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EVALUATION OF POLYMORPHISM OF ICAM-1 GENE IN A POPULATION ON RUSSIAN FEDERATION TERRITORY

MOKRANE Ahlem[1,2*], PERENKOV Aleksei Dmitrievitch[1], NOVIKOV Dmitry Viktopivitch[1], FOMINA Svetlana Grigorivna[1], NOVIKOV Viktor Vladimirovitch[1]

1. Département de Biologie Moléculaire et Immunologie. Institut de Recherche en Biologie Moléculaire et en Ecologie Régionale. Université d'État Lobatchevski de Nijni Novgorod - Université Nationale de Recherche (UNN). Russie.
2. Département de Biologie et de Physiologie Cellulaire, Faculté des Sciences de la Nature et de la Vie, Université Saad Dahleb Blida-1, B.P. 270, route de Soumaa, Blida, Algérie.

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Abstract

Description of the subject: Cancer is one of the leading causes of death in the world. Currently, colorectal cancer can be described as a basis for a global problem. It is believed that genetic polymorphism is related to the risk of colorectal cancer development. The intercellular adhesion molecule-1 is shown in several types of cells, such as endothelial cells and leukocytes, and plays an important role in several physiological processes. In addition, this molecule is also expressed in various cancer cells, in particular melanoma, colorectal cancer and lymphoma.
Objective: The purpose of this study was to investigate the relationship between the level of ICAM-1 gene expression and genetic polymorphism (rs5498 A/G) in patients with colorectal cancer.
Methods: A total of 115 peripheral blood samples of young adults from Nizhny Novgorod were examined. The ICAM-1 mRNA expression was analyzed by real-time PCR. The genotypic distribution of the rs5498 E469K(A/G) gene polymorphism was carried out using a specific polymerase chain reaction allele.
Results: The results showed a significant difference between control and colorectal cancer patients for the GG genotype (p=0.002; OR=1.35) and for the G allele (p=0.005; OR=2.20). The present study shows the relationship between SNP rs5498 (A/G) and colorectal cancer with AG genotype (p=0.002; OR=3.55).
Conclusion: Our results revealed that polymorphism of rs5498 (E469K) ICAM-1 may be associated with the risk of colorectal cancer.
Keywords: Colorectal cancer; adhesion molecule; cancer cells; polymorphism; genotyping.

ÉVALUATION DU POLYMORPHISME DU GÉNE ICAM-1 DANS UNE POPULATION SUR LE TERRITOIRE DE LA FÉDÉRATION DE RUSSIE

Résumé

Description du sujet : Le cancer est l'une des principales causes de décès dans le monde. Actuellement, le cancer colorectal peut être décrit comme la base d'un problème mondial. On croit que le polymorphisme génétique est lié au risque de développement du cancer colorectal. La molécule d'adhésion intercellulaire-1 est présente dans plusieurs types de cellules, telles que les cellules endothéliales et les leucocytes, et joue un rôle important dans plusieurs processus physiologiques. De plus, cette molécule est également exprimée dans diverses cellules cancéreuses, notamment le mélanome, le cancer colorectal et le lymphome.
Objectifs : Le but de cette étude était d'étudier la relation entre le niveau d'expression des gènes d'ICAM-1 et le polymorphisme génétique (rs5498 A/G) chez les patients atteints de cancer colorectal.
Méthodes : Un total de 115 échantillons de sang périphérique de jeunes adultes de Nijni Novgorod ont été examinés. L'expression de l'ARNm d'ICAM-1 a été analysée par PCR en temps réel. La distribution génotypique du polymorphisme du gène rs5498 E469K (A / G) a été réalisée en utilisant un allèle de réaction en chaîne de la polymérase spécifique.
Résultats : Les résultats ont montré une différence significative entre les contrôles et les patients atteints d'un cancer colorectal pour le génotype GG (p=0,002; OR = 1,35) et pour l'allèle G (p=0,005; OR=2,20). La présente étude montre la relation entre le SNP rs5498 (A / G) et le cancer colorectal avec un génotype AG (p=0,002; OR=3,55).
Conclusion : Nos résultats ont révélé que le polymorphisme d'ICAM-1 rs5498 (E469K) peut être associé au risque de cancer colorectal.
Mots clés: Cancer colorectal; molécule d'adhésion; cellules cancéreuses; polymorphisme, génotypage.

* Auteur correspondant: MOKRANE Ahlem, E-mail: dr.mokrane30@gmail.com

INTRODUCTION

According to the World Health Organization (WHO), colorectal cancer (CRC) is one of the most-diagnosed types of cancer and is the second leading cause of cancer-related death in 2018. Colorectal cancer is the most common form of cancer in the world [1]. Infection is a key factor affecting the development and progression of this disease [2]. In the large intestine, endothelial cells, macrophages and epithelial cells can express the cell adhesion molecule 1 (ICAM-1). Expression of ICAM-1 is associated with the degree and nature of the inflammation. Recent studies showed an increased susceptibility of cancer cells to the expression of ICAM-1. Several mediators can influence the metastatic progression, among these factors the adhesion molecules that are expressed on the cancer cells and the cells of the target organ playing a crucial role. The adhesion molecules generate the initial cell contacts and result in extravasation of the cancer cells and colonization of the organs [3].

The moleculeICAM-1 may be involved in immune surveillance and protection of the first line on the surface of epithelial cells and macrophages in patients with colon cancer. Expression of the ICAM-1 molecule and/or other leukocyte adhesion receptors by neoplastic epithelial cells can promote the direction of leukocyte infiltration and the interaction between leukocytes and epithelial cells in the tumor site of the large intestine [4]. ICAM-1, known as CD54, is a transmembrane glycoprotein, which is generally expressed on immune system cells and endothelial cells [5].

ICAM-1 is a transmembrane glycoprotein belonging to the CAMs superfamily, consisting of five extracellular Ig-like domains, a transmembrane domain and a short cytoplasmic tail [3]. The gene encoding ICAM-1 is located on the short arm of chromosome 19. The expression of ICAM-1 plays an important role in a number of oncological diseases. The level of expression of ICAM-1 is increased in breast, stomach and colorectal cancer [6-8]. A number of studies have revealed that there is a correlation between the expression of ICAM-1 and colorectal cancer [9-11], and the effect of ICAM-1 depends on the protein, if expressed in soluble or membrane form [9]. The purpose of this study was to investigate the relationship between the level of ICAM-1 gene expression and genetic polymorphism (rs5498 A/G) in patients with colon cancer.

MATERIEL AND METHODES

1. Cases and controls

59 samples of peripheral blood from healthy donors and 56 samples of peripheral blood from patients with colon cancer were analyzed. These samples were obtained from the hospital "Nizhny Novgorod Regional Clinical Oncology Center" and were analyzed at the Center for Molecular Biology and Biomedicine of Nizhny Novgorod State University. N.I. Lobachevsky.

2. Genotypic analysis

Genomic DNA was isolated from peripheral blood using phenol-chloroform extraction, SNP rs5498 (A/G) was genotyped using allele specific polymerase chain reaction (PCR). To analyze the variants of the ICAM-1 allele, we used the following oligonucleotides F (5'-CTCACTGTGTGCCTATTCCA-3') with RA (5'-AGCACATTCACGGTCACCTT-3') and F with RG (5'-AGCACATTCACGGTCACCTC-3') to detect allele A and G, respectively. Amplification parameters: 5 min at 94°C and 45 cycles (30 sec at 94°C, 45 sec at 65°C and 60 sec at 72°C) and 2 min at 72°C. The results were analyzed by agarose gel electrophoresis.

3. Real-time PCR

Synthesis of cDNA was performed using reverse transcription, followed by real-time PCR in a Bio-Rad CFX96 Touch device. When simultaneous detection of the mRNA of the ICAM-1 gene and the mRNA of the UBC gene using the following oligonucleotides: F (GAGCTTCGTGTCCTGTATGG), R (CTCATACCGGGGGGAGAGCA), Z (ROX-CCCATTGCCCGAGCTCAAGTGTCTAAA GGA- BHQ-2) and UBC- F (GCACAGCTAGTTCCGTCGCA), UBC- R (TGCATTGTCAAGTGACGAT), UBC- Z (CY5-ATTTGGGTCGCAGTTCTTGTTTGTGGAT-BHQ-2). Amplification parameters: 94°C - 10 min, 49 cycles (94°C for 30 sec, 60°C for 30 sec and 72°C for 30 sec). Simultaneous detection of the relative levels of the mRNA of the ICAM-1 molecule with UBC is present in the polymerase chain reaction in real time.

4. Statistical analysis

We used Hardy-Weinberg to test the genotypes using the χ2 distribution test for the difference in the expected frequencies and the observed ones. All tests with p<0.05 were considered statistically significant. Comparison of the ICAM-1 mRNA level was performed using the Graph Pad Prism 5 computer program.

The correspondence of the distribution of quantitative characteristics to the normal law was evaluated using the Kolmogorov-Smirnov test with the Lillieforce amendment. To compare the two independent groups by quantitative characteristics, a two-sided U-Mann-Whitney test. Differences were considered statistically significant at a level of p<0,05.

RESULTATS

1. Comparison of ICAM-1 gene expression in donors and colorectal cancer patients

In the blood of patients with colorectal cancer (n=56), the ICAM-1 mRNA level was determined (Fig. 1).

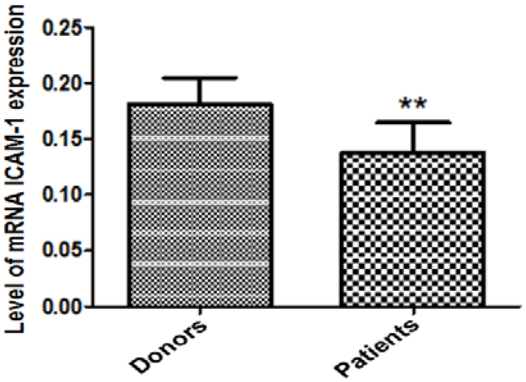

Figure 1 : Level of mRNA expression of the ICAM-1 gene in healthy donors and in patients with colorectal cancer

The level of mRNA ICAM-1 in patients with colorectal cancer showed a significant difference (p <0.05). There is a decrease in ICAM-1 gene expression in the peripheral blood of colorectal cancer patients. It appears that the expression of adhesion molecules ICAM-1 can interact with cells that control immunity (Fig. 1).

2. Comparison of genotypes 5498 A/G ICAM-1 of peripheral blood in healthy donors and colon cancer patients

ICAM-1 polymorphisms are given in Table 1, with two cases of patients with colon cancer, and means of control in accordance with the Hardy-Weinberg equilibrium. The genotypic distribution of ICAM-1 in patients with colon cancer was significantly different and controls (p <0.05), among patients with colon cancer, the distribution of allelic variants of SNP rs 5498 were distributed as follows: AA in 13 patients (23.2%), GA in 38 patients (67.9%) and GG in 5 patients (8.9%). The distribution of genotypes differs significantly from that of healthy donors: AA in 33 healthy donors (55.9%), GA in 22 healthy donors (37.3%) and GG in 4 healthy donors (6.8%).

G allele was significantly associated with the risk of colon cancer (OR = 2. 20, χ2 = 7.79, 95% C.I. = [1.26-3.85], p = 0.005). Frequency of heterozygous GA in cases of patients was more, than in the control group (67.9% vs. 37.3%, χ2 = 13.00, p = 0.002). Individuals with the GA genotype had a 3.55-fold increase in the risk of the disease compared with the AA genotypes. Expression of ICAM-1 gene was higher in patients with colon cancer (p = 0.002) compared to healthy donors. In addition, there was a significant association under the dominant model GG + GA (OR = 4.20, χ2 = 12.81, 95% C.I. = [1.88-9.40], p = 0.0003) (Table 1).

Tableau 1: Allele and genotype frequencies SNP rs5498 E469K (A/G) of the ICAM-1 gene in healthy donors and patients with colon cancer

Alleles, genotypes	Control group (n=59)	Patients with colorectal cancer (n=56)	$\chi 2$; P	OR (95% C.I.)
A : G	0.746 : 0.254	0.571 : 0.429	7.79 ; 0.005	0.45 (0.26–0.79) : 2.20 (1.26 – 3.85)
AA	33 (55.9%)	13 (23.2%)		0.24 (0.11 – 0.53)
AG	22 (37.3%)	38 (67.9%)	13.00; 0.002	3.55 (1.64 – 7.67)
GG	4 (6.8%)	5 (8.9%)		1.35 (0.34 – 5.30)
AG+GG	0.441	0.768	12.81; 0.0003	4.20 (1.88 – 9.40)

Notes: n is the number of samples,χ^2 is the chi-square value, d.f. - number of degrees of freedom, P is the confidence value, OR (odds ratio) is the odds ratio, 95% C.I. (Confidence Interval) - 95% confidence interval.

DISCUSSION

Progression of tumors can be determined by two fundamental factors. Internal cellular changes can cause cellular de-differentiation and aggressive proliferation, or changes in the extracellular microenvironment can promote or prevent tumor growth. It was suggested that the expression of ICAM-1 on the surface of cancer cells could play the role of a suppressor in the progression of the tumor in the host's immune surveillance system [10]. It turns out that the expression of adhesion molecules ICAM-1 can interact with cells that control immunity. Our results (Fig. 1) are consistent with the studies of Tanaka and Yashiro which showed that a decrease in ICAM expression leads to metastasis to the lymph nodes [12 ; 13].

In a study of the ICAM-1 gene in Nizhny Novgorod hospitals, it was found that genetic polymorphisms of ICAM-1 are associated with colon cancer. Our results suggest that the G allele and genotype AG of ICAM-1 are overexpressed in colon cancer cells. Regulation of ICAM-1 is also observed in several types of cancer associated with the progression of the disease [14]. Genetic changes can be considered as prognostic markers for colon cancer disease, they can be used in studies of the ICAM-1 molecule and its role in the development of tumors [15]. The frequencies of alleles of SNP rs5498 A/G vary between ethnic groups of people living in different territories. The lowest frequency of the A (K) allele is recorded among the indigenous population of Africa [16]. American and European populations occupy intermediate value [17], and the highest frequency was found in Asia [18].

There is also a connection between this genotype and the syndrome of differentiation in acute myeloid leukemia [19] and with the degree of differentiation of tumor cells in colorectal cancer [20 ; 21]. However, these associations are often characteristic of individual ethnic groups [22], which determine the need for research of each population separately.

Analysis of frequencies of alleles and genotypes SNP rs5498 A/G revealed associations with certain diseases. Among the people suffering inflammatory diseases (multiple sclerosis, Crohn's disease) [23] or those with myocardial infarction, the frequency of the GG (EE) genotype is higher than in healthy people living in the same territory [24]. An increase in the frequency of genotype AA (KK) is recorded among patients with colorectal cancer [25] and carcinoma of the stomach [26].

During inflammatory processes, the soluble form of ICAM-1 (sICAM-1) is widely distributed in several cells that are activated by cytokines, and then produce a large number of ICAM-1 membranes [27]. Several recent studies have shown that sICAM-1 is considered a biomarker of cancer that has been associated with diagnosis, clinical stage and metastasis [28-32]. ICAM-1 is expressed on the surface of many malignant cells [33-36] and present in soluble form and circulates in plasma of cancer patients at high levels [31 ; 37].

The level of mRNA in the blood of patients with colon cancer with heterozygote AA and AG was higher than in patients with homozygous GG. It was found that the level of mRNA of the ICAM-1 molecule in patients with GG homozygote tended to decrease in comparison with patients having the AG and AA genotype, which is related to the peculiarities of the neoplastic process and the reaction of the organism to the tumor. Metastases in lymph nodes are a common type of metastasis in patients with colorectal cancer

The SNP in the ICAM-1 gene associated with the risk of developing breast cancer, colorectal cancer, and melanoma was detected [38]. Serum sICAM-1 positively correlated with tumor size, metastases, including pancreatic cancer, lung cancer, breast cancer and stomach cancer [39-41]. Our results suggest that ICAM-1 expression is closely related to metastases and can be a useful predictor of predictors in patients with colorectal cancer.

ICAM-1 polymorphism of K469E can induce functional deterioration of the gene product. This genetic product facilitates the mechanism of inflammation and immune response. A set of cytokines produced by inflammation and an immune response participate in the formation of an oncogenic microenvironment playing a decisive role in initiating carcinogenesis of the stomach, which stimulates angiogenesis, damaging DNA and proliferation of epithelial cells and subsequent malignant transformation [42].

CONCLUSION

Our results show that there is no relationship between the polymorphism of ICAM-1 K469E and the susceptibility to cancer. It is observed that the genotype is not linked to the level of ICAM-1 expression. In oncology, the role of ICAM-1 is under intensive research reduces the level of expression of the ICAM-1 molecule in patients with colorectal cancer. The ICAM-1 expression is associated with metastases and can be a useful indicator for predicting colorectal cancer. In this regard, the level of expression and polymorphism of ICAM-1 in patients with colon cancer can provide detailed information on the regulation of this molecule, allowing doctors to provide a new diagnostic marker.

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