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World J Gastroenterol 2007 September 14; 13(34): 4610-4614
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Evidence for the role of gastric mucosa at the secretion of soluble triggering receptor expressed on myeloid cells (strem-1) in peptic ulcer disease

Vassilios Koussoulas, Spyridon Vassiliou, Ekaterini Spyridaki, Maria Demonakou, Ilia Vaki, Charalambos Barbatzas, Helen Giamarellou, Evangelos J Giamarellos-Bourboulis

Vassilios Koussoulas, Spyridon Vassiliou, Charalambos Barbatzas, Department of Gastroenterology, Sismanoglion General Hospital of Athens, University of Athens, Medical School, Greece
Ekaterini Spyridaki, Ilia Vaki, Helen Giamarellou, Evangelos J Giamarellos-Bourboulis, 4th Department of Internal Medicine, University of Athens, Medical School, Greece
Maria Demonakou, Department of Pathology, Sismanoglion General Hospital of Athens, University of Athens, Medical School, Greece
Correspondence to: Vassilios Koussoulas, MD, Sismanoglion General Hospital, 1 Sismanogliou Str., Athens 15126, Greece. kous73@yahoo.gr
Telephone: +30-210-8039798 Fax: +30-210-8024454
Received: 2007-02-21 Accepted: 2007-03-21

Abstract

AIM: To investigate the role of gastric mucosa at the secretion of sTREM-1 in peptic ulcer.

METHODS: Seventy two patients were enrolled; 35 with duodenal, 21 with gastric ulcer and 16 with chronic gastritis. Patients were endoscoped and gastric juice was aspirated. Patients with duodenal and gastric ulcer underwent a second endoscopy post-treatment. Biopsies were incubated in the absence/presence of endotoxins or gastric juice. Supernatants were collected and sTREM-1 and TNFα were measured by enzyme immunoabsorbent assays. Scoring of gastritis was performed before and after treatment according to updated Sydney score.

RESULTS: Patients with duodenal and gastric ulcer and those with chronic gastritis had similar scores of gastritis. sTREM-1 was higher in supernatants of tissue samples of *H pylori*-positive than of *H pylori-negative* patients with gastric ulcer. Median (± SE) sTREM-1 was found increased in supernatants of patients with gastric ulcer before treatment (203.21 ± 88.91 pg/1000 cells) compared to supernatants either from the same patients post-treatment (8.23 ± 5.79 pg/1000 cells) or from patients with chronic gastritis (6.21 ± 0.71 pg/1000 cells) ($P < 0.001$ and < 0.001, respectively). Similar differences for sTREM-1 were recorded among LPS-stimulated tissue samples of patients ($P = 0.001$). Similar differences were not found for TNFα. Positive correlations were found between sTREM-1 of supernatants from patients with both duodenal and gastric ulcer before treatment and the degree of infiltration of neutrophils and monocytes.

CONCLUSION: sTREM-1 secreted by the gastric mucosa is an independent mechanism connected to the pathogenesis of peptic ulcer. sTREM-1 was released at the presence of *H pylori* from the inflamed gastric mucosa in the field of gastric ulcer.

Key words: sTREM-1; Chronic gastritis; Gastric ulcer; Duodenal ulcer

Koussoulas V, Vassiliou S, Spyridaki E, Demonakou M, Vaki I, Barbatzas C, Giamarellou H, Giamarellos-Bourboulis EJ. Evidence for the role of gastric mucosa at the secretion of soluble triggering receptor expressed on myeloid cells (strem-1) in peptic ulcer disease. *World J Gastroenterol* 2007; 13(34): 4610-4614

http://www.wjgnet.com/1007-9327/13/4610.asp

INTRODUCTION

Many aspects of the mechanisms implicated in the pathogenesis of peptic ulcer disease remain unclear[1]. Research has been focused more on derangements of mechanisms of protection and repair of the mucosa of the stomach and duodenum[2]. It appears that most cases of both gastric and duodenal ulcer occur in the setting of infection by *H pylori*. Evidence is mounting in support of *H pylori* as a necessary ingredient in the ulcerative process, similar to acid and pepsin. It is not known whether the bacteria or the accompanying inflammation is the most important factor in the pathophysiology of peptic ulcer disease[3].

Triggering receptor expressed on myeloid cells (TREM)-1 is a recently discovered receptor expressed on the surface of neutrophils and monocytes. Engagement of TREM-1 has been reported to stimulate the synthesis of proinflammatory cytokines[4]. A soluble form of TREM-1, named sTREM-1, was observed and identified at significant levels in serum samples of patients with diseases affecting the gastrointestinal tract[5].

sTREM-1 has been found elavated in the gastric juice

of patients with peptic ulcer. Since its levels were positively correlated to the degree of infiltration of the gastric mucosa by neutrophils, leading thus to the hypothesis that sTREM-1 might be a sign of an inflammatory reaction taking place in the gastric mucosa[6] The latter hypothesis might be strengthened by the lack of expression of TREM-1 on cell membranes of macrophages of healthy intestinal lamina propria[7].

Based on the latter evidence, it is questioned whether sTREM-1 might be produced from the gastric mucosa in the event of peptic ulcer disease. The current study was designed to investigate a role of gastric mucosa for the release of sTREM-1. Furthermore it was investigated whether anti-ulcerative treatment was accompanied by any change of the ability of the mucosa for the secretion of sTREM-1.

MATERIALS AND METHODS

Study group

The study was approved by the Medical and Ethics Committee (6th/11.30.05/26 962) of General Hospital "Sismanoglion", Athens, Greece. A total of 72 patients, 54 men and 18 women, aged 58.92 ± 16.52 (mean ± SD) years were enrolled; 56 patients with peptic ulcer disease and 16 patients with chronic gastritis without peptic ulcer. Admitted patients were divided into three groups based on endoscopic findings, as follows: group A: consisting of 35 patients with duodenal ulcer; group B: consisting of 21 patients with gastric ulcer; and group C, consisting of 16 patients with chronic gastritis.

Informed consent was obtained from all participants. Indications for endoscopy in these patients were abdominal pain or discomfort, epigastric pain with nausea and vomiting, and dyspepsia. All endoscopies were done by the same endoscopist. Peptic ulcer was defined as a circumscribed break in the mucosa in the duodenum (DU) or in the stomach (GU) with apparent depth covered by an exudate, as previously described[8]. All patients with peptic ulcer disease belonged to the Forrest Ⅲ score[9]. *H pylori* infection was defined by the presence of the bacterium both at the histopathologic findings of each biopsy and after a gastric biopsy culture at the proper growth medium[10]. Exclusion criteria for the study were: recent upper GI bleeding, gastric carcinoma, diabetes mellitus, liver cirrhosis, acute or chronic renal failure and the ingestion of any antimicrobial or antisecretory medication for at least 15 d prior to endoscopy.

Interventions and study design

All patients were examined by upper GI endoscopy. Among patients with duodenal and gastric ulcer disease two endoscopies were performed; the first before treatment and the second 15 d after the end of the treatment. Among patients with chronic gastritis only one endoscopy was done; at each endoscopy biopsies were collected. Gastric juice was aspirated immediately after the entrance of the endoscope into the gastric lumen. At the time of endoscopy, three biopsy specimens were obtained from adjacent areas of the gastric antrum. When each biopsy specimen was taken, the forceps were fully opened and aimed at right angles to the gastric lumen to the extent possible to obtain uniformly sized biopsies. Biopsies were obtained from endoscopically intact mucosa distant from focal lesions such as ulcers and erosions. Each biopsy was used for *in vitro* culture.

After diagnosis of peptic ulcer disease or gastritis, esomeprasole 20 mg twice daily was prescribed. It was administered for four weeks in patients with duodenal ulcers, for eight weeks in patients with gastric ulcers and for four weeks in patients with chronic gastritis. For patients with infection by *H pylori*, clarithromycin 500 mg bid and amoxicillin 1000 mg bid for 10 d were also added. The above treatment was administered according to international guidelines[11,12].

In brief, gastric antral mucosal biopsy tissues were weighed and cultured on a culture insert over wells containing RPMI 1640 medium with 10% heat inactivated fetal bovine serum in a 5% CO_2 incubator for 18 h[13]. Biopsies were positioned on the insert with mucosal surfaces up. The first biopsy tissue was left unstimulated and served as control; the second was stimulated with 10 ng/mL of lipopolysccharide of *Escherichia coli* O144:H4 (LPS), and the third with 30 μL of gastric juice of each patient. The total volume of the added growth medium was 2.4 mL; when gastric juice was added it represented 1.25% of the total well volume. At the end of the incubation, the plates were centrifuged for ten minutes at 1400 g; then supernatants were collected from the wells and stored at -70℃, until assayed for estimation of sTREM-1 and TNFα. Results were correlated with histopathological findings.

Estimation of sTREM-1

Estimation of sTREM-1 was performed by a homemade enzyme immunoabsorbent assay in samples of supernatants. Capture antibody of sTREM-1 (R&D InC, Minneapolis, USA) was diluted to 4000 ng/mL and distributed in a 96-well plate at a volume of 0.1 mL per well. After overnight incubation at 25℃, wells were thoroughly washed with a 0.05% solution of Tween in PBS (Merck) (pH: 7.2-7.4). Then 0.1mL of standard concentrations of sTREM-1 (15.1-4000 pg/mL, R & D Inc) diluted with Reagent diluent (1% BSA in PBS, pH 7.2-7.4, 0.2 micron filtered) serving as a buffer or of supernatants was added in wells. After incubation for two hours, wells were washed thrice, and 0.1 mL of one 400 ng/mL dilution of sTREM-1 detection antibody (R&D Inc) was added per well. The plate was then incubated for two hours, and attached antibodies were signalled by streptavidin. Concentrations of sTREM-1 to each well were estimated by the optical density detected at 450 nm after addition of one 1:1 solution of H_2O_2: tetramethylbenzidine as a substrate (R&D Inc). sTREM-1 was expressed in pg/g of tissue. The lowest limit of detection for sTREM-1 was 3.91 pg/g of tissue. All determinations were performed in duplicate; the inter-day variation of the assay was 5.23%.

Estimation of TNFα

Tumor necrosis factor alpha (TNFα) was measured in samples of supernatants with an enzyme immunoabsor-

Table 1 Demographic characteristics of patients enrolled in the study. Updated Sydney scores are given

Parameters	Pre treatment	Post treatment	Chronic gastritis
N of patients	56		16
Age (mean ± SD)	60.13 ± 17.38		57.11 ± 15.81
Male/Female	46/10		8/8
Non smoking/smoking	16/40		6/10
Gastric ulcer	21	0	-
Duodenal ulcer	35	0	-
History of NSAID use	33/52		4/16
H pylori positive/negative	41/11[a]	7/45[b]	11/5
Patients with evidence of gastritis (Total updated Sydney Score > 0)	49/52[a]	34/52[d]	13/16
Site of gastric inflammation			
Antrum (no of patients)	28	21	8
Corpus (no of patients)	8	6	3
Disseminated (no of patients)	13	7	5
Total updated Sydney score (mean ± SD)	4.69 ± 1.93[a]	2.69 ± 1.22[f]	4.27 ± 0.65
Neutrophil infiltration score (mean ± SD)	1.77 ± 0.59[a]	0.81 ± 0.32[f]	1.73 ± 0.73
Monocyte infiltration score (mean ± SD)	2.15 ± 0.68[a]	1.05 ± 0.61[f]	1.73 ± 0.38
Lymphocyte infiltration score (mean ± SD)	0.87 ± 0.35[a]	0.13 ± 0.08[c]	0.69 ± 0.32
Mucosal atrophy score (mean ± SD)	0.55 ± 0.17[a]	0.38 ± 0.11[e]	0.58 ± 0.30
Intestinal metaplasia (mean ± SD)	0.29 ± 0.04[a]	0.13 ± 0.08[e]	0.19 ± 0.07
Density of *H pylori* (mean ± SD)	1.56 ± 0.28[a]	0.33 ± 0.07[f]	1.45 ± 0.39

[a]*P vs* chronic gastritis, non significant; [b,d,f]$P < 0.01$, [c]$P < 0.05$, *vs* pre-treatment scores. [e]*P vs* pre-treatment scores; non significant.

bent assay (EIA, Amersham, London, UK). Lowest limits of detection were 6.25 pg/g of tissue. All measurements were performed in duplicate and cytokine concentrations were expressed as pg/g of tissue.

Histopathology

Formalin-fixed, paraffin-embedded tissue samples were routinely cut at 3-4 μm and stained with haematoxylin and eosin alcian blue PAS (Periodic Acid Schiff) (at pH: 2.5) and Giemsa. Immunochemistry was performed for *H pylori* detection with 1:100 dilution (Biocare Med., California, USA).

The presence of gastritis was evaluated in each biopsy sample after separate scoring for each of the following parameters: (a) disease activity as mucosal infiltration by neutrophils; (b) chronic inflammation expressed as infiltration by monocytes and lymphocytes; (c) degree of mucosal atrophy; and (d) intestinal metaplasia. Each parameter was scored from 0 to 3 (0: absent, 1: mild, 2: moderate, 3: marked). In the case of intestinal metaplasia scores indicated the following findings: 0: absence; 1: complete or type Ⅰ; 2: incomplete or type Ⅱ; and 3: incomplete or type Ⅲ. As a consequence total Sydney score of gastritis ranged between 0 and 15, according to previously reported criteria of the updated Sydney System[14]. The extent of gastric inflammation in the antrum, corpus or both was also recorded. The density of *H pylori* was also evaluated semiquantitatively by the same criteria[15]. Specimens were classified by one pathologist who was unaware of the corresponding laboratory findings.

Statistical analysis

Patients of three groups were further divided into subgroups according to the absence or presence of *H pylori*. Concentrations of sTREM-1, and TNFα were expressed by their median ± 95% confidence intervals (CI) or range. Updated Sydney classification scores were given by their means (± Standard Deviation, SD). Comparison between groups was made by Mann-Whitney *U* test with a correction according to Bonferroni; for qualitative data comparisons were performed by χ^2 test. Correlations between sTREM-1, and TNFα and the gastritis score or the density of *H pylori* were performed according to Spearman's rank of order. Any *P* value less than 0.05 was considered as significant.

RESULTS

Patients' characteristics are given in Table 1. All patients suffering from duodenal ulcers had presence of *H pylori* on tissue biopsy.

No differences were recorded between patients with duodenal and gastric ulcer disease before treatment and patients with chronic gastritis regarding histological parameters of gastritis according to updated Sydney score. Differences in total updated Sydney score, and several parameters of chronic gastritis before and after treatment among patients with peptic ulcer disease and patients with chronic gastritis are shown in Table 1.

Concentrations of sTREM-1 and of TNFα in supernatants of samples of gastric mucosa taken from patients with either duodenal ulcer disease or gastric ulcer disease or chronic gastritis pre-treatment are shown in Table 2. sTREM-1 was higher in supernatants of tissue samples of *H pylori*-positive than of *H pylori-negative* patients with gastric ulcer. That was also found when mucosa samples were stimulated by LPS. Respectively, similar differences were not found for TNFα. They were also not found for both sTREM-1 and TNFα between *H pylori*-positive and *H pylori-negative* patients with chronic gastritis.

In the above subgroups of patients, concentrations of sTREM-1 were higher in supernatants of gastric mucosa of *H pylori*-positive patients with gastric ulcers than of mucosa of *H pylori*-positive patients with duodenal ulcer after stimulation by LPS ($P < 0.05$). Concentrations of sTREM-1 were also higher in supernatants of gastric mucosa of patients with duodenal ulcer than of patients with gastritis either without or with stimulation by LPS (*P* of comparisons: < 0.01 and < 0.01, respectively). Similar differences for sTREM-1 were found between gastric ulcer and chronic gastritis for *H pylori*-positive patients (*P* of comparisons < 0.01 and < 0.01, respectively). No changes were found when gastric juice was added in cultures. Respective differences in concentrations of TNFα were not observed.

Comparisons of concentrations of sTREM-1 and TNFα between supernatants in unstimulated, and LPS-stimulated samples of gastric mucosa in patients with duodenal and gastric ulcer pre and post treatment respectively, are shown in Table 3. In the presence of LPS, TNFα was increased in supernatants of biopsies taken from *H pylori*

Table 2 Concentrations of soluble triggering receptor expressed on myeloid cells-s (sTREM-1) and tumor necrosis factor-alpha (TNFα) of supernatants of tissue samples taken from patients with either duodenal or gastric ulcer disease or chronic gastritis at pre-treatment

Parameters	Duodenal ulcer		Gastric ulcer		Chronic Gastritis	
	H pylori (+)	*H pylori* (-)	*H pylori* (+)	*H pylori* (-)	*H pylori* (+)	*H pylori* (-)
N	35	0	14	7	9	7
			sTREM-1 [median (range), pg/g of tissue]			
0	32.41 (13.32)	-	317.27 (73.98)[a]	112.41 (38.71)	6.21 (0.81)[c]	5.18 (0.77)
LPS	102.41 (40.43)	-	455.41 (98.53)[b]	214.55 (44.81)	12.67 (2.16)[c]	9.37 (1.55)
Gastric juice	17.91 (7.11)	-	150.14 (41.16)[c]	118.48 (54.93)	10.07 (2.02)[c]	7.42 (1.22)
			TNFα [median (range), pg/g of tissue]			
0	10.62 (2.07)	-	7.58 (1.75)[c]	6.40 (1.52)	8.11 (1.31)[c]	5.98 (1.45)
LPS	28.25 (3.35)	-	45.33 (13.06)[c]	21.44 (8.12)	19.07 (4.72)[c]	17.87 (2.11)
Gastric juice	18.02 (5.97)	-	10.76 (2.08)[c]	8.51 (2.05)	10.17 (3.23)[c]	9.13 (1.61)

Patients were divided as either *H pylori*-positive or *H pylori*-negative. LPS: Endotoxin of Escherichia *coli* O144:H4. [a]$P < 0.05$, [b]$P < 0.01$, *vs H pylori* negative patients. [c]P *vs H pylori* negative patients. non-significant.

Table 3 Influence of treatment on the secretion of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and tumor necrosis factor-alpha (TNFα) by the mucosa of *H pylori*-positive patients with gastric and duodenal ulcers

Parameters	*H pylori*-positive with gastric ulcer		*H pylori*-positive with duodenal ulcer	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
		sTREM-1 [median (range), pg/g of tissue]		
0	203.21 (88.91)	8.23 (5.79)[b]	86.82 (35.41)	3.90 (2.84)[d]
LPS	418.87 (127.56)	14.31 (7.11)[b]	144.90 (58.79)	6.13 (4.07)[d]
		TNFα [median (range), pg/g of tissue]		
0	12.67 (226.79)	9.51 (8.02)[a]	12.47 (133.45)	10.31 (20.41)[a]
LPS	31.07 (231.89)	20.12 (13.51)[a]	34.05 (150.36)	17.88 (23.11)[a]

[b]$P < 0.001$, [d]$P < 0.01$, *vs* pre treatment; [a]P: non-significant, *vs* pre treatment.

Table 4 Correlations between sTREM-1 and TNFα and parameters of gastritis score in non and LPS stimulated supernatants of *H pylori* positive patients with duodenal and gastric ulcer and of patients with chronic gastritis

Parameters of Gastritis score	Supernatants of mucosa sampled from *H pylori*-positive patients with duodenal ulcer disease pre-treatment			
	Absence of LPS		Presence of LPS	
	sTREM-1	TNFα	sTREM-1	TNFα
Neutrophils infiltration	P = NS	P = NS	P = NS	P = NS
Monocytes infiltration	P = NS	$P < 0.01$	$P < 0.05$	$P < 0.01$
	Supernatants of mucosa sampled from *H pylori*-positive patients with gastric ulcer disease pre-treatment			
Neutrophils infiltration	P = NS	$P < 0.05$	$P < 0.01$	$P < 0.05$
Monocytes infiltration	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$
	Supernatants of mucosa sampled from *H pylori*-positive patients with chronic gastritis			
Neutrophils infiltration	P = NS	$P < 0.05$	P = NS	$P < 0.05$
Monocytes infiltration	P = NS	$P < 0.05$	P = NS	$P < 0.01$

negative patients with gastric ulcer before treatment and with chronic gastritis ($P < 0.05$ and < 0.05, respectively).

Correlations of sTREM-1 and TNFα between supernatants of patients with duodenal and gastric ulcer pre treatment and of patients with chronic gastritis when cultured in the absence/presence of LPS and parameters of gastritis score are shown in Table 4. In the absence of LPS sTREM-1 concentrations were significantly correlated with monocytes infiltration in *H pylori* positive patients with gastric ulcer. In the presence of LPS sTREM-1 was significantly correlated with both monocytes and neutrophils infiltration in *H pylori* positive patients with gastric ulcer; respectively, significant correlations were also observed between sTREM-1 and monocytes infiltration in *H pylori* positive patients with duodenal ulcer. Respectively, both in the absence/presence of LPS TNFα concentrations were significantly correlated with monocytes and neutrophils infiltration in *H pylori* positive patients with and gastric ulcer; respectively, significant correlations were also observed between TNFα and monocytes infiltration in *H pylori* positive patients with duodenal ulcer. No significant correlation was found between any of the latter scores and sTREM-1 or TNFα of supernatants of biopsies taken from patients post-treatment.

DISCUSSION

Among patients suffering from chronic active gastritis only a minority evolves to peptic ulcer disease[15], rendering the question what might be the underlying mechanism leading several patients with gastritis to peptic ulcer and others not. Recent data revealed that sTREM-1 was found increased in the gastric juice of patients with peptic ulcer disease compared to patients with chronic gastritis[7]. That finding might lead to the hypothesis that sTREM-1 might constitute an independent factor leading from gastritis to peptic ulcer.

The present study applied a unique design. It is the first time, to our knowledge, in the literature where the ability of

the gastric mucosa for the release of sTREM-1 and TNFα was studied among patients with either duodenal ulcer or gastric ulcer or chronic gastritis without signs of peptic ulcer disease. Supernatants of biopsies taken from the enrolled patients were stimulated with LPS and gastric juice of patients. It is known that *H pylori*-as a Gram negative bacterium-secretes LPS that mediates to the gastric inflammation[16]. As described by others, cell loss and apoptosis of gastric mucous cells was enhanced by *H pylori* LPS with less potency compared to the same effect by *E. coli* LPS. The low immunological potency of *H pylori* LPS may contribute to low-grade gastritis[17]. In an attempt to simulate the latter process cultured biopsies were stimulated with LPS. Inflammation of the gastric mucosa was significantly reduced after treatment whereas *H pylori* was also eradicated (Table 1). Although the proper treatment was administered in patients with chronic gastritis second endoscopy was not performed; the latter was thought to be of no significance because sTREM-1 concentrations were already minimal pre treatment.

Results revealed that gastric mucosa of *H pylori* positive patients with both duodenal and gastric ulcer disease was potent to secrete sTREM-1. The potency for secretion of sTREM-1 was lost post-treatment. The release of sTREM-1 was higher by *H pylori* infected gastric mucosa than by gastric mucosa not infected by *H pylori*. The effect of *H pylori* on the release of sTREM-1 by mucosa of patients with duodenal ulcer could not be assessed since all patients with duodenal ulcer in the studied cohort were *H pylori*-positive.

Similar kinetics to sTREM-1 were not found for TNFα. TNFα was found increased in strict correlation with the degree of mucosal inflammation independently from the underlying pathogenetic status. The latter was highlighted by the fact that TNFα was increased post treatment when gastric mucosa was stimulated by LPS (Table 4).

The main assumption revealed from the presented study was that sTREM-1 was secreted by the activated inflammatory cells that infiltrate the gastric mucosa; inflammatory cells were immigrated to the inflamed gastric mucosa attracted by *H pylori* or its components. The treatment of inflamed gastric mucosa and the eradication of *H pylori* ceased the secretion of sTREM-1. It is of great importance that the latter assumption exists only in the status of gastric and duodenal ulcer disease. The release of sTREM-1 was independent from the density of mucosal inflammation at patients with no evidence of peptic ulcer. The pattern of release of sTREM-1 by the activated inflammatory cells and probably their intracellular activity should be further investigated.

The independent contribution of sTREM-1 release in the pathogenesis of gastric ulcer is further aggravated by the observation that gastric juice could not influence the activity of the inflamed mucosa per se. Stimulation of inflamed gastric mucosa with gastric juice was not lead to a significant increase to the release of sTREM-1 and TNFα (Table 4).

The present study revealed for the first time in the literature that sTREM-1 secreted by the gastric mucosa is an independent mechanism connected to the pathogenesis of gastric and duodenal ulcer. sTREM-1 was released at the presence of *H pylori* from the inflamed gastric mucosa in the field of gastric ulcerative process. The exact pathogenetic mechanisms needs to be further clarified.

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