observed during the last decades, and the RCC annual mortality-to-incidence ratio is on the top among genito-

Corresponding authors: Da-Tian Bau, Ph.D. and Paulus S. Wang, Ph.D., Terry Fox Cancer Research Laboratory, China Medical University Hospital, 2 Yuh-Der Road, Taichung 40447, Taiwan, R.O.C. Tel: +886-4-22052121 ext. 1523, E-mail: artbau2@gmail.com; datian@mail.cmuh.org.tw
*These authors contributed equally to this study.
Received: April 19, 2013; Revised (Final Version): September 11, 2013; Accepted: January 2, 2014.
©2014 by The Chinese Physiological Society and Airiti Press Inc. ISSN : 0304-4920. http://www.cps.org.tw

urinary tract tumors (18). Recently, epidemiologic studies suggested that cigarette smoking, hypertension, obesity, occupational exposures, diet, and family history of cancer are associated with RCC susceptibility (12, 13, 17), and the genetic susceptibility involved in the etiology of RCC was largely unknown and of great interested for scientists in cancer genomics.

Early from this century, researchers have got interested in caveolae to define how these lipid domains involved in the etiology of various types of human cancer (4). Caveolin-1 (Cav-1), caveolin-2 and caveolin-3 are the major structural proteins of caveolae and Cav-1 is most abundant and principal structural protein (6, 10). From the viewpoint of proteomics, the alterations in the expression of Cav-1 in carcinogenesis varied considerably among different types of cancer. For instance, it has been demonstrated that Cav-1 is down-regulated in sarcoma, lung carcinoma, and ovarian carcinoma (3, 21, 22). However, elevated expression of Cav-1 has been associated with the metastasis of esophageal squamous cell carcinoma and prostate cancer and negatively correlated with patient survival (11, 24). As for RCC, Steffens and his colleagues reported that over expression of Cav-1 in the tumor cell cytoplasm can serve as a predictor for the poor prognosis of RCC patients (19). Although the alterations depended much on the tumor site, there is no denying that Cav-1 played an important role in carcinogenesis.

The proteomic evidence for the involvement of Cav-1 in RCC encouraged scientists to conduct further investigations to enlighten the role and its function as diagnostic and prognostic markers in serum and/or urine of RCC. Above this, it is more valuable to study whether different genotypes of *Cav-1* gene are associated with RCC susceptibility to provide predictors at the DNA level for early prediction and prevention. Thus, the aims of this study were to determine the genotypic frequency of six polymorphisms of the *Cav-1* gene at C521A (rs1997623), G14713A (rs3807987), G21985A (rs12672038), T28608A (rs3757733), T29107A (rs7804372), and G32124A (rs3807992), and their associations with RCC susceptibility in Taiwan. To the best of our knowledge, this is the first study evaluating the contribution of *Cav-1* genotypes to RCC oncology all over the world.

Materials and Methods

Study Population and Sample Collection

The hospital-based study consisted of 92 RCC patients and 580 age- and gender-matched cancer-free controls selected from the Health Examination Cohort of the hospital. The patients, diagnosed with RCC, were recruited at the outpatient clinics of general surgery at the China Medical University Hospital in central Taiwan. The clinical characteristics of the patients including their histological details were all graded and defined by expert surgeons (Dr. Wu's team). All the age- and gender-matched cancer-free controls were genetically unrelated to the RCC patients and had no individual history of cancer. The exclusion criteria of the control group included previous malignancy, metastasized cancer from other or unknown origin and any familial or genetic diseases, and those whose genotypes could not be identified in our system. Extra exclusion criteria of the controls were that if they had symptoms suggestive of RCC, such as hematuria. The study was approved by the Institutional Review Board of the China Medical University Hospital and written-informed consent was obtained from all the participants.

Genotyping Design and Conditions

Each participant donated 3-5 ml venous blood and their genomic DNA was prepared within 2 days from their peripheral blood leucocytes using a QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan) and further processed according to our regular methodology in *Cav-1* genotyping (1, 2, 8, 11, 14, 20, 23, 25). Briefly, the following primers were used: for *Cav-1* C521A (rs1997623), 5'-GTGTCCGCTTCTGC TATCTG-3' and 5'-GCCAAGATGCAGAAGGAG TT-3'; for *Cav-1* G14713A (rs3807987), 5'-CCTTCCAG-TAAGCAAGCTGT-3' and 5'-CCTCTCAATCTT-GCCATAGT-3'; for *Cav-1* G21985A (rs12672038), 5'-GGTGTCAGCAAGGCTATGCT-3' and 5'-CCA-GACACTCAGAATGTGAC-3'; for *Cav-1* T28608A (rs3757733), 5'-GCTCAACCTCATCTGAGGCA-3' and 5'-GGCCTATTGTTGAGTGGATG-3'; for *Cav-1* T29107A (rs7804372), 5'-GCCTGAATTG-CAATCCTGTG-3' and 5'-ACGGTGTGAACACG-GACATT-3'; and for *Cav-1* G32124A (rs3807992), 5'-GGTGTCTTGCAGTTGAATG-3' and 5'-ACGGAGCTACTCAGTGCCAA-3'. The following uniform cycling conditions were performed: one cycle at 94°C for 5 min; 35 cycles of 94°C for 30 s, 55°C for 30 s, and 72°C for 30 s; and a final extension at 72°C for 10 min. The PCR products were subject to 3% gel electrophoresis after the digestion of Avr II, Bfa I, Hae III, Tsp509 I, Sau3AI and Nla III, restriction enzymes for *Cav-1* C521A (cut from 485 bp C type into 170+315 bp T type), *Cav-1* G14713A (cut from 268 bp A type into 66+202 bp G type), *Cav-1* G21985A (cut from 251+43 bp A type into 153+98+43 bp G type), *Cav-1* T28608A (cut from 298 bp T type into 100+198 bp A type), *Cav-1* T29107A (cut from 336 bp A type into 172+164 bp T type), and *Cav-1* G32124A (cut from

Table 1. Frequency distributions of baseline clinical characteristics among renal cell carcinoma patients and healthy controls

Characteristics	Patients (n = 92)			Controls (n = 580)			*P*-value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			58.8 (11.7)			58.3 (11.5)	0.8971
Age group (years)							
≦60	47	51.1%		307	52.9%		0.8223
>60	45	48.9%		273	47.1%		
Gender							
Male	59	64.1%		371	64.0%		1.0000
Female	33	35.9%		209	36.0%		
Smoking status							
Smokers	41	44.6%		220	37.9%		0.2499
Non-smokers	51	55.4%		360	62.1%		
Alcoholism status							
Drinkers	37	40.2%		209	36.0%		0.4848
Non-drinkers	55	59.8%		371	64.0%		
Hypertension							
Yes	61	66.3%		302	52.1%		**0.0130***
No	31	33.7%		278	47.9%		
Diabetes							
Yes	21	22.8%		104	17.9%		0.2523
No	71	77.2%		476	82.1%		
Family cancer history							
Yes	6	6.5%		17	2.9%		0.1125
No	86	93.5%		563	97.1%		

*Statistically significant

213+142+67 bp A type into 142+118+95+67 bp T type), respectively.

Statistical Analyses

To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotype frequencies of *Cav-1* single nucleotide polymorphisms (SNP) in the control subjects from those expected under the Hardy-Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's *Chi*-square test or Fisher's exact test (when the expected number in any cell was less than five) was used to compare the distribution of the *Cav-1* genotypes between cases and controls. Cancer risk associated with the genotypes was estimated as odds ratio (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. The data was recognized as significant when the statistical *P*-value was less than 0.05. All statistical tests were performed using SAS, Version 9.1.3 (SAS Institute Inc., Cary, NC, USA) on two sided probabilities.

Results

Frequency distributions of baseline clinical characteristics among renal cell carcinoma patients and healthy controls are presented in Table 1. Since we have matched the patients and healthy controls in age, gender and personal behaviors, there is no difference in the frequency distributions of these clinical characteristics ($P > 0.05$) (Table 1). Noticeably, hypertension seems to be a risky factor for RCC ($P = 0.0130$) (Table 1).

In Table 2, the frequency distributions of the genotypes for the *Cav-1* C521A, G14713A, G21985A, T28608A, T29107A and G32124A of all the subjects are presented. Among them, the genotypic distributions of *Cav-1* G14713A and T29107A were significantly different between RCC and control groups ($P = 0.0170$ and 0.0011, respectively) (Table 2). As for *Cav-1* C521A, G21985A, T28608A and G32124A, the distributions were not different between the two groups (all $P > 0.05$) (Table 2). Overall, the genotypes of two SNPs on *Cav-1,* G14713A and T29107A, are associated with RCC risk and may be biomarkers for Taiwan RCC

Table 2. Distribution of *Cav-1* genotypes among renal cell carcinoma patients and healthy controls

Genotype	Patients	%	Controls	%	*P*-value[a]
C521A_rs1997623					0.4453
CC	89	96.7%	568	97.9%	
AC	3	3.3%	12	2.1%	
AA	0	0.0%	0	0.0%	
G14713A_rs3807987					**0.0170***
GG	69	75.0%	371	64.0%	
AG	22	23.9%	156	26.9%	
AA	1	1.1%	53	9.1%	
G21985A_rs12672038					0.9029
GG	55	60.4%	336	57.9%	
AG	29	31.9%	197	34.0%	
AA	7	7.7%	47	8.1%	
T28608A_rs3757733					0.8705
TT	58	62.4%	345	59.5%	
AT	28	30.1%	188	32.4%	
AA	7	7.5%	47	8.1%	
T29107A_rs7804372					**0.0011***
TT	29	31.5%	285	49.1%	
AT	48	52.2%	191	32.9%	
AA	15	16.3%	104	18.0%	
G32124A_rs3807992					0.5829
GG	51	55.4%	290	50.0%	
AG	34	37.0%	233	40.2%	
AA	7	7.6%	57	9.8%	

[a]*P* based on *Chi*-square test and Fisher's exact test (when any cell examined is less than five); *Statistically significant

early detection and prediction. The typical polymerase chain reaction-restriction fragment length polymorphism analysis for the genotypes of two significant SNPs (*Cav-1* G14713A and T29107A) were shown in Fig. 1.

The distributions of allelic frequencies for the *Cav-1* C521A, G14713A, G21985A, T28608A, T29107A and G32124A among RCC patients and controls are shown in Table 3. The two *Cav-1* SNPs found to be significantly associated with RCC risk in Table 2, G14713A and T29107A, were also found to be associated with higher RCC in their allelic frequency analysis ($P = 0.0033$ and 0.0352, respectively) (Table 3). As for the other four SNPs, the distributions of their allelic frequencies were not significantly different between the control and RCC patient groups (all $P > 0.05$) (Table 3).

The two significant SNPs of *Cav-1* gene, *Cav-1* G14713A and T29107A, were further analyzed by haplotype distribution analysis to evaluate their combinative contribution to RCC susceptibility (Table 4). Compared with the wild-type GG/TT haplotype of *Cav-1* G14713A/T29107A, the GG/AT or GG/AA group has a higher risk of RCC (OR = 2.06, 95% CI = 1.19-3.55). Other combinations of AG/TT, AG/AT or AG/AA, and AA/TT, AA/AT or AA/AA conferred non-significant 0.75-fold (95% CI = 0.31-1.83), 1.57-fold (95% CI = 0.77-3.19) and 0.16-fold (95% CI = 0.02-1.19) effect on RCC risk compared to the wild-type GG/TT haplotype, respectively (Table 4). After adjusted with individual age, gender and behaviors, the trends and significances still unaltered.

Discussion

To our knowledge, this is the first paper to identify and validate the association between the RCC risk and *Cav-1* genotype. In 2010, Moore and his colleagues found that among kidney transplant donors, AA genotype of *Cav-1* tagged SNP rs4730751, was significantly associated with allograft failure (16). The knockdown aberration of Cav-1 expression level has been recently proved to be related to altered cell migration and matrix metalloproteinases (MMPs) activity, and reduced angiogenesis in response to VEGF of the endothelial cells (15). From the viewpoint of

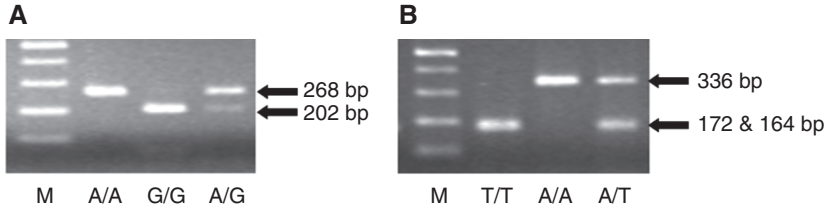

Fig. 1. Polymerase chain reaction-restriction fragment length polymorphism analysis of the G14713A (A) and T29107A (B) genotypes of *Cav-1* gene presented on 3% agarose electrophoresis. M: 100 bp DNA size marker, (A) A/A, A/G and G/G presented for indivisible homozygote, heterozygote, and divisible homozygote, respectively. (B) A/A, A/T and T/T presented for indivisible homozygote, A/T: heterozygote, and T/T: divisible homozygote, respectively.

Table 3. Distribution of *Cav-1* alleles among renal cell carcinoma patients and healthy controls

Allele	Patients	%	Controls	%	*P*-value[a]
C521A_rs1997623					0.4747
Allele C	181	98.3%	1148	99.0%	
Allele A	3	1.7%	12	1.0%	
G14713A_rs3807987					**0.0033***
Allele G	160	87.0%	898	77.4%	
Allele A	24	13.0%	262	22.6%	
G21985A_rs12672038					0.6719
Allele G	139	76.4%	869	74.9%	
Allele A	43	23.6%	291	25.1%	
T28608A_rs3757733					0.6085
Allele T	144	77.4%	878	75.7%	
Allele A	42	22.6%	282	24.3%	
T29107A_rs7804372					**0.0352***
Allele T	106	57.6%	761	65.6%	
Allele A	78	42.4%	399	34.4%	
G32124A_rs3807992					0.2900
Allele G	136	73.9%	813	70.1%	
Allele A	48	26.1%	347	29.9%	

[a]*P* based on *Chi*-square test; *Statistically significant

Table 4. Distribution of *Cav-1* G14713A/ T29107A haplotypes among renal cell carcinoma patients and healthy controls

G14713A/ T29107A haplotype	Patients	%	Controls	%	Odds Ratio (95% CI)[a]	Adjusted Odds Ratio (95% CI)[b]	*P*-value[c]
GG/TT	22	23.9%	182	31.4%	1.00 (Reference)	1.00 (Reference)	
GG/AT or GG/AA	47	51.1%	189	32.6%	**2.06 (1.19-3.55)***	**2.09 (1.16-3.58)***	**0.0087***
AG/TT	7	7.6%	77	13.3%	0.75 (0.31-1.83)	0.78 (0.34-1.93)	0.6679
AG/AT or AG/AA	15	16.3%	79	13.6%	1.57 (0.77-3.19)	1.55 (0.76-3.24)	0.2563
AA/TT, AA/AT or AA/AA	1	1.1%	53	9.1%	0.16 (0.02-1.19)	0.16 (0.02-1.28)	0.0559

[a] 95% CI, 95% confidence interval;
[b] 95% CI, 95% confidence interval, and date were calculated by unconditioned logistic regression adjusted for age, gender, smoking, and alcohol drinking behaviors;
[c] *P* based on *Chi*-square test;
*Statistically significant

cancer proteomics, altered expression level of Cav-1 has been related to the carcinogenesis of a few types of cancer (3, 7, 11, 21, 22, 24). The genetic analysis of *Cav-1* showed that the altered expression levels of Cav-1 in different cancer cell lines may not be caused by spontaneous mutations on *Cav-1* gene (5, 7). All these findings raised our curiosity that whether the personal susceptibility to RCC was determined at upstream of the molecular biology central dogma, the DNA level *via* inherited polymorphic genotypes.

In this study, up to six SNPs of *Cav-1*, C521A (rs1997623), G14713A (rs3807987), G21985A (rs12672038), T28608A (rs3757733), T29107A (rs7804372), and G32124A (rs3807992), were genotyped and analyzed of their distributions among the 92 RCC patients and 580 non-cancer healthy subjects in Taiwan. The results showed that individual genotypes of *Cav-1* G14713A and T29107A were associated with the susceptibility of RCC (Table 2), while the genotypes of other four *Cav-1* SNPs were not. In addition, the haplotypic analysis about *Cav-1* G14713A and T29107A showed that compared with G14713A/T29107A wild-type GG/TT haplotype, those subjects with "GG/AT or GG/AA" haplotypes were of higher RCC risk, while those with other haplotypes, including AG/TT, "AG/AT or AG/AA", "AA/TT, AA/AT or AA/AA", were of similar level of odds ratio to those of wild-type GG/TT haplotype (Table 4). The haplotype analysis also supported the findings in allelic frequency analysis that A allele of G14713A was protective, and A allele of T29107A was risky for RCC susceptibility (Table 3). The similar trends of significance in the "GG/AT or GG/AA" subgroup after age- and behavior-adjustments strengthen the accuracy and reliability of our findings, also, the frequencies of *Cav-1* polymorphisms variant alleles were similar to those reported in the NCBI website in other Asian population studies. Take the minor A allele frequency of *Cav-1* G14713A for instance, the proportion is 22.6% in our control group which is very close to the proportions of 16.7% for Beijing and 22.2% for Tokyo populations in NCBI.

We are also interested in the interaction of Cav-1 genotypes and life-style factors on RCC risk. However, it was found that neither the *Cav-1* G14713A AA genotype nor the *Cav-1* T29107A TT genotype has significant interaction with smoking, alcohol drinking, or hypertension, diabetes or family cancer history on RCC risk (data not shown). The sample size may be a limitation of this study and further validation of our findings with enlarged case sample and functional phynotypic studies are needed.

In conclusion, this is the first report to provide evidence for *Cav-1* G14713A and T29107A, but not C521A, G21985A, T28608A, or G32124A, were associated with higher RCC risk. People with GG/AT or GG/AA haplotype at *Cav-1* G14713A/T29107A were specifically of elevated risk to RCC, and were suggested to adapt and take better care of their personal behavior and diet in their daily life.

Acknowledgments

We are grateful to Fang-Jing Li, Yi-Ting Chang, Tsai-Ping Ho and Tissuebank of China Medical University Hospital for their technical assistance, clinical sample and data collection. The study was supported by the grants from Terry Fox Cancer Research Foundation and China Medical University Hospital (DMR-102-017).

References

1. Bau, D.T., Chang, C.H., Tsai, R.Y., Wang, H.C., Wang, R.F., Tsai, C.W., Yao, C.H., Chen, Y.S., Shyue, S.K. and Huang, C.Y. Significant association of *caveolin-1* genotypes with bladder cancer susceptibility in Taiwan. *Chinese J. Physiol*. 54: 153-160, 2011.
2. Bau, D.T., Tsai, M.H., Tsou, Y.A., Wang, C.H., Tsai, C.W., Sun, S.S., Hua, C.H., Shyue, S.K. and Tsai, R.Y. The association of *Caveolin-1* genotypes with oral cancer susceptibility in Taiwan. *Ann. Surg. Oncol*. 18: 1431-1438, 2011.
3. Belanger, M.M., Roussel, E. and Couet, J. Caveolin-1 is down-regulated in human lung carcinoma and acts as a candidate tumor suppressor gene. *Chest* 125: 106S, 2004.
4. Carver, L.A., Schnitzer, J.E., Anderson, R.G.W. and Mohla, S. Role of caveolae and lipid rafts in cancer: workshop summary and future needs. *Cancer Res*. 63: 6571-6574, 2003.
5. Conde, M.C., Ramirez-Lorca, R., Lopez-Jamar, J.M., Molero, E., Ramirez-Armengol, J.A., Moreno Nogueira, J.A., Pascual, M.H., Ruiz, A., Martin-Cordova, C.G., Real, L.M. and Royo, J.L. Genetic analysis of caveolin-1 and eNOS genes in colorectal cancer. *Oncol. Rep*. 16: 353-359, 2006.
6. Galbiati, F., Engelman, J.A., Volonte, D., Zhang, X.L., Minetti, C., Li, M., Hou, H., Jr., Kneitz, B., Edelmann, W. and Lisanti, M.P. Caveolin-3 null mice show a loss of caveolae, changes in the microdomain distribution of the dystrophin-glycoprotein complex, and T-tubule abnormalities. *J. Biol. Chem*. 276: 21425-21433, 2001.
7. Han, S.E., Park, K.H., Lee, G., Huh, Y.J. and Min, B.M. Mutation and aberrant expression of Caveolin-1 in human oral squamous cell carcinomas and oral cancer cell lines. *Int. J. Oncol*. 24: 435-440, 2004.
8. Hsu, C.M., Yang, M.D., Tsai, C.W., Ho, C.Y., Chang, W.S., Chang, S.C., Jeng, L.B., Tsai, Y., Tsai, F.J. and Bau, D.T. The contribution of *caveolin-1* genotype and phenotype to hepatocellular carcinoma. *Anticancer Res*. 33: 671-677, 2013.
9. Jemal, A., Murray, T., Ward, E., Samuels, A., Tiwari, R.C., Ghafoor, A., Feuer, E.J. and Thun, M.J. Cancer statistics, 2005. *CA: A Cancer J. Clin*. 55: 10-30, 2005.
10. Juhasz, M., Chen, J., Tulassay, Z., Malfertheiner, P.A. and Ebert, M.P. Expression of caveolin-1 in gastrointestinal and extraintestinal cancers. *J. Cancer Res. Clin. Oncol*. 129: 493-497, 2003.
11. Kato, K., Hida, Y., Miyamoto, M., Hashida, H., Shinohara, T., Itoh, T., Okushiba, S., Kondo, S. and Katoh, H. Overexpression of caveolin-1 in esophageal squamous cell carcinoma correlates with lymph node metastasis and pathologic stage. *Cancer* 94: 929-933, 2002.
12. Lindblad, P. Epidemiology of renal cell carcinoma. *Scand. J. Surg*. 93: 88-96, 2004.
13. Lipworth, L., Tarone, R.E. and McLaughlin, J.K. The epidemiology of renal cell carcinoma. *J. Urol*. 176: 2353-2358, 2006.
14. Liu, L.C., Su, C.H., Wang, H.C., Tsai, C.W., Chang, W.S., Ho, C.Y., Wu, C.I., Li, F.J., Lin, C.H., Lane, H.Y. and Bau, D.T. Significant association of caveolin-1 (*CAV1*) genotypes with breast cancer in Taiwan. *Anticancer Res*. 31: 3511-3516, 2011.
15. Madaro, L., Antonangeli, F., Favia, A., Esposito, B., Biamonte, F., Bouche, M., Ziparo, E., Sica, G., Filippini, A. and D'Alessio, A. Knock down of caveolin-1 affects morphological and functional hallmarks of human endothelial cells. *J. Cell. Biochem*. 114: 1843-1851, 2013.
16. Moore, J., McKnight, A.J., Simmonds, M.J., Courtney, A.E., Hanvesakul, R., Brand, O.J., Briggs, D., Ball, S., Cockwell, P.,

Patterson, C.C., Maxwell, A.P., Gough, S.C.L. and Borrows, R. Association of caveolin-1 gene polymorphism with kidney transplant fibrosis and allograft failure. *J. Am. Med. Assoc.* 303: 1282-1287, 2010.

17. Murai, M. and Oya, M. Renal cell carcinoma: etiology, incidence and epidemiology. *Curr. Opin. Urol*. 14: 229-233, 2004.
18. Schrader, A.J., Sevinc, S., Olbert, P.J., Hegele, A., Varga, Z. and Hofmann, R. Gender-specific characteristics and survival of renal cell carcinoma. *Urologe A*. 47: 1182, 1184-1186, 2008.
19. Steffens, S., Schrader, A.J., Blasig, H., Vetter, G., Eggers, H., Trankenschuh, W., Kuczyk, M.A. and Serth, J. Caveolin 1 protein expression in renal cell carcinoma predicts survival. *BMC Urol*. 11: 25, 2011.
20. Tsou, Y.A., Tsai, C.W., Tsai, M.H., Chang, W.S., Li, F.J., Liu, Y.F., Chiu, C.F., Lin, C.C. and Bau, D.T. Association of caveolin-1 genotypes with nasopharyngeal carcinoma susceptibility in Taiwan. *Anticancer Res*. 31: 3629-3632, 2011.
21. Wiechen, K., Diatchenko, L., Agoulnik, A., Scharff, K.M., Schober, H., Arlt, K., Zhumabayeva, B., Siebert, P.D., Dietel, M., Schafer, R. and Sers, C. *Caveolin-1* is down-regulated in human ovarian carcinoma and acts as a candidate tumor suppressor gene. *Am. J. Pathol*. 159: 1635-1643, 2001.
22. Wiechen, K., Sers, C., Agoulnik, A., Arlt, K., Dietel, M., Schlag, P.M. and Schneider, U. Down-regulation of caveolin-1, a candidate tumor suppressor gene, in sarcomas. *Am. J. Pathol*. 158: 833-839, 2001.
23. Wu, H.C., Chang, C.H., Tsou, Y.A., Tsai, C.W., Lin, C.C. and Bau, D.T. Significant association of caveolin-1 (*Cav1*) genotypes with prostate cancer susceptibility in Taiwan. *Anticancer Res*. 31: 745-749, 2011.
24. Yang, G., Truong, L.D., Wheeler, T.M. and Thompson, T.C. Caveolin-1 expression in clinically confined human prostate cancer: a novel prognostic marker. *Cancer Res*. 59: 5719-5723, 1999.
25. Yang, M.D., Tsai, R.Y., Liu, C.S., Chang, C.H., Wang, H.C., Tsou, Y.A., Wang, C.H., Lin, C.C., Shyue, S.K. and Bau, D.T. Association of *Caveolin-1* polymorphisms with colorectal cancer susceptibility in Taiwan. *World J. Gastrointest. Oncol*. 2: 326-331, 2010.