ANTICANCER RESEARCH *43*: 343-349 (2023)
doi:10.21873/anticanres.16169

Association of Matrix Metalloproteinase-2 Genotypes With Prostate Cancer Risk

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Abstract. *Background/Aim: Prostate cancer is one of the most commonly diagnosed malignancies among males, especially in Western populations. Matrix metalloproteinase-2 (MMP-2) plays a critical role in extracellular regulation and metastasis. However, its genotypes have seldom been examined among patients with prostate cancer (PCa). Therefore, the purpose of the study was to evaluate the association of genotypes at MMP-2 promoter -1306 (rs243865) and -735 (rs2285053) with PCa risk in a Taiwanese cohort. Materials and Methods: The profiles of MMP-2 rs243865 and rs2285053 genotypes were examined among 218 PCa patients and 436 healthy controls by polymerase chain reaction-restriction fragment length polymorphism methodologies. Results: The percentages of wild-type CC, and variant CT and TT genotypes on MMP-2 rs243865 were 88.5, 10.6, and 0.9% in the PCa case group and 85.6, 13.5, and 0.9% in the control group, respectively (p for trend=0.5544). The allelic frequency distribution showed that the variant T allele at MMP-2 rs24386 5 was not associated with PCa risk (p=0.3250). As for MMP-2 rs2285053, the results were also non-significant. In addition, there was no association between the genotypes of MMP-2 rs243865 or rs2285053 with age or smoking status on PCa risk. Conclusion: rs11568818 and rs11568819 at MMP-2 promoter region played minor roles in determining individual PCa risk.*

Prostate cancer (PCa) is the second most prevalent malignancy, and the fifth leading death-causing cancer among males worldwide, with about 1,414,000 newly diagnosed cases and 375,304 deaths in 2020 (1). According to global cancer statistics, PCa is the most frequently diagnosed cancer in 112 countries, and the leading death-causing malignancy in 48 countries including USA (2). According to world cancer statistics, PCa cases are predicted to continue to increase due to the trend of global aging (3). From the epidemiological viewpoint, black race, family cancer history, and aging, are three most well-known risk factors for PCa (4). In addition, fitness (5), diabetes mellitus (6), obesity (7), risky diet (8), and over-supplementation of vitamin E (9) may also contribute to the etiology of PCa. However, lack of targets in PCa therapy urge the identification of genetic markers.

The extracellular matrix (ECM) is a meshwork of crosslinked macromolecules that form a dynamic scaffold outside of the cells. It provides homeostasis of the micro-environment, and its imbalances may associate with cancer progression and metastasis (10, 11). Noticeably, matrix metalloproteinases (MMPs, also named matrix metallopeptidases or matrixins) play

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Key Words: Genotype, MMP-2, polymorphism, prostate cancer.

Table I. *Demographics of the prostate cancer cases and control subjects.*

Characteristics	Controls (n=436)			Cases (n=218)			*p*-Value
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			63.9±6.6			63.6±6.9	0.58[a]
<55	275	63.1%		142	65.1%		0.67[b]
≥55	161	36.9%		76	34.9%		
Smoking behavior							
Ever smoker	336	77.0%		177	81.2%		0.27[b]
Non-smoker	100	23.0%		41	18.8%		
Family history							
First degree (Father, brother and/or son)	5	1.1%		17	7.8%		<0.001[b]
Second degree	2	0.5%		4	1.8%		
No history	429	98.4%		197	90.4%		

[a]Based on unpaired Student's *t*-test; [b]based on Chi-square test.

a critical role in tissue remodeling, which is associated with multiple physiological or pathological processes such as angiogenesis, cirrhosis, arthritis, and metastasis *via* their degradation of the ECM components (11-13). In literature, MMP-2 has been shown to closely relate to the metastatic behavior of tumors (14-17). In addition, mounting evidence has shown that MMP-2 over-expression was associated with higher risk of metastasis among various types of cancer (18-23).

MMP-2 is located on chromosome 16q21. This endopeptidase is expressed in a variety of tissues throughout the body (24-26). One of the main functions of MMP-2 is to digest type IV collagen, the major constituent of the cell membrane (27). In literature, it has been reported that *MMP-2* rs243865 and rs2285053 may affect its mRNA and protein expression levels, leading to an increase in the metastatic potential of several types of cancer, such as breast, esophageal, colorectal, oral cancer, and leukemia (28-32). In 2014, *MMP-2* rs243865 genotypes were first investigated for their association with PCa in Turkey (33). In that study, 61 PCa patients and 46 healthy subjects were examined for their *MMP-2* rs243865 genotypes. The *MMP-2* rs243865 CT genotypes were found to be 2.17 times more frequent in the PCa patient group than in the control group without statistical significance (p=0.149) (33). Furthermore, Adabi *et al*. examined the genetic contribution of *MMP-2* rs243865 to PCa in Iran in 2015. They recruited 139 benign prostatic hyperplasia patients as controls and found no association between *MMP-2* rs243865 polymorphism and PCa risk (34). In 2018, Bialkowska *et al*. reported that there is no positive association between *MMP-2* rs243865 genotypes and PCa risk (35). In that study, they recruited 197 healthy men and 197 PCa patients from Poland. Evidence for the association of *MMP-2* rs2285053 genotypes with cancers is inconclusive, and there is none about PCa (36, 37). Another study investigated 150 patients with cervical cancer and 120 healthy individuals in China and reported that *MMP-2* rs2285053 genotypes were associated with cervical cancer susceptibility (36). Also, T allele in *MMP-2* rs2285053 were associated with reduced risk of breast cancer (37).

According to the above information, we aimed at evaluating the association of *MMP-2* rs243865 and rs2285053 genotypes with PCa risk in a representative (case:control=436:218) Taiwanese population for the first time.

Materials and Methods

PCa study population. The current study was approved and supervised by the IRB of China Medical University Hospital (DMR104-IRB-158). All the research protocols were conducted according to the principles of the Declaration of Helsinki. The 436 healthy controls were matched according to age and sex from the Health Examination Cohort of China Medical University Hospital by two folds in sample size of the PCa cases (n=218). The inclusion and exclusion criteria of sampling have been published in our previous papers (38, 39). Some demographic characteristics for all the participants in this study are summarized and compared in Table I.

MMP-2 rs243865 and rs2285053 genotyping. DNA was extracted from the whole blood of each participant as previously published (40-42). In the present study, the profiles of *MMP-2* rs243865 and rs2285053 genotypes among 218 PCa and 436 controls were determined by using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methodology. The sequences of forward and reverse primers for *MMP-2* rs243865 are: 5'-CTTCCTAGGCTGGT CCTTACTGA-3' and 5'-CTGAGACCTGAAGAGCTAAAGAGCT-3', and those for *MMP-2* rs2285053 are 5'-GGATTCTTGGCTTGGC GCAGGA-3' and 5'-GGGGGCTGGGTAAAATGAGGCTG-3'. The primers for *MMP-2* rs243865 and rs2285053 genotyping are the same as we have previously published (42, 43). The PCR condition was set as: 5 min initial step at 94˚C; 40 cycles of 94˚C for 30 s, 55˚C for 30 s, and 72˚C for 30 s; and a final extension step at 72˚C for 10 min. Then, the PCR adducts were subjected to full digestion by *Xsp* I (for *MMP-2* rs243865) and *Hinf* I (for *MMP-2* rs2285053) overnight. The profiles of *MMP-2* rs243865 and rs2285053 of each sample were identified by 3% agarose gel electrophoresis and imagined under UVC irradiation.

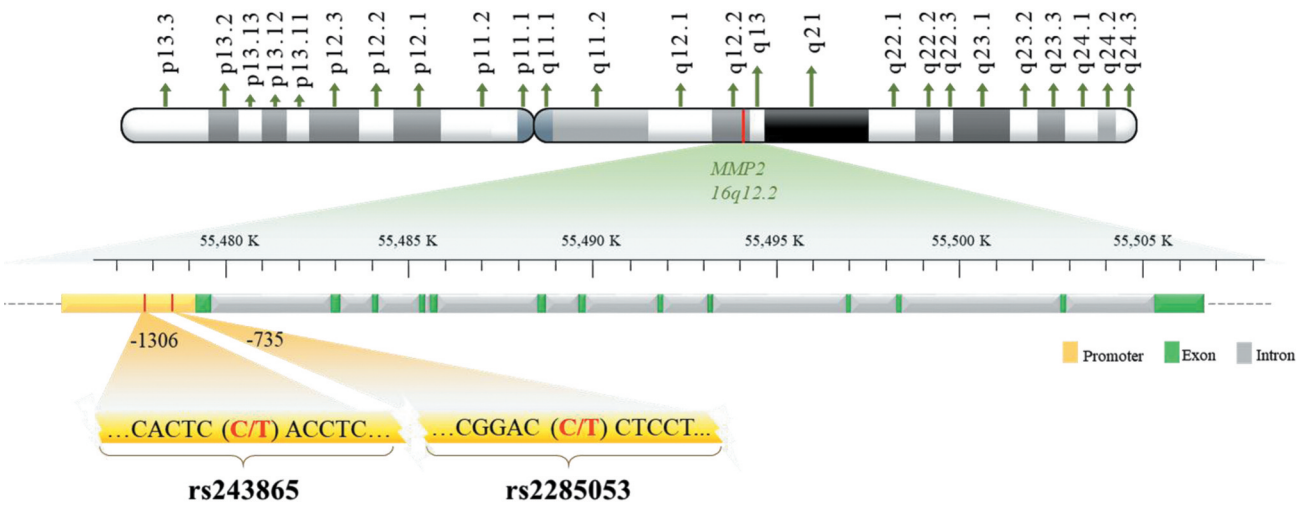

Figure 1. *Physical map of MMP-2 rs243865 and rs2285053 polymorphic sites.*

MMP-2 rs243865 and rs2285053 statistical analysis. The comparison of the ages between the PCa patient and control groups is presented as the mean plus standard deviation (SD), and unpaired *Student's t*-test was used. The Pearson's chi-square or Fisher exact test was used for the evaluation of the associations of *MMP-2* rs243865 and rs2285053 genotypes, and the significant associations were also evaluated as odds ratios (ORs) and 95% confidence intervals (CIs). Results were considered statistically significant at *p*-value <0.05.

Results

Comparison of selected demographics between the PCa patient and control groups. We stratified the 218 PCa cases and 436 controls according to their age and found no difference in the distribution of younger (<50-years-old) or elder (≥50 years old) age among the PCa cases and controls. Furthermore, there is no difference in the distribution of ever smokers or non-smokers between the PCa case and control groups. Moreover, 7.8% and 1.8% of the PCa patients had first- and second-degree relatives suffering from any type of cancer, respectively, whereas only 1.1% and 0.5% of the controls, respectively had a family history of the disease (Table I). This difference was found to be significant ($p<0.001$).

Association of MMP-2 rs243865 and rs2285053 genotypes and PCa risk. The physical map of *MMP-2* rs243865 and rs2285053 is shown in Figure 1. The genotypic frequency of *MMP-2* rs243865 and rs2285053 in the control group fitted well with the Hardy-Weinberg equilibrium ($p=0.1357$ and 0.1511 for *MMP-2* rs243865 and rs2285053, respectively) (Table II). The genotypic frequency of *MMP-2* rs243865 was not differentially distributed between the PCa patient and control groups (p for trend=0.5544) (Table II, top panel). In detail, the CT and TT at *MMP-2* rs243865 were not associated with any altered risk for PCa (OR=0.75 and 0.97, 95%CI=0.45-1.26 and 0.18-5.32, $p=0.3366$ and 1.0000, respectively) (Table II, top panel). In the dominant model, combined CT and TT genotypes conferred no altered risk for PCa (OR=0.77, 95%CI=0.47-1.26, $p=0.3514$) (Table II, top panel). As for *MMP-2* rs2285053, the genotypic frequency was not differentially distributed between the PCa patient and control groups (p for trend=0.7464) (Table II, bottom panel). In detail, the CT and TT at *MMP-2* rs2285053 were not associated with any altered risk for PCa (OR=1.11 and 1.25, 95%CI=0.77-1.59 and 0.60-2.63, $p=0.6340$ and 0.6913, respectively) (Table II, bottom panel). In the dominant model, combined CT and TT genotypes conferred no altered risk for PCa (OR=1.13, 95%CI=0.80-1.59, $p=0.5398$) (Table II, bottom panel).

Association of MMP-2 rs243865 and rs2285053 allelic frequencies and PCa risk. The results of the allelic analysis showed that the variant T allele at *MMP-2* rs243865 was not significantly associated with PCa risk (OR=0.79, 95%CI=0.50-1.26, $p=0.3250$). In detail, the distribution of T allele frequencies was not significantly different (7.7% and 6.2%) in the healthy control and PCa case groups, respectively (Table III). As for *MMP-2* rs2285053, the results of the allelic analysis showed that the variant T allele was not significantly associated with PCa risk (OR=1.12, 95%CI=0.84-1.50, $p=0.4291$). In detail, the distribution of T allele frequencies was not significantly different (18.8% and 20.6%) in the healthy control and PCa case groups, respectively (Table III).

Table II. *Genotypic frequency distributions of matrix metalloproteinase-2 rs243865 and rs2285053 among the prostate cases and healthy controls.*

Genotypes	Controls, n (%)	Cases, n (%)	OR (95%CI)	*p*-Value[a]
Promoter -1306 rs243865				
CC	373 (85.6)	193 (88.5)	1.00 (Reference)	
CT	59 (13.5)	23 (10.6)	0.75 (0.45-1.26)	0.3366
TT	4 (0.9)	2 (0.9)	0.97 (0.18-5.32)	1.0000
CT+TT	63 (14.4)	25 (11.5)	0.77 (0.47-1.26)	0.3514
p_{trend}				0.5544
p_{HWE}				0.1357
Promoter -735 rs2285053				
CC	292 (67.0)	140 (64.2)	1.00 (Reference)	
CT	124 (28.4)	66 (30.3)	1.11 (0.77-1.59)	0.6340
TT	20 (4.6)	12 (5.5)	1.25 (0.60-2.63)	0.6913
CT+TT	144 (33.0)	78 (35.8)	1.13 (0.80-1.59)	0.5398
p_{trend}				0.7464
p_{HWE}				0.1511

OR: Odds ratio; CI: confidence interval; [a]data based on Chi-square test with Yates' correction (n≥5) or Fisher's exact test (n<5); p_{trend}: *p*-value based on trend analysis; p_{HWE}: *p*-value based on Hardy-Weinberg Equilibrium.

Table III. *Allelic frequencies for matrix metalloproteinase-2 rs243865 and rs2285053 polymorphisms among the prostate cases and healthy controls.*

Genotypes	Controls, n (%)	Cases, n (%)	Odds ratio (95% Confidence interval)	*p*-Value[a]
rs243865				
Allele C	805 (92.3)	409 (93.8)	1.00 (Reference)	
Allele T	67 (7.7)	27 (6.2)	0.79 (0.50-1.26)	0.3250
rs2285053				
Allele C	708 (81.2)	346 (79.4)	1.00 (Reference)	
Allele T	164 (18.8)	90 (20.6)	1.12 (0.84-1.50)	0.4291

[a]Data based on Chi-square test with Yates' correction.

Discussion

The incidence of PCa has been increasing in Taiwan since 1979 (44). In the present study, the contribution of *MMP-2* rs243865 and rs2285053 genotypes to PCa susceptibility among males in Taiwan was firstly investigated. According to the literature, MMP-2 is responsible for regulating the ECM contents and closely relates to the metastatic behaviors of a panel of cancers. *MMP-2* rs243865 T allele has also been associated with elevated PCa risk in a meta-analysis in 2017 (45).

To our surprise, the T allele of *MMP-2* rs243865 was not a contributor of personal PCa susceptibility (Table II and Table III). On the contrary, it seems to be a protective factor (Table II). To the best of our knowledge, the current study is the first to reveal the contribution of *MMP-2* promoter genotypes to PCa in Taiwan. When comparing the findings of Weng's and ours, our samples are more genetically conserved (all Taiwanese) and representative (case:control=218:436). They collected 6 reports from USA, Brazil, India, Turkey, and Iran (45). had a smaller sample size (with the exception of that from the USA), not larger than 200 controls and 200 cases. In the USA, they used mixed ethnicities for genotyping investigation (45). Therefore, the difference in the genetic patterns and the small sample size may have caused the different results and conclusion of this study with our own.

The minor allelic frequencies of *MMP-2* rs243865 and rs2285053 were 7.7% and 18.8% in our study (Table III), very similar to those of 5.5% and 24.2% in East Asian as seen on NCBI (https://www.ncbi.nlm.nih.gov/snp/rs243865 and https://www.ncbi.nlm.nih.gov/snp/rs2285053).

We have also examined the associations of *MMP-2* rs243865 and rs2285053 genotypes with age and smoking behaviors. There was no difference in the distributions of *MMP-2* rs243865 or rs2285053 genotypes among PCa patients and controls stratified by younger (<50-years-old) or elder (³50-years-old) (data not shown). In addition, there was no difference in the distributions of *MMP-2* rs243865 or rs2285053 genotypes among PCa patients and controls

stratified by their smoking behavior (data not shown). Unfortunately, clinical data, such as metastatic status and survival time, were not available for analysis. We now aim to collect fresh samples from PCa patients for genotype-phenotype analysis. It has been shown many times that MMP-2 plays a critical role in PCa cell and animal models; however, no report has directly provided evidence that *MMP-2* genotypes may be involved in the etiology of PCa (22, 23).

In 2020, Kiani *et al*. reported that the frequency of *MMP-2* promoter -1575 A/A+A/G genotypes was higher in PCa-patients with diabetes mellitus (p=0.003) and in smokers (p=0.005) and was associated with an elevated risk of PCa (46). This result suggested that *MMP-2* polymorphic sites, other than the commonly studied ones (such as rs243865 and rs2285053) should be evaluated. Our results do not support the hypothesis of Weng's meta-analysis reporting that *MMP-2* rs243865 T allele was associated with an elevated PCa risk (45). On the contrary, our results are more consistent with the hypothesis of Zhou's meta-analysis indicating that *MMP-2* rs243865 genotypes are not associated with PCa risk (47). Although the current evidence showed that *MMP-2* rs243865 genotypes seem not to contribute to the determination of personal PCa susceptibility; they may contribute to the prediction of metastasis and prognosis of PCa, which have not been well-studied. In addition, it is not exclusive that other *MMP-2* polymorphic sites may serve as novel PCa markers for diagnosis and/or prognosis. The role of *MMP-2* rs243865 and rs2285053 genotypes in PCa should be validated in larger and multiple populations.

In conclusion, this study examined the genotypic patterns of *MMP-2* rs243865 and rs2285053 among Taiwanese and revealed that neither *MMP-2* rs243865 nor rs2285053 was associated with personal susceptibility to PCa. Further studies with larger and multiple populations are needed to validate the current findings.

Conflicts of Interest

The Authors declare no conflicts of interest regarding this study.

Authors' Contributions

Research design: Li PH, Liao CH, and Huang WC; patient and questionnaire summary: Wu HC, Liao CH, and Hsu SW; experimental work: Tsai CW, Wang ZH and Chang WS; statistical analysis: Chen KY, Hsia TC and Li PH; article writing: Tsai CW and Bau DT; manuscript preparation and discussing: Li PH, Liao CH, Huang WC, Chang WS, Wu HC, Hsu SW, Chen KY, Hsia TC, Wang ZH, Tsai CW and Bau DT.

Acknowledgements

The Authors are grateful to Yu-Hsin Lin, Yu-Ting Chin and Tai-Lin Huang for their excellent technical assistance. All the participants in this study are appreciated. The Authors appreciate the Tissuebank of China Medical University Hospital for their excellent help in sample collection. This study was supported with grants from Taichung Armed Forces General Hospital (TCAFGH-D-110019) and China Medical University Hospital (DMR-112-167). The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

References

1 Wang L, Lu B, He M, Wang Y, Wang Z and Du L: Prostate cancer incidence and mortality: Global status and temporal trends in 89 countries from 2000 to 2019. Front Public Health *10*: 811044, 2022. PMID: 35252092. DOI: 10.3389/fpubh.2022.811044

2 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *71(3)*: 209-249, 2021. PMID: 33538338. DOI: 10.3322/caac.21660

3 Culp MB, Soerjomataram I, Efstathiou JA, Bray F and Jemal A: Recent global patterns in prostate cancer incidence and mortality rates. Eur Urol *77(1)*: 38-52, 2020. PMID: 31493960. DOI: 10.1016/j.eururo.2019.08.005

4 Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O and Bray F: International variation in prostate cancer incidence and mortality rates. Eur Urol *61(6)*: 1079-1092, 2012. PMID: 22424666. DOI: 10.1016/j.eururo.2012.02.054

5 Reiter-Brennan C, Dzaye O, Al-Mallah MH, Dardari Z, Brawner CA, Lamerato LE, Keteyian SJ, Ehrman JK, Blaha MJ, Visvanathan K and Marshall CH: Fitness and prostate cancer screening, incidence, and mortality: Results from the Henry Ford Exercise Testing (FIT) Project. Cancer *127(11)*: 1864-1870, 2021. PMID: 33561293. DOI: 10.1002/cncr.33426

6 Cai H, Xu Z, Xu T, Yu B and Zou Q: Diabetes mellitus is associated with elevated risk of mortality amongst patients with prostate cancer: a meta-analysis of 11 cohort studies. Diabetes Metab Res Rev *31(4)*: 336-343, 2015. PMID: 25066306. DOI: 10.1002/dmrr.2582

7 Allott EH, Masko EM and Freedland SJ: Obesity and prostate cancer: weighing the evidence. Eur Urol *63(5)*: 800-809, 2013. PMID: 23219374. DOI: 10.1016/j.eururo.2012.11.013

8 Peisch SF, Van Blarigan EL, Chan JM, Stampfer MJ and Kenfield SA: Prostate cancer progression and mortality: a review of diet and lifestyle factors. World J Urol *35(6)*: 867-874, 2017. PMID: 27518576. DOI: 10.1007/s00345-016-1914-3

9 Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, Minasian LM, Ford LG, Parnes HL, Gaziano JM, Karp DD, Lieber MM, Walther PJ, Klotz L, Parsons JK, Chin JL, Darke AK, Lippman SM, Goodman GE, Meyskens FL Jr and Baker LH: Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA *306(14)*: 1549-1556, 2011. PMID: 21990298. DOI: 10.1001/jama.2011.1437

10 Pickup MW, Mouw JK and Weaver VM: The extracellular matrix modulates the hallmarks of cancer. EMBO Rep *15(12)*: 1243-1253, 2014. PMID: 25381661. DOI: 10.15252/embr.201439246

11 Woessner JF Jr: Matrix metalloproteinases and their inhibitors in connective tissue remodeling. FASEB J *5(8)*: 2145-2154, 1991. PMID: 1850705.

12 Murphy G and Docherty AJ: The matrix metalloproteinases and their inhibitors. Am J Respir Cell Mol Biol *7(2)*: 120-125, 1992. PMID: 1497900. DOI: 10.1165/ajrcmb/7.2.120
13 Singh RD, Haridas N, Patel JB, Shah FD, Shukla SN, Shah PM and Patel PS: Matrix metalloproteinases and their inhibitors: correlation with invasion and metastasis in oral cancer. Indian J Clin Biochem *25(3)*: 250-259, 2010. PMID: 21731196. DOI: 10.1007/s12291-010-0060-8
14 Kesanakurti D, Chetty C, Dinh DH, Gujrati M and Rao JS: Role of MMP-2 in the regulation of IL-6/Stat3 survival signaling *via* interaction with α5β1 integrin in glioma. Oncogene *32(3)*: 327-340, 2013. PMID: 22349830. DOI: 10.1038/onc.2012.52
15 Wu W, Gao H, Li X, Peng S, Yu J, Liu N, Zhan G, Zhu Y, Wang K and Guo X: β-hCG promotes epithelial ovarian cancer metastasis through ERK/MMP2 signaling pathway. Cell Cycle *18(1)*: 46-59, 2019. PMID: 30582718. DOI: 10.1080/15384101.2018.1558869
16 Li Y, Song T, Chen Z, Wang Y, Zhang J and Wang X: Pancreatic stellate cells activation and matrix metallopeptidase 2 expression correlate with lymph node metastasis in pancreatic carcinoma. Am J Med Sci *357(1)*: 16-22, 2019. PMID: 30466735. DOI: 10.1016/j.amjms.2018.10.001
17 Liu SQ, Xu CY, Wu WH, Fu ZH, He SW, Qin MB and Huang JA: Sphingosine kinase 1 promotes the metastasis of colorectal cancer by inducing the epithelial mesenchymal transition mediated by the FAK/AKT/MMPs axis. Int J Oncol *54(1)*: 41-52, 2019. PMID: 30365116. DOI: 10.3892/ijo.2018.4607
18 Mendes O, Kim HT and Stoica G: Expression of MMP2, MMP9 and MMP3 in breast cancer brain metastasis in a rat model. Clin Exp Metastasis *22(3)*: 237-246, 2005. PMID: 16158251. DOI: 10.1007/s10585-005-8115-6
19 Qin L, Liao L, Redmond A, Young L, Yuan Y, Chen H, O'Malley BW and Xu J: The AIB1 oncogene promotes breast cancer metastasis by activation of PEA3-mediated matrix metalloproteinase 2 (MMP2) and MMP9 expression. Mol Cell Biol *28(19)*: 5937-5950, 2008. PMID: 18644862. DOI: 10.1128/MCB.00579-08
20 Kuo HY, Huang YS, Tseng CH, Chen YC, Chang YW, Shih HM and Wu CW: PML represses lung cancer metastasis by suppressing the nuclear EGFR-mediated transcriptional activation of MMP2. Cell Cycle *13(19)*: 3132-3142, 2014. PMID: 25486572. DOI: 10.4161/15384101.2014.949212
21 Wu D, Deng S, Li L, Liu T, Zhang T, Li J, Yu Y and Xu Y: TGF-β1-mediated exosomal lnc-MMP2-2 increases blood-brain barrier permeability *via* the miRNA-1207-5p/EPB41L5 axis to promote non-small cell lung cancer brain metastasis. Cell Death Dis *12(8)*: 721, 2021. PMID: 34285192. DOI: 10.1038/s41419-021-04004-z
22 Chen Q, Zhao X, Zhang H, Yuan H, Zhu M, Sun Q, Lai X, Wang Y, Huang J, Yan J and Yu J: MiR-130b suppresses prostate cancer metastasis through down-regulation of MMP2. Mol Carcinog *54(11)*: 1292-1300, 2015. PMID: 25154741. DOI: 10.1002/mc.22204
23 Taghizadeh S, Soheili ZS, Sadeghi M, Samiei S, Ranaei Pirmardan E, Kashanian A, Zakeri F, Latifi-Navid H and Shams Najafabadi H: sFLT01 modulates invasion and metastasis in prostate cancer DU145 cells by inhibition of VEGF/GRP78/MMP2&9 axis. BMC Mol Cell Biol *22(1)*: 30, 2021. PMID: 34011277. DOI: 10.1186/s12860-021-00367-5
24 Turner RJ and Sharp FR: Implications of MMP9 for blood brain barrier disruption and hemorrhagic transformation following ischemic stroke. Front Cell Neurosci *10*: 56, 2016. PMID: 26973468. DOI: 10.3389/fncel.2016.00056
25 Ko HS, Park BJ, Choi SK, Kang HK, Kim A, Kim HS, Park IY and Shin JC: STAT3 and ERK signaling pathways are implicated in the invasion activity by oncostatin M through induction of matrix metalloproteinases 2 and 9. Yonsei Med J *57(3)*: 761-768, 2016. PMID: 26996579. DOI: 10.3349/ymj.2016.57.3.761
26 Mohamed HG, Idris SB, Mustafa M, Ahmed MF, Åstrøm AN, Mustafa K and Ibrahim SO: Influence of type 2 diabetes on prevalence of key periodontal pathogens, salivary matrix metalloproteinases, and bone remodeling markers in sudanese adults with and without chronic periodontitis. Int J Dent *2016*: 6296854, 2016. PMID: 26989414. DOI: 10.1155/2016/6296854
27 Monaco S, Sparano V, Gioia M, Sbardella D, Di Pierro D, Marini S and Coletta M: Enzymatic processing of collagen IV by MMP-2 (gelatinase A) affects neutrophil migration and it is modulated by extracatalytic domains. Protein Sci *15(12)*: 2805-2815, 2006. PMID: 17088321. DOI: 10.1110/ps.062430706
28 Ye S: Polymorphism in matrix metalloproteinase gene promoters: implication in regulation of gene expression and susceptibility of various diseases. Matrix Biol *19(7)*: 623-629, 2000. PMID: 11102751. DOI: 10.1016/s0945-053x(00)00102-5
29 Groblewska M, Mroczko B, Kozlowski M, Niklinski J, Laudanski J and Szmitkowski M: Serum matrix metalloproteinase 2 and tissue inhibitor of matrix metalloproteinases 2 in esophageal cancer patients. Folia Histochem Cytobiol *50(4)*: 590-598, 2012. PMID: 23264224. DOI: 10.5603/20327
30 Kapral M, Wawszczyk J, Jurzak M, Dymitruk D and Weglarz L: Evaluation of the expression of metalloproteinases 2 and 9 and their tissue inhibitors in colon cancer cells treated with phytic acid. Acta Pol Pharm *67(6)*: 625-629, 2010. PMID: 21229878.
31 Patel BP, Shah PM, Rawal UM, Desai AA, Shah SV, Rawal RM and Patel PS: Activation of MMP-2 and MMP-9 in patients with oral squamous cell carcinoma. J Surg Oncol *90(2)*: 81-88, 2005. PMID: 15844188. DOI: 10.1002/jso.20240
32 Lin CM, Zeng YL, Xiao M, Mei XQ, Shen LY, Guo MX, Lin ZY, Liu QF and Yang T: The relationship between MMP-2 -1306C>T and MMP-9 -1562C>T polymorphisms and the risk and prognosis of T-cell acute lymphoblastic leukemia in a Chinese population: a case-control study. Cell Physiol Biochem *42(4)*: 1458-1468, 2017. PMID: 28719899. DOI: 10.1159/000479210
33 Yaykaşli KO, Kayikçi MA, Yamak N, Soğuktaş H, Düzenli S, Arslan AO, Metın A, Kaya E and Hatıpoğlu ÖF: Polymorphisms in MMP-2 and TIMP-2 in Turkish patients with prostate cancer. Turk J Med Sci *44(5)*: 839-843, 2014. PMID: 25539555.
34 Adabi Z, Mohsen Ziaei SA, Imani M, Samzadeh M, Narouie B, Jamaldini SH, Afshari M, Safavi M, Roshandel MR and Hasanzad M: Genetic polymorphism of MMP2 gene and susceptibility to prostate cancer. Arch Med Res *46(7)*: 546-550, 2015. PMID: 26319608. DOI: 10.1016/j.arcmed.2015.08.004
35 Białkowska K, Marciniak W, Muszyńska M, Baszuk P, Gupta S, Jaworska-Bieniek K, Sukiennicki G, Durda K, Gromowski T, Prajzendanc K, Cybulski C, Huzarski T, Gronwald J, Dębniak T, Scott RJ, Lubiński J and Jakubowska A: Association of zinc level and polymorphism in MMP-7 gene with prostate cancer in Polish population. PLoS One *13(7)*: e0201065, 2018. PMID: 30036379. DOI: 10.1371/journal.pone.0201065
36 Zhang H, Li G, Zhang Z, Wang S and Zhang S: *MMP-2* and *MMP-9* gene polymorphisms associated with cervical cancer

risk. Int J Clin Exp Pathol *10(12)*: 11760-11765, 2017. PMID: 31966538.

37 Dofara SG, Chang SL and Diorio C: Gene polymorphisms and circulating levels of MMP-2 and MMP-9: a review of their role in breast cancer risk. Anticancer Res *40(7)*: 3619-3631, 2020. PMID: 32620601. DOI: 10.21873/anticanres.14351

38 Liao CH, Wu HC, Hu PS, Hsu SW, Shen TC, Hsia TC, Chang WS, Tsai CW and Bau DT: The association of matrix metalloproteinase-1 promoter polymorphisms with prostate cancer in taiwanese patients. Anticancer Res *38(7):* 3907-3911, 2018. PMID: 29970511. DOI: 10.21873/anticanres.12675

39 Chang WS, Tsai CW, Ji HX, Wu HC, Chang YT, Lien CS, Liao WL, Shen WC, Tsai CH and Bau DT: Associations of cyclooxygenase 2 polymorphic genotypes with bladder cancer risk in Taiwan. Anticancer Res *33(12)*: 5401-5405, 2013. PMID: 24324075.

40 Yang MD, Lin KC, Lu MC, Jeng LB, Hsiao CL, Yueh TC, Fu CK, Li HT, Yen ST, Lin CW, Wu CW, Pang SY, Bau DT and Tsai FJ: Contribution of matrix metalloproteinases-1 genotypes to gastric cancer susceptibility in Taiwan. Biomedicine (Taipei) *7(2)*: 10, 2017. PMID: 28612708. DOI: 10.1051/bmdcn/2017070203

41 Shih LC, Tsai CW, Lin TC, Wang YC, He JL, Hsu CL, Hsia TC, Tsai FJ, Yang JS, Hsu YM, Bau DT and Chang WS: Association of *EZH2* genotypes with oral cancer risk. In Vivo *36(6)*: 2669-2677, 2022. PMID: 36309370. DOI: 10.21873/invivo.13002

42 Yueh TC, Tsao HY, Chien WC, Tsai CW, Pei JS, Wu MH, Chen CP, Chen CC, Wang ZH, Mong MC, Yang YC, Hung YC, Bau DT and Chang WS: The contribution of *matrix metalloproteinase-7* promoter genotypes to hepatocellular carcinoma susceptibility. Anticancer Res *42(11)*: 5275-5282, 2022. PMID: 36288882. DOI: 10.21873/anticanres.16034

43 Fu CK, Mong MC, Yu CC, Yang MD, Wang ZH, Yang YC, Chen JC, Pei JS, Hsia NY, Tsai CW, Chang WS and Bau DT: Association of Matrix Metallopeptidase-2 genotypes with risk of gastric cancer in Taiwan. Anticancer Res *42(4)*: 1749-1755, 2022. PMID: 35346993. DOI: 10.21873/anticanres.15651

44 Hung CF, Yang CK and Ou YC: Urologic cancer in Taiwan. Jpn J Clin Oncol *46(7)*: 605-609, 2016. PMID: 27052114. DOI: 10.1093/jjco/hyw038

45 Weng H, Zeng XT, Wang XH, Liu TZ and He DL: Genetic association between Matrix *Metalloproteinases gene* polymorphisms and risk of prostate cancer: a meta-analysis. Front Physiol *8*: 975, 2017. PMID: 29249982. DOI: 10.3389/fphys.2017.00975

46 Kiani A, Kamankesh M, Vaisi-Raygani A, Moradi MR, Tanhapour M, Rahimi Z, Elahi-Rad S, Bahrehmand F, Aliyari M, Aghaz F, Mozafari H, Rezvani N, Haghnazari L and Pourmotabbed T: Activities and polymorphisms of MMP-2 and MMP-9, smoking, diabetes and risk of prostate cancer. Mol Biol Rep *47(12)*: 9373-9383, 2020. PMID: 33165815. DOI: 10.1007/s11033-020-05968-5

47 Zhou H and Zhu X: Association between matrix-metalloproteinase polymorphisms and prostate cancer risk: a meta-analysis and systematic review. Cancer Manag Res *10*: 5247-5259, 2018. PMID: 30464622. DOI: 10.2147/CMAR.S177551

Received November 7, 2022
Revised November 15, 2022
Accepted November 16, 2022