MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 2386-2391
DOI: 10.12659/MSM.896979

Received: 2015.12.03
Accepted: 2015.12.22
Published: 2016.07.08

Evaluation of ICAM-1 and VCAM-1 Gene Polymorphisms in Patients with Periodontal Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: This work was self-funded by the Department of Periodontology, Clinical School of Stomatology, First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, P.R. China

Background: We aimed to investigate the potential genetic relationships between the polymorphisms of gene rs5498 *ICAM-1* and rs1041163 *VCAM-1* and chronic periodontitis in a Chinese population within Heilongjiang.

Material/Methods: Genomic DNA was extracted from oral mucosa cells of 584 periodontal patients and 182 healthy individuals. Genotyping of the rs5498 *ICAM-1* and rs1041163 *VCAM-1* gene polymorphisms was performed with the Multiplex SNaPshot technique.

Results: Statistically significant associations were identified between the chronic periodontal patients and the controls in the gene polymorphisms of rs5498 *ICAM-1* (P=0.007) and rs1041163 *VCAM-1* (P=0.029). The distribution of rs5498 (P=0.029) and rs1041163 (P=0.049) differed significantly across the mild, moderate, and severe groups of periodontitis.

Conclusions: Our findings indicate that *ICAM-1* rs5498 and *VCAM-1* rs1041163 polymorphisms contribute to chronic periodontitis, and *ICAM-1* rs5498 and *VCAM-1* rs1041163 gene polymorphisms might be associated with periodontitis severity in the Heilongjiang Chinese population. Further studies should be conducted to determine whether these polymorphisms could be used as biomarkers of periodontitis.

MeSH Keywords: **Chronic Periodontitis • Inflammation • Polymorphism, Genetic**

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/896979

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Background

Periodontal disease is characterized by Gram-negative bacteria in the oral cavity, along with chronic inflammation [1,2], which could consequently lead to the destruction of the soft tissue and resorption of the periodontal bone. It was suggested that the alteration or progression of the disease may be associated with the host immune response to these bacteria, and that inflammatory cells in diseased periodontal tissues are related to the disease progression [3,4]. Recruitment and retention of these cells are determined by cell adhesion molecules, which are suggested to be involved in the pathogenesis of inflammatory diseases [5]. Evidence shows that cell adhesion molecules can be up-regulated as a result of stimulation from certain pro-inflammatory cytokines, and can act as co-stimulatory receptors in the activation of inflammatory cells [6].

Cellular adhesion molecule (CAM), an adhesion protein on the surface of the gums, epithelium of gingival sulcus, and junctional epithelium, is an important component of the adhesion between cells and their extracellular matrix [7]. CAM is involved in the occurrence and development of periodontitis, mainly through the participation of cell information transmission, inflammation, and immune response [8,9]. With the assistance of the specificity of CAM on the junctional epithelium, polymorphonuclear leukocyte (PMN) can enter the gingival and periodontal pocket, playing the role of sterilization. The level of CAM is positively correlated with the degree of periodontal inflammation [10].

Intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) belong to the Ig superfamily [11,12]. ICAM-1 is widely expressed on leucocytes, endothelial cells, monocytes, synovial cells, fibroblasts, and epithelial cells [13,14]. In immunological and inflammatory reactions, ICAM-1 and VCAM-1 have the ability to promote cell adhesion and recruit leucocytes. These abilities of ICAM-1 and VCAM-1 were found to be involved in rheumatoid arthritis [15]. In confirmation of this information, a study also showed that the plasma and synovial fluid levels of ICAM-1 and VCAM-1 were significantly higher in rheumatoid arthritis patients in comparison with normal healthy controls [16]. The *ICAM1* gene is located on locus 19p13.3-p13.2 [17]. As an indispensable participant in the initiation of the immunological response, ICAM-1 mediates adhesion of leukocytes against the blood vessel wall, enabling them to enter the tissues by transendothelial migration [18]. The *VCAM1* gene is located on locus 1p31-32 [19]. As an endothelial receptor for VLA-4 and integrin α4β7, *VCAM1* contributes to the initiation of the T cell response to alloantigens [20]. The polymorphisms of *ICAM1* and *VCAM1* genes may affect the function of the immune response [21]. Several studies have indicated that polymorphisms of rs5498 T>C in exon 6 of the *ICAM1* gene and rs1041163 T>C in the *VCAM1* gene promoter are associated with various diseases, such as coronary artery disease, stenosis, myocardial infarction, and arthrosclerosis [22–24]. Because the pathophysiology of periodontitis is similar to that of these diseases, which is inflammatory in nature, and no case-control study has been conducted on the associations between *ICAM-1* and *VCAM-1*gene polymorphisms and chronic periodontitis, we evaluated their roles in the susceptibility to periodontal diseases and investigated the potential associations between the polymorphisms and chronic periodontitis in the Heilongjiang Chinese population.

Scientific rationales

Previous studies indicated that *ICAM-1* rs5498 and *VCAM-1* rs1041163 gene polymorphisms are associated with various diseases, including coronary artery disease, stenosis, and arthrosclerosis. Since the pathophysiology of these diseases is inflammation, similar to that of periodontitis, and because ICAM-1 and VCAM-1 are known to be involved in the occurrence and development of periodontitis, we hypothesized that the polymorphisms were also associated with periodontitis.

Main findings

ICAM-1 rs5498 and VCAM-1 rs1041163 polymorphisms contribute to chronic periodontitis, and ICAM-1 rs5498 and VCAM-1 rs1041163 gene polymorphisms might be associated with periodontitis severity in the Heilongjiang Chinese population.

Practical implications

Our study is the first to investigate the relationships between ICAM-1 and VCAM-1 polymorphisms and periodontitis.

Material and Methods

Ethics statement

This study was approved by the Ethics Committee of The First Affiliated Hospital of Harbin Medical University and each subject signed informed consent prior to enrollment in the current study. All procedures in this study were in accordance with the Declaration of Helsinki [25].

Subjects

In this study, 766 nonsmoking subjects, who were admitted to the First Affiliated Hospital of Harbin Medical University between September 2012 and December 2014, were recruited. There were 584 patients with periodontitis (284 females and 300 males; age range: 20–50 years) among whom 228 had mild, 212 had moderate, and 144 had severe chronic periodontitis.

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We recruited another 182 subjects as healthy controls (98 females and 84 males; age range: 20–50 years). All periodontal examinations were conducted by the same investigator/dentist/clinician. Periodontitis was diagnosed based on probing depth (PD), clinical attachment loss (CAL), and bleeding on probing index (BPI), in addition to radiographic findings. The exclusion criteria were: history or current manifestations of systemic diseases; patients with diabetes mellitus, immunological disorders, hepatitis, HIV infection, or cardiovascular events; patients using orthodontic appliances; patients needing premedication for dental treatment; patients using anti-inflammatory drugs on a regular basis; patients with acute necrotizing ulcerative gingivitis; and pregnant or lactating women.

The diagnostic criteria of chronic periodontitis were: (1) presence of local factors such as plaque and calculus; (2) more than 2 sites had a PD ≥5 mm, and CAL was ≥1 mm in every quadrant, and the number of the teeth with alveolar bone absorption more than 2/3 the root length was ≤8. The severity of chronic periodontitis was categorized as: (1) the mild group: PD ≤4 mm, CAL: 1–2 mm, and the alveolar bone absorption is less than 1/3 the root length; (2) the moderate group: PD ≤6 mm, CAL: 3–5 mm, and the alveolar bone absorption is 1/3 to 1/2 the root length; and (3) the severe group: PD >6 mm, CAL ≥5 mm, and the alveolar bone absorption is more than 1/2 the root length. Healthy subjects (182) without periodontal disease, systemic inflammatory disease, or surgical treatment within 4 weeks were enrolled as controls. Patients with absence of periodontitis were diagnosed based on: (1) at least 22 teeth *in situ*; (2) no site with PD >3 mm; and (3) no presence of CAL. No pathogenic tooth mobility was found in healthy controls and none had a history of periodontitis or tooth loss. Furthermore, no bleeding on probing or radiographic evidence of bone loss was observed among these subjects. All subjects signed informed consent forms prior to enrollment in the current study.

DNA extraction

Sterile cotton swabs were used to scrape oral mucosal cells. The buccal swabs were naturally dried at room temperature and their surfaces were stripped and transferred to Eppendorf tubes. Genomic DNA was extracted by the Swab Gen DNA Kit and stored at –20°C for later genotyping.

Identification of *ICAM-1* and *VCAM-1* polymorphisms

We analyzed 2 single-nucleotide polymorphisms (SNPs) with the Multiplex SNaPshot kit for rs5498 T>C in exon 6 of the ICAM1 gene and rs1041163 T>C in the VCAM1 gene. The primers for ICAM-1 rs5498 were: Forward: 5'-GTAAAGGACCTCTGGGTTACT-3' Reverse: 5'-AGGCTTCTGGATCTCCTCTT-3'. The primers for VCAM-1 rs1041163 were: Forward: 5'-ACTCACAGAGCACATTCACG-3' Reverse: 5'-AGATCTTGAGGGCACCTAC-3'. The PCR protocol was: initial denaturation at 94°C for 5 min, 33 cycles of amplification at 94°C for 30 s, annealing at 55°C for 30 s, and extension for 30 s at 72°C, followed by a final extension for 5 min at 72°C. PCR products were purified with Shrimp Alkaline Phosphatase (SAP) and preserved at 4°C. The primers and sequences of the SNaPshot extension reaction were: rs5498-R-R-60: 5'-ttttttttttttttttttttttttttttttttttttttttAGCACATTCACGGTCACCT-3'. rs1041163-Y-F-34: 5'-tttttttttttGCTAGTATTTCCTGAATCAATTT-3'. The reaction protocol was: 25 cycles of extension at 96°C for 10 s, at 51°C for 5 s, and at 60°C for 30s, followed by 1 cycle at 4°C. The products were purified with 0.3 µl SAP and 1.7 µl ddH_2O and stored at 4°C. Analysis using ABI 3730XL sequencer was: 1 µl product, 0.2 µl Genescan™-120LIZ Size Standard and 8.8 µl deionized formamide were mixed in a 96-well-plate, denatured at 95°C for 5 min, and directly analyzed by use of an ABI 3730XL sequencer.

Statistical analysis

Allelic and genotypic frequencies were obtained by manual counting. Contingency data were used with chi-square tests for the comparisons between observed genotype frequencies and those expected under Hardy-Weinberg equilibrium. Chi-square tests were conducted to compare the genotypes distributions of the groups with SPSS version 18 software. The odds ratios (OR) were calculated with their 95% confidence intervals (CI). P values less than 0.05 were regarded as indicating statistical significance.

Results

The distributions of the ICAM-1genotypes are shown in Table 1. At the SNP level, a trend in genotype distribution was observed for rs5498 (CC *vs.* CT *vs.* TT, *P*=0.007). Although there was a trend toward a higher proportion of the rs5498 'C' allele in the patients with chronic periodontitis compared to the controls, the trend did not achieve statistical significance (*P*=0.472). As shown in Table 2, the genotype distributions of VCAM-1 were different between the patients and the controls, with a trend in genotype distribution observed for rs1041163 (CC *vs.* CT *vs.* TT, *P*=0.029). Moreover, a higher prevalence of 'T' alleles was observed in the periodontal patients than in the controls (*P*=0.009). The odds of having chronic periodontitis among subjects with T/C at ICAM-1 rs5498 was 1.666 times the odds of having the disease among subjects with T/T at ICAM-1 rs5498, with 95% confidence interval (1.154 and 2.404). The distributions of rs5498 genotypes were significantly different across the 3 severity groups of periodontitis patients (CC *vs.* CT *vs.* TT, *P*=0.021; CC *vs.* CT+TT, *P*=0.029; Table 3). As shown in Table 4, similar results were obtained for rs1041163 (CC *vs.* CT *vs.* TT, *P*=0.049).

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Table 1. Genotype and allele frequency distribution of ICAM-1 rs5498.

	Controls (n=182)		Cases (n=584)		χ^2	P	OR (95%CI)	
	N (frequency)		N (frequency)					
T/T	94	(51.6%)	252	(43.2%)	9.893	0.007	1.000	
T/C	60	(33.0%)	268	(45.9%)			0.600	(0.416–0.866)
C/C	28	(15.4%)	64	(11.0%)			1.952	(1.156–3.303)
Allele								
T	248	(68.1%)	772	(66.1%)	0.517	0.472	1.031	(0.950–1.118)
C	116	(31.9%)	396	(33.9%)			0.940	(0.793–1.114)

ICAM-1 – intercellular adhesion molecule 1; OR – odds ratios; 95%CI – 95% confidence intervals.

Table 2. Genotype and allele frequency distribution of VCAM-1 rs1041163.

	Controls (n=182)		Cases (n=584)		χ^2	P	OR (95%CI)	
	N (frequency)		N (frequency)					
C/C	7	(3.8%)	8	(1.4%)	7.069	0.029	1.000	
C/T	40	(22.0%)	100	(17.1%)			1.143	(0.156–1.344)
T/T	135	(74.2%)	476	(81.5%)			0.709	(0.468–1.072)
Allele								
C	54	(14.8%)	116	(9.9%)	6.764	0.009	1.494	(1.106–2.018)
T	310	(85.2%)	1052	(90.1%)			0.946	(0.902–0.991)

VCAM-1 – vascular cell adhesion molecule 1; OR – odds ratios; 95%CI – 95% confidence intervals.

Table 3. Genotype and allele frequency distribution of ICAM-1 rs5498 among mild, moderate and severe cases.

	Mild cases (n=228)		Moderate cases (n=212)		Severe cases (n=144)		χ^2	P
	N (frequency)		N (frequency)		N (frequency)			
Genotype								
C/C	16	(7.0%)	32	(15.1%)	16	(11.1%)	11.519	0.021
C/T	104	(45.6%)	88	(41.5%)	76	(52.8%)		
T/T	108	(47.4%)	92	(43.4%)	52	(36.1%)		
C/C	16	(7.1%)	32	(15.1%)	16	(11.1%)	7.099	0.029
C/T+ T/T	209	(92.9%)	180	(84.9%)	128	(88.9%)		

ICAM-1 – intercellular adhesion molecule; OR – odds ratios; 95%CI – 95% confidence intervals.

Discussion

It has been proven that periodontitis, a complex multifactorial disease, is determined by both environmental and genetic factors. In addition to the pathogenic bacteria and other environmental factors (e.g., smoking and stress) [26,27] involved in the pathogenesis of periodontitis, there is also evidence suggesting that genetic factors might participate in the etiology of periodontitis [28]. Recently, growing interest has been focused on identifying allelic variants of genes that can be used to assess the risk of periodontal diseases [29]. *ICAM-1* and *VCAM-1* polymorphisms are currently being investigated and have been found to be associated with several diseases, including stenosis, coronary artery disease, and arthrosclerosis [30,31]. To the best of our knowledge, however, our study is the first to investigate the association between these polymorphisms and periodontitis.

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Table 4. Genotype and allele frequency distribution of VCAM-1 rs1041163 among mild, moderate and severe cases.

	Mild cases (n=228)	Moderate cases (n=212)	Severe cases (n=144)	χ^2	P
	N (frequency)	N (frequency)	N (frequency)		
Genotype					
C/C	4 (1.8%)	0 (0%)	4 (2.8%)	9.559	0.049
C/T	48 (21.1%)	32 (15.1%)	20 (13.9%)		
T/T	176 (77.2%)	180 (84.9%)	120 (83.3%)		

VCAM-1 – vascular cell adhesion molecule 1; OR – odds ratios; 95%CI – 95% confidence intervals.

There was a significant difference in the rs5498 polymorphism of the ICAM-1 gene between the chronic periodontal patients and the controls. The genotype distribution of VCAM-1 rs1041163 was also significantly different between the patients and the controls. Moreover, a significantly higher prevalence of 'T' allele was observed in the patients than in the controls. These results suggest that rs5498 and rs1041163 polymorphisms may contribute to chronic periodontitis. Among the mild, moderate, and severe cases of periodontitis, the genotypes of rs5498 were found to have different distributions; similar results were obtained for the genotypes of rs1041163, suggesting that both rs5498 and rs1041163 may affect periodontitis severity.

The exact biological function of intronic SNPs is currently unclear. However, the probable mechanism underlying the function is as follows. Both ICAM-1 and VCAM-1 mRNAs are expressed by non-stimulated hepatocyte growth factor (HGF) [32]. In addition, ICAM-1 is induced by pro-inflammatory cytokines, such as IL-1β, TNF-α, IFN-γ, and IL-2 [33,34]. *Escherichia coli* LPS [35] and VCAM-1 are induced by IL-1β. ICAM-1 mediates the middle screw rotary body into the process of human gingival epithelium as an adhesion receptor on leukocytes and endothelial cells [36,37]. A previous study suggested the ICAM-1 plays an important role in the early stage and progression of chronic periodontitis [38]. VCAM-1, combined with monocytes and lymphocytes, can activate vascular endothelial cells to express vascular adhesion molecules [39]. The release of cytokines and enzymes promotes the progress of inflammation. Animal studies have shown that suppressing the expression of VCAM-1 can significantly inhibit the inflammatory responses [40]. In order to control the inflammatory responses, it is critical to effectively suppress the expression of VCAM-1. These results indicate that SNPs of ICAM-1 and VCAM-1 may cause susceptibility to periodontitis, and that different distributions may result in different severities of periodontitis. It is thus possible to intervene in and control the progression of periodontitis and to treat periodontitis on the SNP level by identifying the polymorphisms of ICAM-1 and VCAM-1.

The pathophysiology of periodontitis, similar to that of some other complex diseases, is characterized by various biological pathways [41,42], which ultimately lead to the same clinical manifestation. It is important to note that the number and type of genes involved in the same disease may not be the same in different ethnic populations. Accordingly, a functional SNP may be in linkage disequilibrium with distinct markers in different ethnic groups. Therefore, we cannot deny the possibility that functional rs5498 and rs1041163, together with the other uncovered functional variants in linkage disequilibrium, might synergistically influence diseases.

Taken together, our study shows that *ICAM-1* rs5498 and VCAM-1 rs1041163 gene regions may affect the susceptibility to chronic periodontitis in the Heilongjiang Chinese population. These 2 polymorphisms might also affect the severity of periodontitis. Our work provides the first evidence of the involvement of human *ICAM-1* and *VCAM-1*genes in chronic periodontitis. However, the basic functions of *ICAM-1* and *VCAM-1*gene mutations remain to be further elucidated.

Conclusions

Our findings indicate that *ICAM-1* rs5498 and *VCAM-1* rs1041163 polymorphisms participate in the pathogenesis of chronic periodontitis, and that the gene polymorphisms at both *ICAM-1* rs5498 and *VCAM-1* rs1041163 might be associated with periodontitis severity in the Heilongjiang Chinese population. Future studies should focus on the application of these polymorphisms in the diagnosis and treatment of periodontitis as biomarkers.

Conflict of interest

We declare that we have no conflicts of interest.

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References:

1. Dzink JL, Tanner AC, Haffajee AD, Socransky SS: Gram negative species associated with active destructive periodontal lesions. J Clin Periodontol, 1985; 12: 648–59
2. Socransky SS, Haffajee AD, Cugini MA et al: Microbial complexes in subgingival plaque. J Clin Periodontol, 1998; 25: 134–44
3. Kinane DF: Causation and pathogenesis of periodontal disease. Periodontol 2000, 2001; 25: 8–20
4. Assuma R, Oates T, Cochran D et al: IL-1 and TNF antagonists inhibit the inflammatory response and bone loss in experimental periodontitis. J Immunol, 1998; 160: 403–9
5. Ulbrich H, Eriksson EE, Lindbom L: Leukocyte and endothelial cell adhesion molecules as targets for therapeutic interventions in inflammatory disease. Trends Pharmacol Sci, 2003; 24: 640–47
6. Hosokawa Y, Hosokawa I, Ozaki K et al: Cytokines differentially regulate ICAM-1 and VCAM-1 expression on human gingival fibroblasts. Clin Exp Immunol, 2006; 144: 494–502
7. Takeichi M: The cadherins: cell-cell adhesion molecules controlling animal morphogenesis. Development, 1988; 102: 639–55
8. Roth GA, Moser B, Roth-Walter F et al: Infection with a periodontal pathogen increases mononuclear cell adhesion to human aortic endothelial cells. Atherosclerosis, 2007; 190: 271–81
9. Koundouros E, Odell E, Coward P et al: Soluble adhesion molecules in serum of smokers and non-smokers, with and without periodontitis. J Periodontal Res, 1996; 31: 596–99
10. Miller DR, Lamster IB, Chasens AI: Role of the polymorphonuclear leukocyte in periodontal health and disease. J Clin Periodontol, 1984; 11: 1–15
11. Osborn L, Hession C, Tizard R et al: Direct expression cloning of vascular cell adhesion molecule 1, a cytokine-induced endothelial protein that binds to lymphocytes. Cell, 1989; 59: 1203–11
12. Nakashima Y, Raines EW, Plump AS et al: Upregulation of VCAM-1 and ICAM-1 at atherosclerosis-prone sites on the endothelium in the ApoE-deficient mouse. Arterioscler Thromb Vasc Biol, 1998; 18: 842–51
13. Steffen BJ, Breier G, Butcher EC et al: ICAM-1, VCAM-1, and MAdCAM-1 are expressed on choroid plexus epithelium but not endothelium and mediate binding of lymphocytes *in vitro*. Am J Pathol, 1996; 148: 1819–38
14. Hubbard AK, Rothlein R: Intercellular adhesion molecule-1 (ICAM-1) expression and cell signaling cascades. Free Radic Biol Med, 2000; 28: 1379–86
15. Klimiuk PA, Sierakowski S, Latosiewicz R et al: Soluble adhesion molecules (ICAM-1, VCAM-1, and E-selectin) and vascular endothelial growth factor (VEGF) in patients with distinct variants of rheumatoid synovitis. Ann Rheum Dis, 2002; 61: 804–9
16. Littler AJ, Buckley CD, Wordsworth P et al: A distinct profile of six soluble adhesion molecules (ICAM-1, ICAM-3, VCAM-1, E-selectin, L-selectin and P-selectin) in rheumatoid arthritis. Br J Rheumatol, 1997; 36: 164–69
17. Motsinger AA, Brassat D, Caillier SJ et al: Complex gene-gene interactions in multiple sclerosis: a multifactorial approach reveals associations with inflammatory genes. Neurogenetics, 2007; 8: 11–20
18. Domanski L, Kloda K, Pawlik A et al: Correlation between ICAM1 and VCAM1 gene polymorphisms and histopathological changes in kidney allograft biopsies. Arch Med Sci, 2013; 9: 276–82
19. Kloda K, Domanski L, Pawlik A et al: Effect of the ICAM1 and VCAM1 gene polymorphisms on delayed graft function and acute kidney allograft rejection. Ann Transplant, 2010; 15: 15–20
20. van Seventer GA, Newman W, Shimizu Y et al: Analysis of T cell stimulation by superantigen plus major histocompatibility complex class II molecules or by CD3 monoclonal antibody: costimulation by purified adhesion ligands VCAM-1, ICAM-1, but not ELAM-1. J Exp Med, 1991; 174: 901–13
21. Hansson GK, Libby P: The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol, 2006; 6: 508–19
22. Hwang SJ, Ballantyne CM, Sharrett AR et al: Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study. Circulation, 1997; 96: 4219–25
23. Davies MJ, Gordon JL, Gearing AJ et al: The expression of the adhesion molecules ICAM-1, VCAM-1, PECAM, and E-selectin in human atherosclerosis. J Pathol, 1993; 171: 223–29
24. Cybulsky MI, Iiyama K, Li H et al: A major role for VCAM-1, but not ICAM-1, in early atherosclerosis. J Clin Invest, 2001; 107: 1255–62
25. General Assembly of the World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. J Am Coll Dent, 2014; 81: 14–18
26. Pihlstrom BL, Michalowicz BS, Johnson NW: Periodontal diseases. Lancet, 2005; 366: 1809–20
27. Kornman KS: Mapping the pathogenesis of periodontitis: A new look. J Periodontol, 2008; 79: 1560–68
28. Kornman KS, di Giovine FS: Genetic variations in cytokine expression: a risk factor for severity of adult periodontitis. Ann Periodontol, 1998; 3: 327–38
29. Loos BG, John RP, Laine ML: Identification of genetic risk factors for periodontitis and possible mechanisms of action. J Clin Periodontol, 2005; 32(Suppl.6): 159–79
30. Borozdenkova S, Smith J, Marshall S et al: Identification of ICAM-1 polymorphism that is associated with protection from transplant associated vasculopathy after cardiac transplantation. Hum Immunol, 2001; 62: 247–55
31. Bielinski SJ, Pankow JS, Li N et al: ICAM1 and VCAM1 polymorphisms, coronary artery calcium, and circulating levels of soluble ICAM-1: the multiethnic study of atherosclerosis (MESA). Atherosclerosis, 2008; 201: 339–44
32. Min JK, Lee YM, Kim JH et al: Hepatocyte growth factor suppresses vascular endothelial growth factor-induced expression of endothelial ICAM-1 and VCAM-1 by inhibiting the nuclear factor-kappaB pathway. Circ Res, 2005; 96: 300–7
33. Rothlein R, Czajkowski M, O'Neill MM et al: Induction of intercellular adhesion molecule 1 on primary and continuous cell lines by pro-inflammatory cytokines. Regulation by pharmacologic agents and neutralizing antibodies. J Immunol, 1988; 141: 1665–69
34. Tosi MF, Stark JM, Smith CW et al: Induction of ICAM-1 expression on human airway epithelial cells by inflammatory cytokines: effects on neutrophil-epithelial cell adhesion. Am J Respir Cell Mol Biol, 1992; 7: 214–21
35. Sawa Y, Ueki T, Hata M et al: LPS-induced IL-6, IL-8, VCAM-1, and ICAM-1 expression in human lymphatic endothelium. J Histochem Cytochem, 2008; 56: 97–109
36. Dixon DR, Reife RA, Cebra JJ, Darveau RP: Commensal bacteria influence innate status within gingival tissues: A pilot study. J Periodontol, 2004; 75: 1486–92
37. Schroeder HE, Listgarten MA: The gingival tissues: the architecture of periodontal protection. Periodontol 2000, 1997; 13: 91–120
38. Rezavandi K, Palmer RM, Odell EW et al: Expression of ICAM-1 and E-selectin in gingival tissues of smokers and non-smokers with periodontitis. J Oral Pathol Med, 2002; 31: 59–64
39. Nakamura S, Ohtani H, Watanabe Y et al: *In situ* expression of the cell adhesion molecules in inflammatory bowel disease. Evidence of immunologic activation of vascular endothelial cells. Lab Invest, 1993; 69: 77–85
40. Kim I, Moon SO, Kim SH et al: Vascular endothelial growth factor expression of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin through nuclear factor-kappa B activation in endothelial cells. J Biol Chem, 2001; 276: 7614–20
41. Scannapieco FA: Periodontal inflammation: from gingivitis to systemic disease? Compend Contin Educ Dent, 2004; 25: 16–25
42. Ohyama H, Kato-Kogoe N, Kuhara A et al: The involvement of IL-23 and the Th17 pathway in periodontitis. J Dent Res, 2009; 88: 633–38

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