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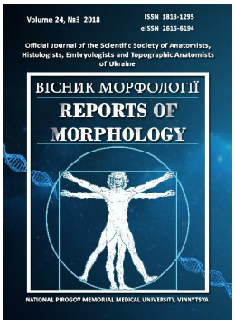

The role of the CagA gene in the occurrence of the inflammatory response of the gastric mucosa in patients with chronic Helicobacter pylori-associated gastritis

Vernigorodskiy S.V., Sukhan D.S.
National Pirogov Memorial Medical University, Vinnytsya, Ukraine

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CORRESPONDING AUTHOR
e-mail: vernset@ukr.net
Vernygorodskyi S.V.

Currently, Helicobacter pylori infection (H. pylori) is recognized as one of the most important risk factors for gastrocarcinogenesis. It is known that this infection does not directly cause neoplastic changes in the gastric mucosa, and this is due to a number of consecutive events due to the long persistence of the pathogen in the human body. The initial stage of this cascade, of course, is the inflammatory response, due to the body's ability to adapt to extraneous infection, which is the inevitable result of the interaction of H. pylori with cells of the gastric epithelium. This direct damaging effect is enhanced by the production of vacuolating cytotoxin and the release of products of the cytotoxin-associated CagA gene, which, at a pathomorphological level, is manifested by inflammatory infiltration of the gastric mucosa (GM) to some extent. On the relationship between the degree of contamination and the activity of the inflammation of the GM in people infected with the CagA strain, today there are different, often conflicting opinions, which is why in this work we set the goal of establishing the relationship between the nature of the inflammatory response and the presence of the CagA gene in H. pylori- infected patients. The purpose of the study is to determinate the relationship between the nature of the inflammatory response and the genetic features of the H. pylori strain (CagA genotype).We examined 365 patients, among whom 40 people were included in the control group (18 women and 22 men, whose average age was 45,33±15,46 and 42,82±12,31, respectively) without any gastroenterological pathology in the anamnesis , patients with chronic non-atrophic gastritis (188 people) and chronic atrophic gastritis (137 people). A close relationship was established between the presence of the CagA gene, activity and the degree of contamination for chronic non-atrophic gastritis (CNG): for a low degree of contamination, Fisher's exact test was = 0.002, p<0.05, for a moderate degree - 0.012, p<0.05, for a high degree - 0,012, p<0.05. Accordingly, in chronic atrophic gastritis (CAG): for a low degree of contamination Fisher's exact test = 0.011, p<0.05, for a moderate degree - 0.003, p<0.05, for a high degree - 0.001, p<0.05. There is also a close relationship between the degree of contamination and the activity of chronic gastritis (CG): in patients with a high degree of contamination, CG activity was determined, as a rule, for stage 2-3. In our study, the inflammatory response depended on the presence or absence of the H. pylori strain in the patient, which contains the CagA genotype, which, in our opinion, plays a key role in triggering a cascade of inflammatory changes in the GM and progression of chronic gastritis.

Keywords: *Helicobacter pylori, CagA, chronic gastritis, morphological changes.*

Introduction

The correlation of chronic inflammation with gastric cancer was established in 1863 by the famous German pathologist R. Virchow [27]. The discovery of Helicobacter pylori has revolutionized previous perceptions of the nature of gastroduodenal pathology and noted this unique infectious agent as a specific cause of CG, peptic ulcers and stomach cancer. The International Kyoto Consensus first proposed an etiological classification of gastritis and recommended that H. pylori-induced CG should be considered as an infectious disease requiring treatment

not so much to alleviate symptoms as to prevent complications such as peptic ulcer and gastric cancer [7, 32, 36]. The property of H. pylori to induce the development of inflammatory, dysplastic, metastatic and neoplastic changes depends on factors related to the microorganism itself, the organism of the host and the environment. The main pathogenicity genes include: CagA (cytotoxin-associated gene A); VacA (vacuolating cytotoxin); IceA (induced by contact with epithelium); BabA (blood group antigen-binding adhesin). H. pylori genes in the so-called "pathogenicity island" cag (cagA pathogenicity island, cag PAI) due to the activation of NF-kB (nucleic factor kappa-B) are involved in the development of an inflammatory response by initiating a cascade of signal transduction, leading to interleukin IL-8 production. As a result, proinflammatory cytokines and cellular (Th-1-mediated) immune response lead to further progression of inflammatory response [4, 17, 18, 28, 22].

The high frequency of peptic ulcer disease and the onset of MALT-lymph in Europe is due to the presence of CagA. CagA strains of H. pylori are also associated with pronounced epithelial cell proliferation and GM metaplasia [6]. In western countries, there have also been reports that individuals infected with CagA-positive strains are more likely to develop stomach ulcer and cancers than those infected with H. pylori CagA-negative strains. However, there was no such dependence on the inhabitants of East Asia [40]. Most authors argue that there is a close correlation [9, 10, 11, 14, 24, 26], others believe that CagA-positive / negative strains of H.pylori are not related to the development of severe gastroduodenal pathology and do not find any significant differences in the activity of inflammation and colonization in different types of H. pylori infection [4, 13, 19].

That is why the *purpose* of our study was to establish the relationship between the nature of the inflammatory response and the genetic features of the H. pylori strain (presence of CagA genotype).

Materials and methods

The study group consisted of 325 people with CG diagnosis: 111 women (mean age 49.85±13.41) and 214 men (mean age 48.81±13.61). The control group included 40 persons (18 female and 22 male, mean age 45.33±15.46 and 42.82±12.31, respectively) without gastrointestinal pathology in history (Table 1). Among patients with CG, the following groups were isolated: chronic non-atrophic gastritis (188 persons) and chronic atrophic gastritis (137 people). In the survey, the ethical principles of the Helsinki Declaration of the World Medical Association (World Medical Association Declaration Helsinki, 1964) were followed. All patients were informed and signed informed consent, confirming their voluntary participation in the study.

In the course of fibroesophagogastroduodenoscopy, multiple biopsies were performed - 2 biopsies from the body and antrum of the stomach and 1 from the angle of the stomach. Pathologist examination of biopsies for the diagnosis was performed in accordance with the requirements of the morphological section of the modified Sydney-Houston system [5, 23]. Determination of the persistence of H. pylori in GM was performed using urease test [20], cytologically by Pappenheimer [21] and histologically - colored by Giemsa and toluidine blue by B. Slater [31]. The genotyping of helicobacter infection was performed using a polymerase chain reaction. For further comparative analysis with the results of genotyping H. pylori we used own data obtained from the inspection of 40 practically healthy persons, among which 17 were infected with H. pylori. To determine the degree of dysplasia, the criteria proposed by WHO experts [3], and developed on the basis of the Vienna classification of neoplasia of the gastrointestinal epithelium [30] were used. In the presence of H. pylori infection, all cases of observations were divided into two groups: H. pylori-positive and H. pylori-negative.

Table 1. Distribution of patients according to nosology depending on age.

Age (years) / Nosology	up to 25 (m/f)	26-44 (m/f)	45-59 (m/f)	60 and >(m/f)
Normal GM	4 (2/2)	19 (11/8)	11 (7/4)	6 (2/4)
CNG without dysplasia	10 (7/3)	27 (18/9)	14 (9/5)	5 (3/2)
CNG with dysplasia: Mild Severe	4 (3/1) 3 (2/1) 1 (1/0)	42 (29/13) 29 (20/9) 13 (9/4)	56 (36/20) 33 (21/12) 23 (15/8)	30 (20/10) 17 (11/6) 13 (9/4)
CAG without dysplasia	-	8(5/3)	10(6/4)	22 (14/8)
CAG with dysplasia: Mild Severe	2 (1/1) 2 (1/1) -	19 (14/5) 15 (12/3) 4 (2/2)	43 (28/15) 31 (19/12) 12 (9/3)	33 (21/12) 19 (13/6) 14 (8/6)
Total	**20 (13/7)**	**115 (77/38)**	**134 (86/48)**	**96 (60/36)**

Statistical processing was performed using Microsoft Office Excel 2007 and "Statistica 5.0". Calculated the average arithmetic value M, its error m. The reliability of the difference between the average values was estimated by the Students criterion, the difference was considered to be valid at $p<0.05$. In order to check the statistical hypotheses of absolute and relative frequencies in independent samples, the chi square (χ^2) criterion was used, with the frequency of the investigated event less than 5 observations for the analysis of frequency differences in the two independent groups used Fisher's exact criterion, the confidence intervals given in the work, were constructed for confidence probability p=95%. In all statistical analysis procedures, the achieved level of significance (p) was calculated, with the critical level of significance taken equal to 0.05.

Results

In the control group, both in H. pylori-negative patients (-) and in H. pylori-positive (+), GM maintained its histoarchitectonics, regardless of the presence of CagA +.

The cytological smear is usually clean. In the two H. pylori (+) individuals, focal degenerative changes in the pyloric glands were established. At the same time, according to anamnesis, they also had signs of dyspepsia. In histological analysis, GM in practically healthy individuals consisted of a subepithelial layer which width was determined by the depth of the pits and glands, the ratio of which was approximately 1:3. Gastric pits were located close to each other. Surface epithelium cells, as a rule, had a highly prism form and a clear polar differentiation.

At morphological analysis of GM of patients with CNG CagA negative (CagA-) helicobacter infection without dysplasia it was established that in the group of inactive CNG surface and pit epithelium cells, exocrinocytes of fundal and pyloric glands in histological sections and smears-imprints retained their structure, were located predominantly in layers and groups, looked monomorphic, the nuclei were pushed to the periphery of cells, round-oval, their contour was equal. Chromatin homogeneous coarse-grained, intensely colored. The cytoplasm is weakly basophilic. Exocrinocytes of the glandular epithelium of the antral department of GM were located in groups and palisade-like structures, had larger sizes in comparison with superficial ones. The nuclei in them were located eccentrically, more oval, some of them containing single small correct form of the nucleolus.

In 15 (55.56%) patients with acute H. pylori (CagA-) CNG without dysplasia and 8 with mild dysplasia (29.63%) epithelial cells had a similar look, but dystrophic changes were accompanied by the appearance of dysregeneration in the form of hyperchromatosis, a violation of the location of nuclei and a nuclear-cytoplasmic ratio, as well as a basophilia of the cytoplasm of individual epithelial cells, more often present a few neutrophils and lymphocytes that were mainly infiltrated in GM lamina propria with its slight perivascular edema (Fig. 1), indicating weak activity and corresponded to the first stage according to L.Y. Aruina et al. (1998) [1].

The division of gastritis in the stage of activity was determined by the degree of neutrophilic infiltration of GM lamina propria. At the first stage of activity there was a slight leukocyte infiltration of GM lamina propria, while in the second occurred infiltration of the surface and pit epithelium with enhanced leukodiapedesis and the inflow of inflammatory cells to the lumen of the stomach. In the third stage, along with the pronounced infiltration of GM lamina propria and the epithelial layer, there were so-called "intra-pit abscesses", similar to "crypt-abscesses" in inflammatory diseases of the colon [1, 2, 16]. Their formation was through massive leukodiapedesis through the thickness of the epithelium to the lumen of the pits, and also accompanied by a powerful destruction of the epithelial layer.

At moderate and high levels of contamination, which corresponded to the 2nd and 3rd stages of CNG activity, both in CagA- and CagA+ H. pylori-infected patients, the above features increased significantly. At the same time,

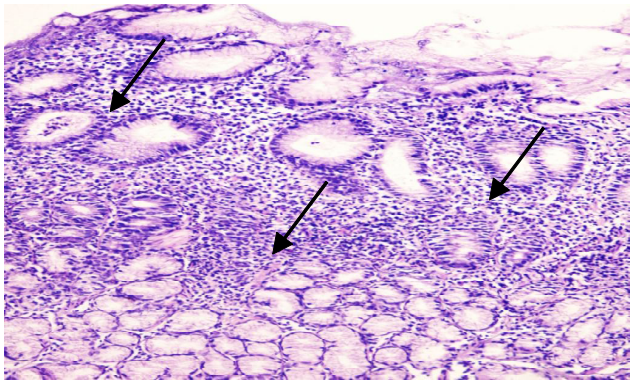

Fig. 1. Lymphoplasmacytic infiltration of the mucous membrane lamina propria with admixture of segmental neutrophils and dystrophic changes of surface and pit epithelium. Chronic non-atrophic active (stage 1) gastritis without dysplasia. CagA-. The arrows show the areas of lymphoplasmacytic infiltration of the mucous membrane lamina propria. Hematoxylin-eosin. x100.

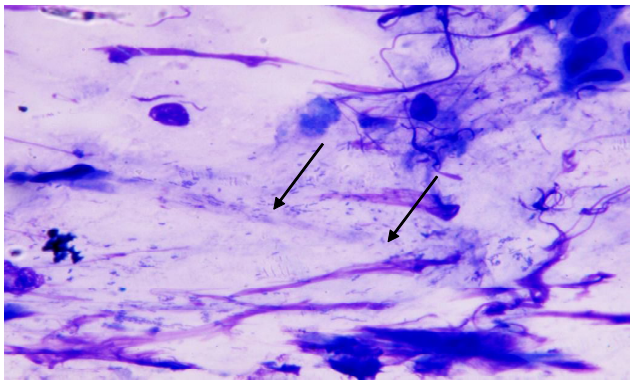

Fig. 2. Moderate degree of contamination of GM, more than 20 H. pylori bacteria in the field of vision (x1000) in a patient with CNG (CagA+). The arrows show the areas of the H. pylori conglomeration. Bacterioscopy by Pappenheimer. x1000.

among and intraepithelial localization of microorganisms in comparison with the low degree of contamination and the first stage of activity prevailed in the cytoplasm of the superficial and pit epithelium with a high degree of contamination and 3 stages of activity in 76% of H. pylori CagA+ patients.

At the same time, in patients with CNG with CagA-negative (CagA-) among and intraepithelial localization of microorganisms was observed in 10% of patients with high degree of contamination and 3 stages of activity compared with low and 1 stage. However, in patients with CAG CagA+, among and intraepithelial localization of microorganisms was observed only in 35% of cases with a high degree of contamination and 3 stages of activity, and CagA- in 5%. With a low degree of contamination and 1 stage of activity in both groups of CG H. pylori was determined predominantly in the adjacent to the surface epithelium mucus.

For CNG (CagA+) with moderate and high contamination in smears-imprints, an increase in the number of layer and groups of epithelial cells, as well as in the glandular structures, was likely to be attributed to the weakening of

intercellular connections (associated with both the activity of inflammation - leukopedesis and with the persistence of helicobacter infection) and easier getting into the imprint (Fig. 2).

Part of the epithelial structures was characterized by signs of dystrophy, manifested by the flattening of cellular forms, vacuolation of the cytoplasm, weakening of the contours of the membranes, loosening of the chromatin structure. The cells of the glandular epithelium were also represented in a greater number, among them observed moderate polymorphism. Along with the epithelial cells producing mucus, the presence of groups and glandular structures of proliferating cells with basophilic cytoplasm and absence of signs of secretion in the part of cells, a small increase in the nuclear-cytoplasmic ratio, starting with the generative zone of the gland, was confirmed. Such a picture created the impression of some polymorphism of epithelial cells. The intensity of mononuclear infiltration (degree of inflammation) in patients with CNG and CAG showed mild, moderate and severe degree of inflammation. At a significant degree of inflammation, along with the increase in the density of infiltration, formed clusters, which pushed the glands with the spread of it deep into the mucous membrane, up to the basal part. The accumulation of lymphocytes in mucous membrane lamina propria was diverse in terms of volume, cell density, structure and depth of occurrence. At a minimal and moderate extent, the formation of small groups of lymphocytes in the basal parts of the mucous membrane was observed. An increase in the volume of mononuclear inflammatory infiltrates in mucous membrane lamina propria occurred due to the formation of follicles. They were observed as bundles of oval or round shape, which consisted of tightly adjacent small lymphocytes. In a number of follicles there were light centers - reproduction, indicating a sufficient immune response of the body. The level of colonization of the mucosal by CagA (+) strains of H. pylori directly correlated with activity and degree of inflammation, both patients with CNG and CAG.

Dysplastic changes in the gastric epithelium in patients with CNG were detected in 43 H. pylori-, among which light dysplasia was observed in 28 (65.12%), and severe in 15 (34.88%). While GM dysplasia was registered at 89 H. pylori + patients with CNG, among which in CagA- 12 patients with dysplasia - 8 cases were with mild dysplasia (66.67%), while the severity was twice as low - 4 (33.33%). In the morphological analysis of dysplastic changes in GM of patients with CNG CagA+ H. pylori strains, it was found that among 77 patients with dysplasia, it was mild in 46 (59.74%) and severe in 31 (40.26%) (Table 2).

The activity of CAG, as well as CNG, irrespective of the presence of dysplasia, correlated positively with the bacterial colonization of GM: cases with severe (+++) infection respectively was mainly second or third stage of CAG activity (Table 3).

CAG with the first stage of activity in cytological preparations and on histological sections, painted with toluidine blue, heliobacteria were well visualized in the form of curved sticks. At a weak degree colonization - single (up to 20 in the field of view with an increase of 1000 times) bacterial bodies were found in the pit mucus, more often outside the epithelium in some fields of view.

Table 2. Characteristics of the examined patients depending on the presence of the gene CagA H. pylori.

Nosology	*CagA (-)N, m/f*	*CagA (+)N, m/f*
Normal GM	12 (6/6)	5 (3/2)
CNG without dysplasia	15 (8/7)	11 (7/4)*
CNG with dysplasia Mild Severe	12 8 (5/3) 4 (2/2)	77 * 46 (30/16)* 31 (21/10)*
CAG without dysplasia	12 (7/5)	9 (6/3)
CAG with dysplasia Mild Severe	16 12 (8/4) 4 (2/2)	48* 31 (22/9)* 17 (11/6)*
Total:	**67 (38/29)**	**150 (100/50)**

Notes: * p < 0,05- in comparison with the norm.

Table 3. Characteristics of the examined patients depending on the stage of contamination, the stage of activity and the presence of CagA.

Nosology	*CagA(-)*			*CagA(+)*		
	+	++	+++	+	++	+++
CNG inactive	11	5	4	7	5	0
CNG active	**3**	**2**	**2**	**20**	**23**	**33**
1 stage	2	1	1	9	6	3
2 stage	1	1	1	8	10	13
3 stage	0	0	0	3	7	17
CAG inactive	7	6	5	3	0	1
CAG active	**3**	**3**	**4**	**15**	**10**	**28**
1 stage	1	2	1	8	2	3
2 stage	2	1	3	6	7	8
3 stage	0	0	0	1	1	17
Total	**24**	**16**	**15**	**45**	**38**	**62**

For moderate colonization of GM by heliobacteria, the location of microbes, in the mucus, and in the lumen of the pits near the epithelium, was typically, where we observed from 20 to 50 bacteria in the field of view, which coincides with the data of Aruin, 1998 [1]. In cases of severe contamination along with epithelial cells and glandular structures, more than 50 microbial bodies were found as in the pits in the form of bacterial accumulation in many fields of vision and in adjacent to the surface epithelium of the mucus, gastric pits, and sometimes in the lumen of the glands.

Histological analysis of GM of patients with CAG for 2 stages of activity was characterized by diffuse leukocyte infiltration both in the surface and in the pit epithelium, and segmental leukocytes sometimes destroy the neck of the glands (Fig. 3). In the 3 stages of CAG activity, neutrophils were detected in both the surface and pit epithelium and in

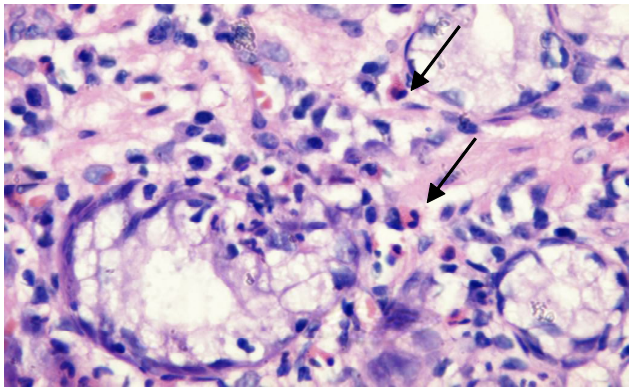

Fig. 3. Chronic atrophic active (stage 2) gastritis CagA+. Leukocyte infiltration of the mucous membrane lamina propria of the antral part of the stomach. The arrows show segmented neutrophils in mucous membrane lamina propria. Hematoxylin-eosin. x1000.

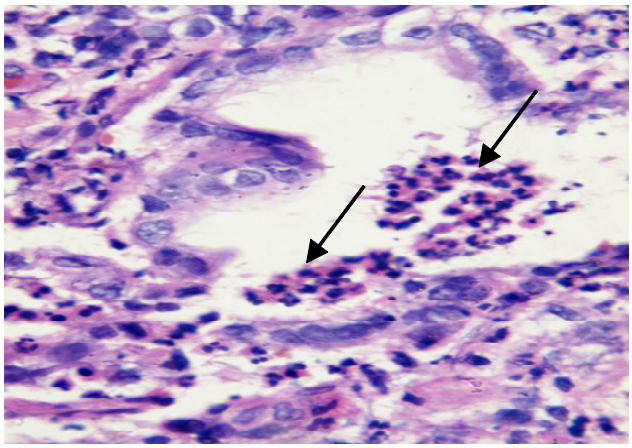

Fig. 4. Chronic atrophic active (stage 3) gastritis. CagA+. Leukodiapedesis with the formation of "intra-pit abscess". The arrows show the accumulation of segmental leukocytes inside the stomach pits. Hematoxylin-eosin. x1000.

the lumen of the glands with the formation of intrapit and glandular abscesses (Fig. 4).

In some sites, micro-erosions were observed as a small surface defect of the epithelial layer. Also, areas of epithelium of regenerative type with basophilic nuclei with high activity of inflammation were observed. Most often erosions were combined with the 2nd and 3rd stage of inflammation activity, as well as with the strong H. pylori contamination.

The parameters for CAG patients were follow: 31 (64%) of 48 patients had mild dysplasia and 17 (36%) with severe (see Table 2). At a severe degree of dysplasia, the severity of cellular atypia increased in patients both with CAG and CNG.

In the comparative pathomorphological analysis of GM in H. pylori+ and H. pylori-patients with CAG with dysplastic changes, it should be noted that 1 stage of atrophy was positively correlated with the degree of infectivity ($\chi^2 = 0.046$, $p < 0.05$), while for 2, 3, 4 stages of atrophy ($\chi^2 = 0,2773$, $p > 0,05$; $\chi^2 = 0,382$, $p > 0,05$; $\chi^2 = 0,555$; $p > 0,05$ respectively), such dependence has not been established. In our opinion, this is due to the key role of helicobacter infection, which triggers a cascade of pathological changes in GM. With further progression of atrophic changes in the gastric epithelium, GM loses the ability to synthesize mucin, which leads to the reduction of adhesive properties and the inability of H. pylori to bind to glycoproteins of gastric mucus.

Thus, conducted studies indicate that the presence of CagA positive genotype of helicobacter infection in patients with CG complicates the prognosis of the underlying disease, causing a cascade of pathological changes in GM.

Histologic and molecular genetic comparisons conducted in the studied groups of patients showed that the lowest degree of chronic gastritis activity was observed in GM of body and anthrax in uninfected patients and infected with H. pylori CagA (-) strains, and the minimum bacterial insemination rates - in the body of the stomach in patients infected with the strains of CagA (-) H. pylori.

Study of the activity of inflammation (neutrophil infiltration) of GM in chronic gastritis confirmed the association with helicobacter infection (see Table 3). The statistical analysis revealed a high reliability between inflammation activity and the presence of helicobacter infection (CagA+), and with CNG: for a low degree of contamination, the exact Fisher criterion = 0.002, $p < 0.05$, for moderate degree - 0.012, $p < 0.05$, for high degree - 0.012, $p < 0.05$. Accordingly, for CAG: for a low degree of contamination, the exact Fisher criterion = 0,011, $p < 0,05$, for a moderate degree - 0,003, $p < 0,05$, for a high degree - 0,001, $p < 0,05$. The highest values of gastric activity rates were noted for the antrum department in patients with CNG infected with CagA (+) H. pylori strains and in patients with the third stage of CAG activity infected with H. pylori (+) strains. The highest degree of bacterial insemination was recorded by us in the antral department of the stomach in patients with CNG of the third stage of activity infected with the strains of CagA (+) H. pylori.

Discussion

The main role in the mechanism of neutrophilic chemotaxis plays an epithelium, in which the expression of cytokines, leukotriene B4 and complement activation products occurs with adhesion [15, 28, 42]. The protein that activates neutrophils stimulates the adhesion of leukocytes to endothelial cells, which in turn changes microcirculation, leads to degranulation of tissue basophil granulocytes (mast cells), leukocytes and platelet aggregation and transudation. The leading role in chemotaxis belongs to interleukin-8, the main source of which is the gastric epithelium. Adhesion causes in epitheliocytes reorganization of actin cytoskeleton and increases the expression of the gene encoding interleukin-8, and then triggers the inflammatory cascade with the secretion of various cytokines [33, 39, 41]. In addition to direct bacterial stimulation of the epithelial production of interleukin-8, its expression is enhanced by the factor of tumor necrosis and interleukin-1, which are produced by macrophages and leukocytes, which migrate to the sites of colonization [25, 29]. A vicious circle with a long active process is created. The data we receive are in agreement with the data of N. Tegtmeyer et al. [34], which also revealed the

association of CagA + strains infection of the H. pylori with CG activity, due to the ability to directly stimulate the secretion of the epithelium of interleukin-8, with almost exclusively strains of type 1 (CagA +, VacA +) [34] and do not coincide with the data given by Y. Yamaoka in 1999 [40], which did not establish a significant difference in the relationship between the activity of inflammation with the colonization in different types of H. pylori infection.

It should be noted that most studies have shown that with the presence of H. pylori in the cytotoxin-associated gene, the relative risk of these diseases increases by 2-3 times, and some authors point to an increased risk of developing gastric cancer in CagA + H. pylori infection in 28.4 times [35, 37, 38]. The cellular composition of inflammatory infiltrates of GM is undergoing significant changes in the H. pylori infection, which are more non-specific, and in terms of prediction regarding the risk of pre-cancerous development, should be interpreted in conjunction with other factors and indicators involved in the pathogenesis of dysplastic changes in SOS. In our study, the degree of colonization, as a rule, corresponded to the stage of activity, as in cases of CNG, and in patients with CAG, which coincides with the data [8, 12].

By initiating damage, H. pylori causes chronic inflammation in GM. This inflammation is mediated by multitude pro- and anti-inflammatory cytokines. Genetic polymorphism directly influences changes in the intensity of the cytokine response, which causes definitive clinical effects in humans [35]. Clinical and morphological manifestations of helicobacter infection depend on genetic factors of pathogenicity of the microorganism and genetic predisposition of the infected organism.

The data obtained by us is sufficiently promising for further research of the relationship between helicobacter infection in the epithelium of GM and precancerous changes in the stomach with the features of the clinical course of the disease and the composition of cellular infiltration. Although the role of another H. pylori infectious agent in the gastric cancer etiology has been substantiated, however, not all pathogenetic links in the participation of H. pylori in gastro-carcinogenesis have been fully elucidated. Perhaps they are also due to the effect on the composition of inflammatory cellular infiltration of GM and the production of some cytokines by H. pylori-induced epithelial cells, macrophages and other cells.

Further study of genetic factors of virulence with the use of polymerase chain reaction is promising, since it will allow not only the prediction of the course of chronic gastritis, depending on the strain detected, but also to optimize and develop new differentiated approaches to eradication therapy.

Conclusions

The degree of activity of both chronic non-atrophic and atrophic gastritis depended on the presence of CagA. At the same time, the closest correlation is recorded between the degree of infectivity and the stage of activity. Thus, in chronic non-atrophic gastritis: for a low degree of contamination, the exact Fisher criterion was 0.002, with $p<0.05$, for a moderate degree - 0.012 ($p <0.05$), and for high -0.012 ($p <0.05$). Accordingly, for chronic atrophic gastritis: for a low degree of contamination, Fisher's exact criterion was 0.011, at $p <0.05$, for a moderate degree - 0.003 ($p <0.05$), for a high degree -0.001 ($p <0.05$).

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РОЛЬ CagA ГЕНА У ВИНИКНЕННІ ЗАПАЛЬНОЇ ВІДПОВІДІ СЛИЗОВОЇ ОБОЛОНКИ ШЛУНКУ У ХВОРИХ НА ХРОНІЧНИЙ HELICOBACTER PYLORI-АСОЦІЙОВАНИЙ ГАСТРИТ

Вернигородський С.В., Сухань Д.С.

В теперішній час інфекція Helicobacter pylori (H. pylori) визнана одним із найважливіших факторів ризику гастроканцерогенезу. Відомо, що дана інфекція не викликає безпосередньо неопластичні зміни в слизовій оболонці шлунку, а відбувається це внаслідок ряду послідовних подій за рахунок тривалої персистенції збудника в організмі людини. Початковим етапом даного каскаду, безумовно, є запальна відповідь, яка обумовлена здатністю організму адаптуватися до сторонньої інфекції та є неминучим результатом взаємодії H. pylori з клітинами шлункового епітелію. Цей пошкоджуючий прямий ефект посилюється

продукцією вакуолізуючого цитотоксину й вивільненням продуктів цитотоксин-асоційованого гена CagA, що на патоморфологічному рівні проявляється запальною інфільтрацією слизової оболонки шлунку (СОШ) того чи іншого ступеня. Щодо зв'язку між ступенем обсіменіння (контамінації) та активності запалення СОШ у людей, інфікованих штамом CagA, на сьогодні існують різні, часто суперечливі думки, ось чому в даній роботі ми поставили за мету встановлення взаємозв'язку між характером запальної відповіді та наявності гену CagA у H. pylori-інфікованих хворих. Мета дослідження - встановлення взаємозв'язку між характером запальної відповіді та генетичнихми особливостями штаму H. pylori (наявності генотипу CagA). Нами було обстежено 365 пацієнтів, серед яких до контрольної групи увійшли 40 осіб (18 жіночої та 22 чоловічої статі, середній вік яких становив 45,33±15,46 та 42,82±12,31 років, відповідно) без наявності будь-якої гастроентерологічної патології в анамнезі, хворих на хронічний неатрофічний гастрит (188 осіб) та хронічний атрофічний гастрит (137 осіб). Встановлений, тісний зв'язок між наявністю гену CagA, активністю та ступенем контамінації для хронічного неатрофічного гастриту: для низького ступеня контамінації точний критерій Фішера становив =0,002, p<0,05, для помірного ступеня - 0,012, p<0,05, для високого ступеня - 0,012, p<0,05. Відповідно, при хронічному атрофічному гастриті: для низького ступеня контамінації точний критерій Фішера =0,011, p<0,05, для помірного ступеня - 0,003, p<0,05, для високого ступеня - 0,001, p<0,05. Зареєстрований також тісний зв'язок між ступенем контамінації та активністю хронічного гастриту (ХГ): у хворих з високим ступенем контамінації виявляли, як правило, 2-3 стадію активності ХГ. У нашому дослідженні запальна відповідь залежала від наявності, або відсутності у пацієнта штаму H. pylori, що містив генотип CagA, котрий, на нашу думку, займає ключову роль у запуску каскада запальних змін СОШ та прогресуванні хронічного гастриту.
Ключові слова: *Helicobacter pylori, CagA, хронічний гастрит, морфологічні зміни.*

РОЛЬ CagA ГЕНА В ВОЗНИКНОВЕНИИ ВОСПАЛИТЕЛЬНОГО ОТВЕТА СЛИЗИСТОЙ ОБОЛОЧКИ ЖЕЛУДКА У БОЛЬНЫХ ХРОНИЧЕСКИМ HELICOBACTER PYLORI-АССОЦИИРОВАННЫМ ГАСТРИТОМ

Вернигородский С.В., Сухань Д.С.

В настоящее время инфекция Helicobacter pylori (H. pylori) признана одним из важнейших факторов риска гастроканцерогенеза. Известно, что данная инфекция не вызывает непосредственно неопластические изменения в слизистой оболочке желудка, а происходит это вследствие ряда последовательных событий за счет длительной персистенции возбудителя в организме человека. Начальным этапом данного каскада, безусловно, является воспалительный ответ, который обусловлен способностью организма адаптироваться к посторонней инфекции и является неизбежным результатом взаимодействия H. pylori с клетками желудочного эпителия. Этот повреждающий прямой эффект усиливается продукцией вакуолизирующего цитотоксина и высвобождением продуктов цитотоксин-ассоциированного гена CagA, что на патоморфологическом уровне проявляется воспалительной инфильтрацией слизистой оболочки желудка (СОЖ) той или иной степени. По связи между степенью обсеменения (контаминации) и активности воспаления СОЖ у людей, инфицированных штаммом CagA, на сегодняшний день существуют различные, часто противоречивые мнения, вот почему в данной работе мы поставили цель установления взаимосвязи между характером воспалительного ответа и наличием гена CagA у H. Pylori-инфицированных больных. Цель исследования - установление взаимосвязи между характером воспалительного ответа и генетическими особенностями штамма H. pylori (наличия генотипа CagA). Нами было обследовано 365 пациентов, среди которых в контрольную группу вошли 40 человек (18 женского и 22 мужского пола, средний возраст которых составлял 45,33±15,46 и 42,82±12,31 лет соответственно) без наличия какой-либо гастроэнтерологической патологии в анамнезе, больных хроническим неатрофическим гастритом (188 человек) и хроническим атрофическим гастритом (137 человек). Установлена тесная связь между наличием гена CagA, активностью и степенью контаминации для хронического неатрофического гастрита: для низкой степени контаминации точный критерий Фишера составлял 0,002, p<0,05, для умеренной степени - 0,012, p<0,05, для высокой степени - 0,012, p<0,05. Соответственно, при хроническом атрофическом гастрите: для низкой степени обсеменения точный критерий Фишера был равен 0,011, p<0,05, для умеренной степени - 0,003, p<0,05, для высокой степени - 0,001, p<0,05. Зарегистрирована также тесная связь между степенью контаминации и активностью хронического гастрита (ХГ): так у больных с высокой степенью контаминации определяли, как правило, 2-3 стадию активности ХГ. В нашем исследовании воспалительный ответ зависел от наличия или отсутствия у пациента штамма H. pylori, содержащий генотип CagA, который, по нашему мнению, занимает ключевую роль в запуске каскада воспалительных изменений СОЖ и прогрессировании хронического гастрита.
Ключевые слова: *Helicobacter pylori, CagA, хронический гастрит, морфологические изменения.*