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On The Role Of The Variable Site C. -1082G>A Of The Anti-Inflammatory Cytokine Gene IL10 In The Pathogenesis Of Inflammatory And Ulcerative Lesions Of The Stomach

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Abstract: Interleukin-10 (IL-10) is a key immunoregulatory cytokine that plays an important role in anti-inflammatory and immunosuppressive processes in the body. Objective:This study aims to investigate the association of single nucleotide polymorphism (SNP) c. -1082G>A of the IL10 gene promoter located in the 1q31-32 locus of the first human chromosome with inflammatory and ulcerative lesions of the stomach. Material and methods. The study included 96 unrelated patients of the Uzbek population with inflammatory and ulcerative diseases of the stomach, including: 18 patients with chronic atrophic gastritis, 13 with chronic erosive gastritis and 55 with gastric ulcer. Conclusion. It is assumed that the homozygous AA genotype (c. -1082G>A, rs1800896) of the IL10 gene may be associated with the development of inflammatory and ulcerative gastric lesions, which may be due to reduced production of the anti-inflammatory cytokine IL-10. Further studies with a larger sample are needed to confirm this hypothesis.

Keywords: SNP, c. polymorphism. -1082G>A of the IL10 gene, rs1800896, IL10 -1082G/A, chronic gastritis, erosive gastritis, gastric ulcer, risk of formation.

Introduction: According to modern concepts and data from gastroenterologist specialists in recent years, the increase in the incidence of chronic gastritis (CH) and gastric ulcer disease (GUL), the severity of their course, and the risk of developing oncological complications have made these pathologies a pressing problem of clinical medicine worldwide, as well as in the Republic of Uzbekistan. At the same time, gastric ulcer disease continues to be one of the pressing problems not only in gastroenterology but also in abdominal surgery, as severe, life-threatening complications - gastrointestinal bleeding and perforation continue to occupy a leading place [1, 2, 3, 4, 5].

In the above-mentioned pathologies, in response to H. pylori adhesion, the epitheliocytes (and other cells) of the gastric mucosa produce cytokine proteins. The cytokine system includes a large number of molecules, among which interleukins play a leading role in the implementation of the immune response of the mucous membrane [6].

Interleukin 10 (IL-10), produced by T-cells (Th2), can be considered an antagonist of a number of cytokines. Thus, IL-10 suppresses the production of IF by Th1-cells. In addition, IL-10 inhibits the proliferative response of T-cells to antigens and mitogens, as well as suppresses the secretion of activated monocytes of TNF and IL-6. At the same time, IL-10 stimulates the secretion of IgE. In its inhibitory effect on cellular immunity, IL-10 is synergistic with IL-4. IL-10 stimulates the maturation of trig lymphocytes by affecting dendritic cells. Inhibition of the maturation of dendritic cells that activate Th2, their expression of molecules of the II class of the main complex of histocompatibility and co-stimulatory molecules, and, as a result, suppression of Th2 activation [9].

Studies have shown that IL-10 levels in cerebrospinal fluid increase in patients with schizophrenia and that the polymorphism of the IL10 gene is related to predisposition to schizophrenia [10].

As is known, according to a 2009 study, the A allele

rs1800896 limits the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-8, and increases the risk of prostate cancer [14]. Another study showed that AA homozygotes of this promoter region of the IL10 gene contribute to the reduction of IL-10 protein-cytokine production.

As can be seen from the above, the opinions of researchers differ sharply. Nevertheless, studies on the role of polymorphic variants of the IL10 gene (c. -1082G>A) in the development of chronic non-atrophic gastritis (CHNG), chronic erosive gastritis (CHEG), and gastric ulcer disease (GUL), phenotypic manifestations, and disease prognosis as biomarkers have not been sufficiently studied.

From the above mini-review, it follows that the decrease in the production of IL-10 protein cytokine in homozygous AA individuals of the IL10 polymorphism (c. -1082G>A) may prevent the elimination of elevated oxidative stress. And we, the authors, have a hypothesis-question-assumption that: "One-nucleotide polymorphism c. -1082G>A promoter of the IL10 gene (rs1800896) may make patients of the Uzbek population more vulnerable to inflammatory and ulcerative stomach lesions"!?

The purpose of this study was to confirm or refute the hypotheses - connections between single-nucleotide polymorphism (SNP) c. -1082G>A promoter of the IL10 gene (rs1800896), as a biomarker in some inflammatory and ulcerative lesions of the stomach, such as chronic gastritis, chronic gastritis, and peptic ulcer.

METHODS

A total of 184 patients participated in this study. They were n=96 (I - combined group) unrelated Uzbek patients with inflammatory and ulcerative lesions of the stomach: n=8 patients with chronic atrophic gastritis (CHAG), n=13 patients with chronic erosive gastritis (CHEG), and n=55 patients with gastric ulcer disease (GUL) examined in the gastroenterology department of the Tashkent Medical Academy clinic. As material for the control sample (II group - comparison group) n=88, genomic DNA preparations stored in the DNA bank of the RSNPMC of Hematology of the Ministry of Health of the Republic of Uzbekistan, practically healthy, non-related donors, were used.

In working with the examined patients, ethical principles prescribed by Article 24 of the Constitution of the Republic of Uzbekistan and the Helsinki Declaration of the World Medical Association were observed. All patients were familiarized and signed informed consent confirming their voluntary participation in the study.

Method of genotyping rs1800896 (c. -1082G>A)

To isolate DNA from peripheral blood, the "AmpliPraym RIBO-prep" reagent kit ("AmpliSens," Russia) was used. The concentrations of the isolated DNA were measured on a NanoDrop 2000 spectrophotometer (NanoDropTechnologies, USA) at a wavelength of A260/280 nm. The purity of all isolated DNA samples, determined by the A260/280 ratio, was 1.7/1.8.

The search for gene sequences for oligoprayer selection was carried out in GenBank NCBI (http://www.ncbi.nlm.nih.gov/GenBank). Nucleotide sequences and evaluation of oligoprayer characteristics were performed using the "Oligo v.6.31" program (Molecular Biology Insights Inc., USA). For standard PCR, a DNA amplification kit "Gene Pak® PCR MasterMix Core" ("IsoGene Lab. Ltd.," Russia).

Based on the use of the Fisher test before analyzing the distribution of polymorphic loci of the IL10 rs1800896 gene in the studied categories of patients with inflammatory-ulcerative process in the stomach (n=96) and compared healthy individuals, we initially determined the frequency of genotypes of this polymorphic gene in accordance with Hardy-Weinberg equilibrium (IRV, p>0.05). Further, statistical processing of the results was carried out using the "OpenEpi 2009, Version 9.3" statistical software package.

RESULTS

The obtained primary necessary numerical data for statistics and some calculations - the frequency of occurrence of alleles and genotypes for the polymorphism of the IL10 gene (c. -1082G>A or rs1800896) in the examined groups of patients with peptic ulcer disease and healthy individuals" is presented in Table 1.

Table 1.

Frequency of occurrence of alleles and genotypes by polymorphism of the IL10 gene c. -1082G>A orrs1800896) in the examined groups of patients with inflammatory-ulcerative diseases of the stomach and healthy

№	Indicators	Allele frequency				Genotype (model) frequency					
		G		A		G/G		G/A		A/A	
		n	%	n	%	n	%	n	%	n	%

1	Combined group, n = 96 (NCHG +CHEG+ SYD)	148	77,1	44	22,9	59	61,5	30	31,2	7	7,3
2	NCHG, n = 18	29	80,6	7	19,4	12	66,7	5	27,8	1	5,5
3	CHEG, n = 23	35	76,1	11	23,9	14	60,9	7	30,4	2	8,7
4	SYD, n = 55	84	76,4	26	23,6	33	60,0	18	32,7	4	7,3
5	Compared control group, n = 88	137	77,8	39	22,2	51	57,9	35	39,8	2	2,3

As can be seen from Table 1, the frequency range of alleles occurring according to polymorphism c. -1082G>A of the IL10 gene (rs1800896) in the examined groups of patients with peptic ulcer disease and healthy individuals did not differ sharply. Our data roughly matches the data of South Asians (76-81 versus 76).

For clarity, the differences in the carriage of genotypes of polymorphic loci of the IL10 gene are presented in Diagram 1 (c. -1082G>A) between groups of patients with peptic ulcer disease and healthy individuals.

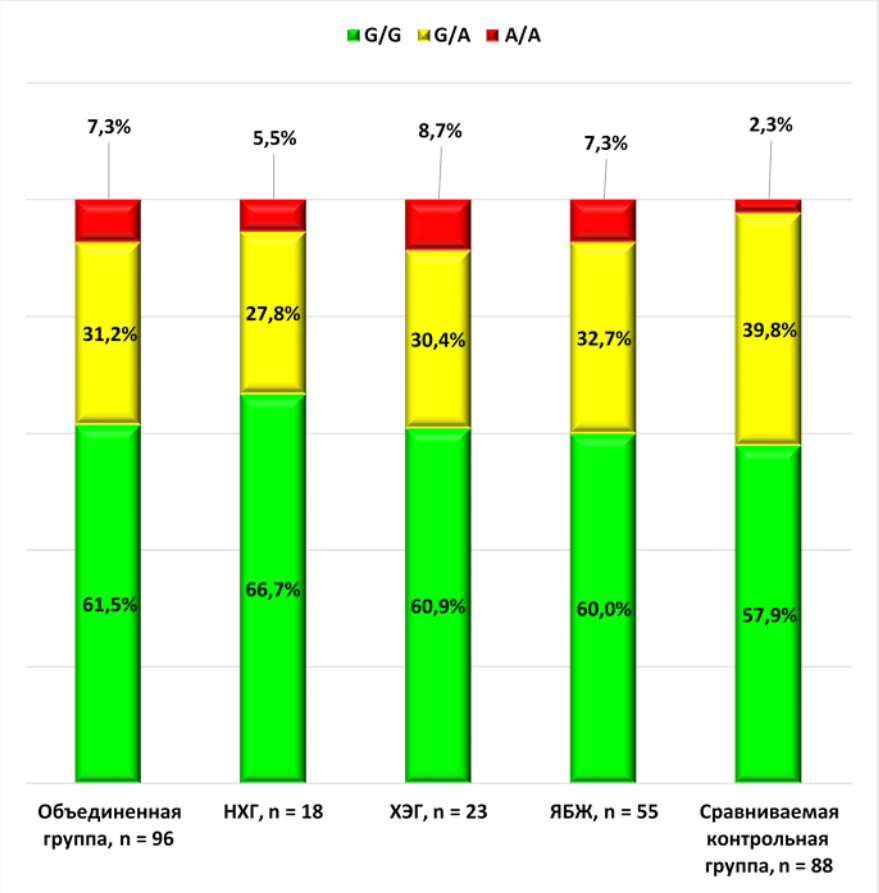

Diagram 1. Differences in the carriage of genotypes (models) of polymorphic loci of the IL10 gene (c. -1082G>A) between groups of patients with gastric inflammatory-ulcerative diseases and healthy individuals

As can be seen from Diagram 1, differences in the carriage of genotypes of polymorphic loci of the IL10 gene (c. -1082G>A) did not differ sharply between the groups of patients with peptic ulcer disease and healthy individuals.

Obtained statistical data (results, calculations)

Distribution of genotype frequencies for the polymorphic IL10 gene (c. -1082G>A) according to Hardy-Weinberg equilibrium (HRV, p>0.05) in the combined group of patients with inflammatory-ulcerative process in the stomach (n=96) and healthy individuals did not differ in their deviation.

Having begun studying the peculiarities of the occurrence of polymorphic loci of the IL10 gene (c. -1082G>A) in the healthy group (n=88), carriage of the major and minor G and A allele was determined in 77.8% (n=137) and 22.2% (n=39) of cases, respectively. Among this category of examined individuals, the G/G, G/A, and A/A genotypes were found in 57.9% (n=51), 39.8% (n=35), and 2.3% (n=2) of cases, respectively (see Table 1, Diagram 1).

At the same time, in the combined group of patients with inflammatory-ulcerative diseases of the stomach (n=96), the frequency of major (G) and minor (A) alleles compared to healthy individuals was recorded in slightly different cases - 77.1% (n=148) and 22.9% (n=44) of cases, respectively. However, from the perspective of all possible genotype variants, there were some distinctive aspects. Thus, compared to healthy individuals, if the major G/G genotype increased to 61.5% (n = 59), then the frequency of the heterozygous variant G/A decreased to 31.2% (n = 30), while the occurrence of the minor variant A/A increased to 7.3% (n = 7).

At the same time, in the combined group of patients with inflammatory-ulcerative diseases of the stomach (n=96), the frequency of major (G) and minor (A) alleles compared to healthy individuals was recorded in slightly different cases - 77.1% (n=148) and 22.9% (n=44) of cases, respectively. However, from the perspective of all possible genotype variants, there were some distinctive aspects. Thus, compared to healthy individuals, if the major G/G genotype increased to 61.5% (n=59), then the frequency of the heterozygous variant G/A decreased to 31.2% (n=30), while the occurrence of the minor variant A/A increased to 7.3% (n=7) (see Table 1 and Diagram 1).

The identified features may indicate the involvement of the minor genotype variant A/A in the polymorphic locus of the IL10 gene (c. -1082G>A) in increasing the likelihood of developing inflammatory-ulcerative diseases of the stomach.

Results of the study of the occurrence of allelic and genotypic variants of the polymorphic locus of the IL10 gene (c. -1082G>A) in the group of patients with chronic gastritis (n=18) compared to healthy individuals, was characterized by an increase in the occurrence of the major G allele (80.6% versus 77.8%) with a decrease in the minor A variant (19.4% versus 22.2%). In addition, among this group of patients, an increase in the frequency of the major G/G genotype (66.7% versus 57.9%) was also detected, while a decrease in the frequency of the heterozygous G/A genotype (27.8% versus 39.8%) and an increase in the frequency of the minor A/A genotype (5.5% versus 7.3%) (see Table 1 and Diagram 1).

At the same time, among patients with HEG (n=23), compared to the previously considered group of patients with CG, the frequency of the major G allele decreased somewhat (76.1% versus 80.6%), and the minor A variant increased somewhat (23.9% versus 19.4%), having more approximate values in the group of healthy individuals (76.1% versus 77.8% and 23.9% versus 22.2%) (see Table 1 and Diagram 1).

Regarding genotype variants among CG patients, compared to the CG group, the proportion of the major G/G genotype decreased to 60.9%, while the occurrence of heterozygous G/A and minor A/A variants increased to 30.4% and 8.7% (5.5% versus 7.3%). At the same time, compared to healthy individuals, the frequency of major G/G (60.9% versus 57.9%) and minor A/A (8.7% versus 2.3%) genotypes remained higher with a decrease in the occurrence of heterozygous variants of the G/A genotype (30.4% versus 39.8%) (see table 1 and diagram 1).

Thus, we obtained data on the occurrence of polymorphic loci of the IL10 gene (c. -1082G>A) among both patients with inflammatory-ulcerative diseases of the stomach and healthy individuals, which have their own characteristics in the distribution of alleles and genotypes for the studied gene. In particular, compared to healthy individuals, the lowest frequency of minor A allele was characteristic of patients with CGN (19.4% versus 22.2%), and the highest frequency was characteristic of the group with HEG (23.9% versus 22.2%). Moreover, compared to healthy individuals, the frequency of the heterozygous variant of the G/A genotype among all patient groups remained significantly lower, while the proportion of the minor A/A genotype increased, reaching its maximum, especially in the group of patients with HEG (8.7% versus 2.3%) (see Table 2 and Diagram 1.2).

Consequently, based on this preliminary analysis, it can be assumed that the minor A/A genotype is involved in the pathogenesis of gastric inflammatory-ulcerative diseases, and this model can serve as a biomarker.

To confirm this assumption, it is advisable and necessary to further conduct a comparative analysis of the differences in the frequency of occurrence of alleles and genotypes between the groups of patients and healthy individuals, determining their statistical significance.

DISCUSSION

The obtained data confirm the significance of the c.-1082G>A polymorphism in the regulation of the inflammatory process in gastric pathologies. A decrease in IL-10 production in carriers of the A allele can contribute to an intensified inflammatory reaction and mucosal damage. Genotyping of this polymorphism can be a useful marker of stomach disease predisposition and a potential target for personalized therapy.

CONCLUSION

The c.-1082G>A polymorphism of the IL10 gene plays a significant role in the pathogenesis of inflammatory and ulcerative lesions of the stomach. Genotyping of

this area can be used to predict the risk of developing these diseases and optimize therapeutic strategies.

The identified tendency for patients to carry the A allele more frequently requires further research on an expanded sample. Future work should include studying the functional influence of this polymorphism on the level of IL-10 expression and its relationship to inflammatory processes in the gastric mucosa.

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