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Expression of ICAM-1 in placental tissues and the association between its gene polymorphisms and pathogenesis of preeclampsia

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Abstract. – OBJECTIVE: The aim of this study was to explore the expression of intercellular adhesion molecule-1 (ICAM-1) in placental tissues of patients with preeclampsia, and to elucidate the association between its polymorphisms and pathogenesis of preeclampsia.

PATIENTS AND METHODS: A total of 100 preeclampsia patients (Preeclampsia group) and 100 normal puerperae (Control group) were selected as research objects. The protein expression of ICAM-1 in placental tissues was detected via Western blotting and immunohistochemical staining. The single nucleotide polymorphisms (SNPs) rs134568, rs128343, and rs201931 in the promoter region of ICAM-1 were typed via conformation difference gel electrophoresis. Chi-square test was used to detect whether the distribution frequency of ICAM-1 genotype was in agreement with Hardy-Weinberg equilibrium. The associations of ICAM-1 alleles and polymorphic sites with pathogenesis of preeclampsia were analyzed as well. Finally, the correlation between GG genotype of ICAM-1 rs134568 and clinicopathological features of preeclampsia was analyzed.

RESULTS: The protein expression of ICAM-1 in placental tissues was significantly higher in Preeclampsia group than that in Control group ($p<0.05$). ICAM-1 SNPs rs134568, rs128343 and rs201931 all met Hardy-Weinberg equilibrium ($p>0.05$). According to gene correlation analysis, ICAM-1 rs134568 polymorphism and alleles were associated with the pathogenesis of preeclampsia ($p<0.05$). However, ICAM-1 rs128343 and rs201931 polymorphisms and alleles had no associations with the pathogenesis of preeclampsia ($p>0.05$). Besides, systolic blood pressure, serum creatinine level and plasma albumin level showed no statistically significant differences between people with GG genotype of ICAM-1 rs134568 in Preeclampsia group and those in Control group ($p>0.05$).

CONCLUSIONS: ICAM-1 expression increased significantly in placental tissues of patients with preeclampsia. In addition, rs134568 in the promoter region of ICAM-1 was associated with the pathogenesis of preeclampsia.

Key Words:
ICAM-1, Preeclampsia, Polymorphism, rs134568.

Introduction

Preeclampsia refers to a group of diseases dominated by hypertension during pregnancy. It is also a systemic disease unique to pregnancy, whose morbidity rate is 2-10% worldwide and 9.4-10.4% in China[1,2]. Preeclampsia is mainly characterized by proteinuria, elevation of blood pressure and edema. In severe cases, it can further develop into eclampsia, with the occurrence of many serious and fatal complications, such as convulsion, coma, cerebral hemorrhage, placental abruption, heart failure, and diffuse intravascular coagulation. Therefore, preeclampsia is one of the major causes of death in pregnant women and perinatal infants[3]. Currently, placental ischemia and oxidative stress theory, vascular endothelial injury theory, inflammation theory, immunity theory and insulin resistance theory are recognized as the pathogenesis of preeclampsia. Meanwhile, the pathogenesis of preeclampsia exhibits typical familial aggregation, indicating that genetic factors play an important role in its pathogenesis[4,5]. Therefore, it is of great significance to further clarify the genetic mechanism of preeclampsia for its targeted therapy in the future.

Intercellular adhesion molecule-1 (ICAM-1) is a member of the adhesion molecule family. Current studies[6,7] have shown that it plays a critical role in cell recognition, signal transduction,

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immune response, growth and differentiation, inflammation and thrombosis, and tumor cell invasion and metastasis. Meanwhile, ICAM-1 gene polymorphisms have been confirmed closely associated with a variety of diseases, such as vasculopathy after heart transplantation and liver cancer patients with hepatitis B infection[8,9]. However, there have been no reports about the expression and polymorphisms of ICAM-1 in preeclampsia.

In the present study, the associations of single nucleotide polymorphisms (SNPs) rs134568, rs128343 and rs201931 in the promoter region of ICAM-1 with the pathogenesis of preeclampsia were analyzed. All our findings might help to provide a certain reference for further exploration of the genetic mechanism of preeclampsia.

Patients and Methods

Patients

A total of 100 preeclampsia patients aged (30.22±6.48) years old and treated in our hospital from April 2017 to July 2019 were selected as research objects (Preeclampsia group). 4 mL of venous blood was drawn, anticoagulated with sodium citrate, and stored in a refrigerator at -20°C for use. Meanwhile, 100 normal full-term puerperae aged (28.02±5.82) years old were enrolled in the Control group during the same period. This investigation was approved by the Ethics Committee of Beijing, Obstetrics and Gynecology Hospital. Informed consent was obtained from all subjects before the study. Patients in Preeclampsia group met the diagnostic criteria in *Guidelines for Diagnosis and Treatment of Gestational Hypertension 2019*, with no history of chronic hypertension, kidney disease, premature rupture of membrane, gestational diabetes, diabetes, and systemic lupus erythematosus.

Western Blotting

Fresh frozen placental tissues were first taken out, cut into pieces and fully ground using a grinder, followed by ultrasonic lysis. The lysate was centrifuged, and the supernatant was collected and sub-packaged into Eppendorf (EP; Hamburg, Germany) tubes. The concentration of extracted protein was measured *via* bicinchoninic acid (BCA) method (Beyotime, Shanghai, China) and ultraviolet spectrophotometry. All protein samples were adjusted to the equal concentration, and stored in a refrigerator at -80°C. The protein samples were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene difluoride (PVDF) membranes (Millipore, Billerica, MA, USA). Next, the membranes were incubated with ICAM-1 primary antibody at 4°C overnight. On the next day, the membranes were incubated again with the goat anti-rabbit secondary antibody in the dark for 1 h. Immuno-reactive protein bands were finally scanned using an Odyssey scanner and quantified (Seattle, WA, USA).

Detection of ICAM-1 Protein Expression in Placental Tissues Via Immunohistochemical Staining

Placental tissue sections were first deparaffinized in an incubator at 60°C for 30 min, and the antigen was retrieved with citrate buffer under high pressure. After incubation with 3% hydrogen peroxide for 20 min, the sections were sealed with 8% goat serum for 30 min. Next, the sections were incubated with ICAM-1 primary antibody [diluted with phosphate-buffered saline (PBS) at 1:200] in a refrigerator at 4°C overnight. On the next day, after rewarming, the sections were incubated again with corresponding secondary antibody at room temperature for 30 min. After washing, the color was developed using diaminobenzidine (DAB) working solution (Solarbio, Beijing, China). The development time was strictly controlled under a light microscope. Finally, the sections were counterstained with hematoxylin, dehydrated with gradient ethanol, and sealed. 10 non-repeated fields of view were randomly selected and photographed under the light microscope (200×).

DNA Extraction

Ethylenediaminetetraacetic acid (EDTA)-anticoagulated blood (4 mL) was drawn in each group, from which genomic DNA was extracted according to the instructions of DNA extraction kit (Service Bio, Wuhan, China). The mass of 2 μL of DNA was measured *via* 1.5% agarose gel electrophoresis, and the concentration of extracted DNA was detected using an ultraviolet spectrophotometer.

Polymerase Chain Reaction (PCR) Amplification

The primers were first designed to amplify ICAM-1 rs134568, rs128343 and rs201931. The

Table I. Primer sequences and product size of different polymorphisms in ICAM-1 promoter region.

Polymorphism	Primer sequence (5′-3′)
rs134568	Forward: AGCTATGTCGATGTCGTAAA Reverse: ACGTAGCTAGTTTACGTAAC
rs128343	Forward: ACGTAGTGTTAGTCGTACAC Reverse: CACACTGTAGTACCCCACAA
rs201931	Forward: ACACGGATGTCGATCGTAC Reverse: ACATGGTGTCGTAGTCGTAG
GAPDH	Forward: CGCTCTCTGCTCCTCCTGTTC Reverse: ATCCGTTGACTCCGACCTTCAC

PCR system (20 μL) consisted of 2.0 μL of DNA template, 10.0 μL of 2×MIX, 0.4 μL of forward primers, 0.4 μL of reverse primers, and 7.2 μL of ddH_2O. The conditions of PCR amplification were as follows: at 95°C for 120 s, at 94°C for 30 s, at 57°C for 90 s, at 72°C for 60 s, for a total of 35 cycles, and extension at 72°C for 10 min. Finally, the amplification of gene fragments was detected using agarose gel electrophoresis. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as the internal reference. The primer sequences used in this study were shown in Table I.

Ligase Detection Reaction

The forward and reverse probes used in this reaction were designed and synthesized by BGI. All forward probes were modified *via* 5'-end phosphorylation and prepared into probe mixture at a concentration of 12.5 pmol/μL. The ligase detection reaction system (3.05 μL) consisted of 0.05 μL of ligase, 1 μL of buffer, 1 μL of PCR products, and 1 μL of probe mixture. The conditions of PCR amplification were as follows: at 95°C for 120 s, at 94°C for 15 s, and at 50°C for 25 s, for a total of 30 cycles. After that, the concentration was measured using an ultraviolet spectrophotometer. The sequencing and fragment analysis of target gene were performed by BGI. All data were analyzed with GeneMapper (Table II).

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analysis. Enumeration data were expressed as frequency and percentage, and measurement data were expressed as mean ± standard deviation. Genotype frequency was calculated and tested using Hardy-Weinberg equilibrium formula. Chi-square test was adopted for multiple comparisons of enumeration data, and *t*-test and analysis of variance were employed for measurement data. $p<0.05$ was considered statistically significant.

Results

Comparison of Clinical Baseline Data Between the Two Groups

As shown in Table III, there were statistically significant differences in age, body mass index (BMI), gravidity, parity, gestational weeks, sys-

Table II. Primer sequences and product size of different polymorphisms in ICAM-1 in ligase detection reaction.

Polymorphism	Probe	Probe sequence (5′-3′)
rs134568	rs134568	P-CTGCTAGTCGTAAACTTTTTTTTTTTTTTTTTTT-FAM
	rs134568-A	TTTTTTTTTCAGTCGTAGTCGTGATGTCTTTTTTTTTAT
	rs134568-G	TTTTTTTTTTTTTACGTAGTGATGCTAGTAGTTTTTAAA
rs128343	rs128343	P-AGCACACGTGTCAGCTTTTTTTTTTTTTT-FAM
	rs128343-C	TTTTTTTTTTTTTTTTTTTTACACACGTAGCTAGTCG
	rs128343-T	TTTTTTTTTTTTTTTTTTTTTCAGCTAGTAGATGCTA
rs201931	rs201931	P-CGATGCTGATGTTACTAGCTCCTTTTTTTTTTTTTTTTT-FAM
	rs201931-A	TTTTTTTTTTTTTTTTTTTTTACGATGTCGTAGTGGATGCT
	rs201931-C	TTTTTTTTTTTTTTTTTTACGTAGTCGTAGTCGTAGTGTC

Table III. Comparison of clinical baseline data between the two groups.

	Preeclampsia group n = 100	Control group n = 100	*p*
Age (Y)	30.22 ± 6.48	28.02 ± 5.82	0.002*
BMI (Kg/m²)	22.22 ± 1.92	19.98 ± 0.72	0.000*
Gravidity (times)	2.99 ± 0.22	2.15 ± 0.42	0.015*
Parity (times)	1.05 ± 0.51	0.31 ± 0.08	0.001*
Gestational weeks (weeks)	33.10 ± 5.21	38.98 ± 1.54	0.000*
Systolic blood pressure (mmHg)	155.45 ± 5.34	125.21 ± 2.03	0.000*
Diastolic blood pressure (mmHg)	100.23 ± 8.06	70.55 ± 7.13	0.000*
Serum creatinine (μmol/L)	65.28 ± 6.29	51.02 ± 4.92	0.026*
Blood urea nitrogen (μmol/L)	5.72 ± 0.32	3.23 ± 0.98	0.001*
Plasma albumin (g/L)	29.11 ± 2.01	33.91 ± 1.82	0.028*
Neonatal birth weight (g)	2531.32 ± 914.36	3623.02 ± 500.01	0.001*
Neonatal birth length (cm)	43.90 ± 2.10	52.19 ± 1.88	0.021*
24-h urine protein quantification (g)	3.21 ± 1.66	0	0.000*

Table IV. Hardy-Weinberg equilibrium test.

	r^2		
Polymorphism	**rs134568**	**rs128343**	**rs201931**
rs134568	–	0.012	0.028
rs128343	0.012	–	0.082
rs201931	0.028	0.082	–

tolic blood pressure, diastolic blood pressure, serum creatinine, blood urea nitrogen, plasma albumin, neonatal birth weight, neonatal birth length and 24-h urine protein quantification between Control group and Preeclampsia group ($p<0.05$).

ICAM-1 Protein Expression in Placental Tissues in the Two Groups

Western blotting and immunohistochemical staining results showed that the protein expression of ICAM-1 in placental tissues was significantly higher in Preeclampsia group than that in Control group ($p<0.05$) (Figure 1).

Hardy-Weinberg Equilibrium Test

Linkage disequilibrium was tested for ICAM-1 rs134568, rs128343 and rs201931 using the Hardy-Weinberg equilibrium formula. It was found that all polymorphisms met the Hardy-Weinberg equilibrium and were constant ($r^2<0.33$) (Table IV).

Associations Between ICAM-1 Gene Polymorphisms and Preeclampsia

The genotype distribution frequency of each polymorphism in the two groups was shown in Table V. The results indicated that gene polymorphism rs134568 was significantly associated with the pathogenesis of preeclampsia ($p<0.05$). However, gene polymorphisms rs128343 and rs201931 had no significant associations with the pathogenesis of preeclampsia ($p>0.05$).

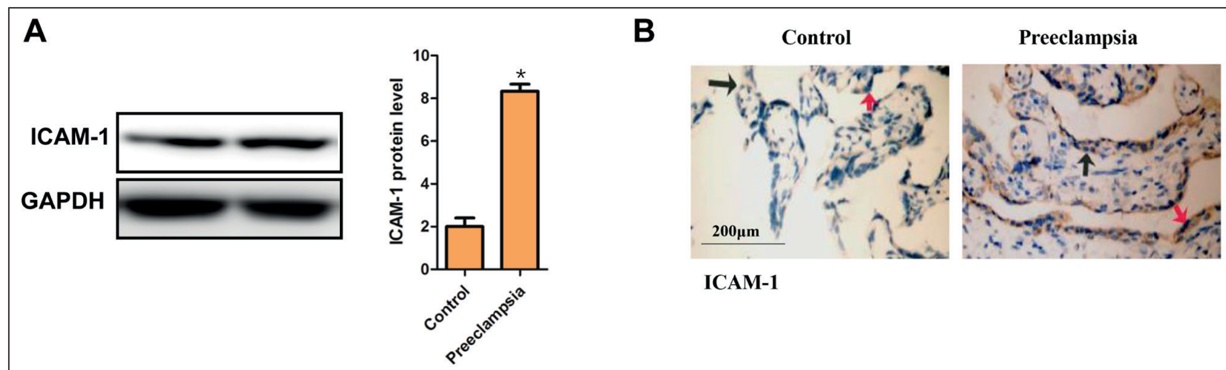

Figure 1. ICAM-1 protein expression in placental tissues in the two groups. **A,** Western blotting results and quantification. *a statistically significant difference *vs*. Control group. **B,** Immunohistochemical staining of ICAM-1 protein in placental tissues. Red arrows: syntrophoblasts, black arrows: cytotrophoblasts (magnification: 200×).

Table V. Genotype distribution of different polymorphisms of ICAM-1.

Group	rs134568			rs128343			rs201931l		
	AA	AG	GG	CC	CT	TT	AA	AC	CC
Preeclampsia group (n = 100)	8%	22%	70%	28%	52%	20%	25%	45%	30%
Control group (n = 100)	24%	52%	24%	27%	45%	28%	33%	34%	33%
χ^2	4.123			0.252			1.233		
p	0.000			0.293			0.134		

Associations Between ICAM-1 Alleles and Preeclampsia

The allele distribution frequency of each polymorphism in the two groups was shown in Table VI. The alleles of rs134568 had an evident association with the pathogenesis of preeclampsia ($p<0.05$). However, the alleles of rs128343 and rs201931 had no evident associations with the pathogenesis of preeclampsia ($p>0.05$).

Correlation Analysis Between GG Genotype of ICAM-1 rs134568 and Clinical Parameters of Preeclampsia

Furthermore, systolic blood pressure, and plasma creatinine and albumin levels had no statistically significant differences between people with GG genotype of ICAM-1 rs134568 in Preeclampsia group and those in Control group ($p>0.05$) (Table VII).

Discussion

Preeclampsia, a pregnancy syndrome clinically, is manifested as proteinuria, hypertension and edema after 20 weeks of pregnancy. It is often accompanied by dysfunction of heart, kidney, liver and brain. Statistics have shown that the morbidity and mortality rates of preeclampsia are extremely high[10]. In particular, preeclampsia is

Table VI. Allele distribution of different polymorphisms of ICAM-1.

Group	rs134568		rs128343		rs201931	
	A	G	C	T	A	CC
Preeclampsia group (n = 100)	29%	81%	56%	44%	47.5%	52.5%
Control group (n = 100)	50%	50%	49.5%	50.5%	50.00%	50.00%
χ^2	1.432		0.662		0.732	
p	0.000*		0.238		0.542	

Table VII. Correlation analysis between GG genotype of ICAM-1 rs134568 and clinical parameters of preeclampsia.

Index	GG genotype		*p*
	Preeclampsia group n = 81	Control group n = 50	
Age (Y)	29.34 ± 2.41	29.04 ± 6.11	0.592
BMI (Kg/m^2)	23.82 ± 1.32	18.44 ± 1.92	0.000*
Gravidity (times)	3.10 ± 0.03	2.63 ± 0.16	0.003*
Parity (times)	1.16 ± 0.38	0.21 ± 0.18	0.000*
Gestational weeks (weeks)	32.19 ± 4.02	38.38 ± 2.03	0.039*
Systolic blood pressure (mmHg)	136.12 ± 2.92	131.54 ± 5.09	0.103
Diastolic blood pressure (mmHg)	93.02 ± 4.11	74.34 ± 2.02	0.000*
Serum creatinine (μmol/L)	58.56 ± 3.92	56.32 ± 3.98	0.172
Blood urea nitrogen (μmol/L)	4.66 ± 0.39	3.49 ± 0.83	0.041*
Plasma albumin (g/L)	30.129 ± 3.59	32.49 ± 2.64	0.078
Neonatal birth weight (g)	2699.45 ± 788.58	3456.03 ± 666.31	0.000*
Neonatal birth length (cm)	42.45 ± 6.34	51.39 ± 3.48	0.032*
24-h urine protein quantification (g)	3.49 ± 0.82	0	0.000*

one of the important causes of death in pregnant and lying-in women and perinatal infants in developing countries. Preeclampsia not only causes maternal multi-system damage, but also is closely correlated with adverse pregnancy outcomes of mothers, such as fetal growth retardation, placental abruption, fetal distress, and deficiency in amniotic fluid[11]. Moreover, preeclampsia seriously affects fetal growth and development, eventually leading to fetal death in severe cases. It has been proved that preeclampsia is a complex polygenic disease, which may not necessarily be caused due to the alteration of a single gene[12]. At the same time, preeclampsia may be affected by the interaction between genes, especially for environmental factors and genetic factors. The occurrence of preeclampsia exhibits significant familial aggregation. Jebbink et al[13] have found that its risk in pregnant women with a family history of preeclampsia is 3-4 times that in normal people. In addition, maternal genotypes determine the genetic susceptibility to preeclampsia. However, no gene has been found as a susceptibility gene for preeclampsia yet[14].

SNP refers to the mutation of a single base on the genomic DNA sequence, and such a mutation rate in people is at least higher than 1%[15]. In recent years, with the completion of the Human Genome Project, how to exploit the traits of complex polygenic diseases using known human genome SNPs has been a hot spot in biology[16]. In the research of candidate gene association, some potentially related genes and polymorphic sites are selected. Meanwhile, their associations with certain diseases have been greatly explored based on the possible pathogenesis of diseases, and it is of great significance for revealing susceptibility genes for complex diseases[17]. At present, candidate gene association research on preeclampsia mainly focuses on related genes to hemodynamics, lipid metabolism, endothelial cell function, immune response, inflammatory response, and oxidative stress[18]. Despite many animal and human studies on the candidate genes for preeclampsia, the results remain inconsistent, and the susceptibility genes for preeclampsia still need attention. Therefore, further clarifying the susceptibility genes for preeclampsia is of great significance for its early prevention, diagnosis and treatment.

In the adhesion molecule family, many members play decisive roles. ICAM-1 is a member of the immunoglobulin superfamily, which has the highest expression in vascular endothelium. ICAM-1, located on chromosome 19p13, plays an important role in the adhesion of immune cells (monocytes and lymphocytes) and endothelial cells[19]. Previous studies[20,21] have found that the protein expression of ICAM-1 increases significantly in the models of portal hypertension and chronic arterial hypertension. At 10 weeks of pregnancy, a large number of ICAM-1 proteins begin to be expressed in the placenta. Meanwhile, its expression in villous interstitial cells reaches a small peak at 14-16 weeks[22]. In this study, the results revealed that the protein expression of ICAM-1 in the placenta was evidently higher in patients with preeclampsia after delivery than that in normal puerperae, which was in accordance with a previous study[23]. ICAM-1 rs134568 polymorphism and alleles was correlated with the pathogenesis of preeclampsia. In addition, systolic blood pressure, plasma creatinine level, and plasma albumin level had no statistically significant differences between people with GG genotype of ICAM-1 rs134568 in Preeclampsia group and those in Control group.

Conclusions

In summary, this study revealed for the first time that there was a potential association between ICAM-1 rs134568 polymorphism and the pathogenesis of preeclampsia. The novelty of this study was that ICAM-1 rs134568 polymorphism could be used as a genetic marker to evaluate the risk of preeclampsia in women.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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