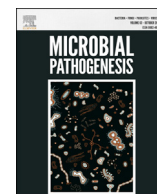


Contents lists available at [ScienceDirect](http://ScienceDirect)

## Microbial Pathogenesis

journal homepage: [www.elsevier.com/locate/micpath](http://www.elsevier.com/locate/micpath)

## Review

The biological functions of IL-17 in different clinical expressions of *Helicobacter pylori*-infectionNader Bagheri <sup>a</sup>, Fatemeh Azadegan-Dehkordi <sup>b</sup>, Hedayatollah Shirzad <sup>b,\*</sup>, Mahmoud Rafeian-Kopaei <sup>c</sup>, Ghorbanali Rahimian <sup>d</sup>, Alireza Razavi <sup>a</sup><sup>a</sup> Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran<sup>b</sup> Cellular and Molecular Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran<sup>c</sup> Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran<sup>d</sup> Department of Internal Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

## ARTICLE INFO

## Article history:

Received 28 April 2014

Received in revised form

4 March 2015

Accepted 11 March 2015

Available online 13 March 2015

## Keywords:

*Helicobacter pylori*

Interleukin-17

Gastritis

Peptic ulcers

Gastric cancer

## ABSTRACT

*Helicobacter pylori* (*H. pylori*) infection is regarded as the major cause of various gastric diseases (gastritis, peptic ulcers and gastric cancer) and induces the production of several cytokines. Interleukin-17 (IL-17) is recently recognized as an important player in the pathophysiology of infectious and immune-mediated gastrointestinal diseases. *H. pylori* infection increases IL-17 in the gastric mucosa of humans. IL-17 usually causes secretion of IL-8 through activation of ERK 1/2 MAP kinase pathway. The released IL-8 attracts neutrophils promoting inflammation. T regulatory cells (Tregs) suppress the inflammatory reaction driven by IL-17, there by favoring bacterial persistence in *H. pylori*-infection. The pathogenesis of *H. pylori*-induced inflammation is not well understood. Inflammation is promoted by both host factors and *H. pylori* factors, such as the proteins cytotoxin associated gene A (*cagA*) and vacuolating cytotoxin A (*vacA*). IL-1 $\beta$ , IL-6, tumor necrosis factor (TNF)- $\alpha$ , TGF- $\beta$ 1, IL-17, IL-18, IL-21 and IL-22 have been reported to be involved in *H. pylori*-induced gastric mucosal inflammation, but the details and relation to different patterns of inflammation remain unclear. Numerous studies have demonstrated important functions of IL-17 in acute and chronic inflammatory processes. This paper reviews the role of IL-17 in gastritis, peptic ulcers and gastric cancer related to *H. pylori*.

© 2015 Elsevier Ltd. All rights reserved.

## 1. Introduction

*Helicobacter pylori* is a spiral shaped gram-negative flagellate bacterium that colonizes the antral region of the human stomach. Approximately half of the world's population is infected with *H. pylori*, and the majority of *H. pylori*-infected patients develop coexisting chronic gastritis. In most infected patients, *H. pylori* colonization does not cause any symptoms such as abdominal pain, which typically occurs when the stomach is empty during night, or a few hours after meals, excessive burping, feeling bloated, feeling sick or vomiting, losing appetite, losing weight and blood or a black color in feces [1]. However, long-term infection with *H. pylori* significantly increases the risk of developing site-specific diseases. Among infected patients, approximately 10% develop peptic ulcer disease, 1–3% develop gastric adenocarcinoma, and 0.1% develop

mucosa-associated lymphoid tissue (MALT) lymphoma [2]. The variable outcomes in *H. pylori*-infected patients likely depend on various factors such as virulence factors of *H. pylori*, inflammatory responses governed by host genetic diversity, or environmental influences (such as smoking, malnutrition, high salt intake, vitamin and antioxidants deficiency), which finally influence the interactions between pathogen and host [3]. Th17 cells are identified as distinct T helper cell populations that play important role in CD4<sup>+</sup> T cell-mediated immunity. In this paper we aimed to review the interaction of *H. pylori* and host focusing on biological functions of IL-17.

## 2. Bacterial virulence factors

Bacterial virulence factors in *H. pylori*-infected patients play an important role for the topology and significantly increased the risk of developing site-specific diseases [4–7]. *H. pylori* produce a number of virulence factors that are essential for colonization of the

\* Corresponding author.

E-mail addresses: [shirzad1951@yahoo.com](mailto:shirzad1951@yahoo.com), [shirzadeh@SKUMS.ac.ir](mailto:shirzadeh@SKUMS.ac.ir) (H. Shirzad).

stomach and survival in the hostile gastric environment. The two best studied bacterial determinants of *H. pylori* infection are the presence of cytotoxin-associated gene A (*cagA*) and vacuolating cytotoxin A (*vacA*) genotype. The *cagA* encodes a high-molecular-weight immunodominant protein. The *cagA* gene product is not itself a virulence factor but is a part of a 40 kb cluster of genes (*cag* pathogenicity island), some of which contribute to pathogenicity [8]. The *cagA* gene product has been shown to be involved in induction of proinflammatory chemokine released by the host cell [9]. A number of studies in western countries have confirmed that infection with *cagA*-positive strains is associated with more severe gastritis and higher prevalence of peptic ulcer and gastric cancer [10]. In addition to *cagA*, the secretion system can also deliver of *H. pylori* peptidoglycan in to host cells. In the host intracellular pattern peptidoglycan interacts with recognition molecule Nod1, which acts as a sensor for peptidoglycan components originating from gram-negative bacteria. The interaction of peptidoglycan with Nod1 leads to activation of NF- $\kappa$ B-dependent proinflammatory responses, such as secretion of IL-8 or  $\beta$ -defensin-2 [11,12]. Brandt et al. recently showed that *cagA* is capable of activating NF- $\kappa$ B, which in turn induces IL-8 expression [13]. These results show that *H. pylori* activates NF- $\kappa$ B through multiple distinct mechanisms. The vacuolating cytotoxin A (*vacA*) gene, which is another important virulence factor of *H. pylori*, encodes an 87 kD protein that induces vacuolation of epithelial cells [14]. The *vacA* gene is present in all strains of *H. pylori* and comprises two variable parts. *VacA* gene is present in all strains and comprises 2 variable parts, the s region (encoding the signal peptide) is present in either the s1 or s2 allele; within type s1, several subtypes (s1a, s1b, and s1c) can be distinguished [9]. The mosaic combination of s and m region allelic types determines the production of the cytotoxin and is associated with pathogenicity of the bacteria [15,16]. As with *cagA* status, there are geographic differences between *vacA* status and the *H. pylori*-related diseases. In Western countries infection with *vacA* s1 strain is more common in patients with peptic ulcer than in those with chronic gastritis. However in Asian populations, the association between *vacA* diversity and clinical outcome is not established [17,18]. Another virulence factor is the neutrophil-activating protein (NAP) of *H. pylori* that contributes to Th1 polarization by stimulating both IL-12 and IL-23 secretion from neutrophils and monocytes [19].

### 3. Interleukin-17 (IL-17)

IL-17 which belongs to a family of cytokines comprises six members including IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F [20]. IL-17A which is commonly called IL-17 plays a crucial role in mammalian immune system. Recently, it was established that CD4<sup>+</sup> T cells that produce IL-17A and IL-17F preferentially could be generated and that they seem to form a separate lineage of Th17 cells [21,22]. These cells express retinoic acid-related orphan receptor gamma-t (ROR $\gamma$ t) as a key transcription factor for their differentiation [23]. In addition to IL-17, these cells may also produce IL-22 and IL-21 [24]. IL-17 which is a protein of 155 amino acids is secreted as a glycoprotein with molecular mass of 35 kDa. Among the members of the IL-17 family there are structural similarities. However, the resemblance of IL-17 is not the same as other cytokines or structural domains [25]. Among the IL-17 family, IL-17F possesses the highest homology of amino acid sequence (60%) to IL-17A [26]. IL-17A and IL-17F might also be secreted as a heterodimeric IL-17F/A cytokine [27]. IL-17 is able to induce the production of granulocyte-macrophage colony stimulating factor (GM-CSF), antimicrobial peptides, endothelial and epithelial cells, cytokines, chemokines and matrix metalloproteinases from fibroblasts. Following bacterial infection, IL-23/IL17 pathway increases

the recruitment of neutrophils, leading to the extracellular clearance of bacteria [28]. Macrophages and dendritic cells (DCs) at the early stages of infection produce IL-23 triggering IL-17 response from tissue-resident T cells. Then, IL-17 acts on endothelial, epithelial and stromal cells, as well as a subset of monocytes producing various pro-inflammatory cytokines and chemokines including TNF- $\alpha$ , IL-1, IL-6, IL-8 and CXC ligand 1 which rapidly recruit neutrophils to the site of infection [28].

### 4. Th17, T regulatory cells (Tregs), and *H. pylori* infection

It has been shown that the expression of the Treg marker Foxp3 in *H. pylori* infected patients is higher than in uninfected subject [29,30]. Also Tregs numbers were positively correlated to the severity of bacterial colonization and TGF- $\beta$  production [30,31]. Removal of Tregs from the memory T cell pool resulted in enhanced T cell responses to *H. pylori* antigens. Tregs may reduce inflammation and tissue destruction, as indicated by the inverse correlation of their numbers and inflammation score [32]. Infected children with higher level of Foxp3 also reveal low level of gastric pathology in comparison to adult subjects [33,34]. This may suggest that Tregs down regulate both immune and inflammatory responses in the gastric mucosa which leads to the persistence of infection. Interestingly, Tregs accumulation was noted close to the lymphoid follicles that are formed in the stomach mucosa during *H. pylori* infection, implicating that these cells may be directly induced by local naive T cells. In humans, the Treg-mediated immune regulation might contribute to *H. pylori* persistence and adequate Treg responses in humans is associated with decreased production of cytokines such as IL-17, IL-6 and IL-23 during *H. pylori* infection [30].

Neutralization of IL-10 and TGF- $\beta$  increases Th17 induction and decreases Treg induction indicating a negative correlation between Th17 and Treg generation (Fig. 1). Following the depletion of CD25<sup>+</sup>Tregs during an acute phase of *H. pylori* infection caused a reduction in *H. pylori* colonization which was correlated with an increase in *H. pylori*-specific Th17, but not Th1 response. These results may suggest that *H. pylori*-induced dendritic cells skew the Th17/Treg balance toward a Treg-biased response suppressing the Th17 immunity through a *cagA* and *vacA* independent, TGF- $\beta$  and IL-10 dependent mechanism [35,36]. In support of these results, it has been shown that *H. pylori* is capable of stimulating human gastric dendritic cells to produce IL-10, potentially supplementing Treg suppression of inflammation in the gastric mucosa [37]. The *H. pylori* specific helper Th17 immunity has been shown to be suppressed which leads to the persistence of *H. pylori* in the stomach.

### 5. IL-17 and gastritis

*H. pylori* infection is the main cause of gastric inflammation [38,39]. *H. pylori*-infected patients develop an antral-predominant gastritis, which over time progresses to involve the corpus [40,41]. IL-17 levels have been shown to be increased in the gastric mucosa of *H. pylori*-infected patients [42]. This study indicated that gastric mucosal IL-17 levels in the antrum was increased in *H. pylori*-infected patients, especially in the chronic phase of *H. pylori* infection. IL-17 mediates the recruitment and activation of polymorphonuclear neutrophils, a key cellular element in the inflammatory lesion associated with *H. pylori* infection [43]. It has been shown that during the early stages of *H. pylori* infection there is a significant rise of IL-17 and IFN- $\gamma$  [44]. Gene expression of IL-6, IL-12 p35, IL-23 p19, IL-12/IL-23 p40 and transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1) are all up-regulated in *H. pylori*-infected subjects [42,45,46]. IL-12 and IL-23 expressions in the stomach are also

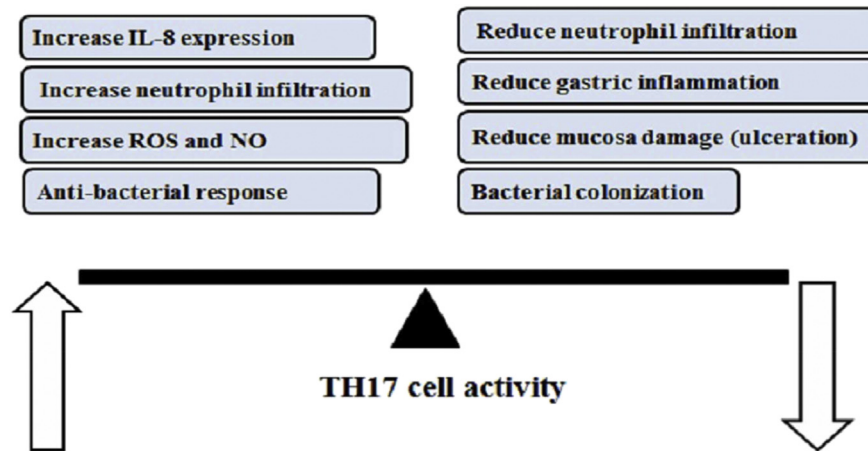


Fig. 1. Role of Th17 cells in *H. pylori*-infected patients and its correlation with clinical parameters.

increased which may indicate the promotion of Th1 and Th17 cell responses, respectively. Therefore, *H. pylori* infection may induce a mixed Th17/Th1 cell response contributing to *H. pylori* colonization and gastric inflammation. Recent studies have shown that adult *H. pylori* gastritis is the consequence of both Th17 and Th1 immune-mediated inflammatory pathways and that both pathways are down regulated in the gastric mucosa of infected children resulting in lower levels of inflammation and ulceration compared with adults [37]. The study of Joo Hyun et al. in *H. pylori*-infected patients with gastritis indicated that a negative correlation between the Th17 cells/FOXP3<sup>+</sup>Tregs ratio and the bacterial density was demonstrated in the *H. pylori*-infected patients with gastritis [34].

## 6. IL-17 and gastric ulcer

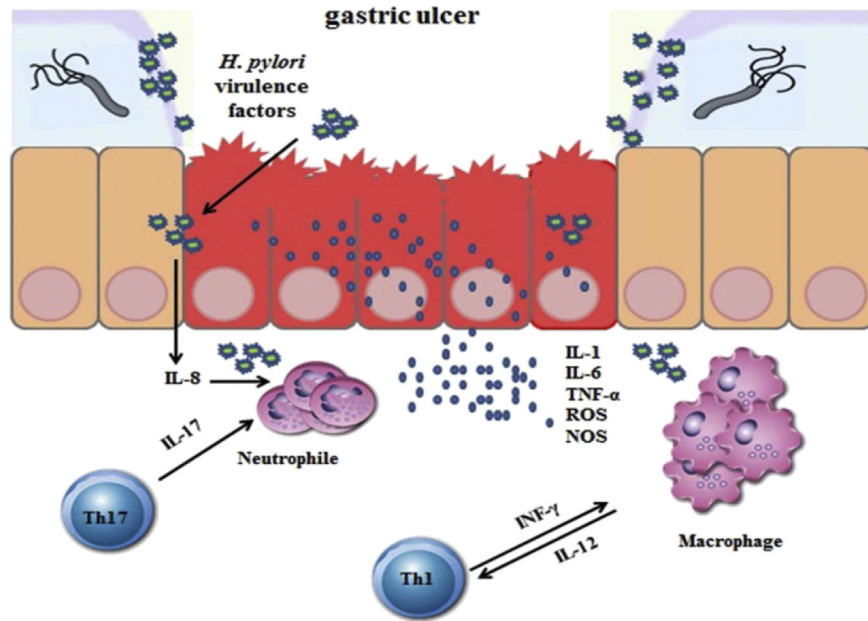
Among infected individuals, approximately 10% develop peptic ulcer disease. *H. pylori* infection increases the IL-17 and IL-17 RNA transcripts in human gastric mucosal and lamina propria mononuclear cells (LPMC) [47]. It has been shown that in gastric LPMC cultures, neutralization of IL-17 results in a significant reduction of IL-8 secretion. As LPMC and gastric epithelial cells express IL-17 receptors, IL-17 acts on these cells to release IL-8. In patients in whom the *H. pylori* is eradicated the IL-17 expression is down-regulated. Moreover, increased levels of IL-8 and IL-17 are detected in antral mucosal tissues of gastric ulcer as well as *H. pylori*-positive nonulcer patients [48]. It has also been shown that at ulcer site, IL-17 has higher correlation with the number of neutrophils and infiltrating mononuclear cells. It should be noted that in *H. pylori*-infected patients, gastric mucosa is an active site for the synthesis of both IL-8 and IL-17. Hence, IL-17 in conjunction with IL-8 might be involved in induction of gastric ulcer as IL-8 contributes to the recruitment of neutrophils at the ulcer site. However, we should be careful about the axis IL-17/IL-8 since several cytokines and chemokines are under the control of IL-17. In addition, the increase in IL-17 and IL-8 seems to be a consequence of the infection rather than a marker of ulcer or gastritis. Analysis of signaling pathways associated with the IL-17-induced IL-8 secretion has revealed that IL-17 activates ERK 1/2 MAP kinases in gastric epithelial cells isolated from *H. pylori*-infected patients and in a gastric epithelial cell line, the effect being more pronounced with *cagA*-positive *H. pylori* strains [49]. Moreover, in the gastric epithelial cell line, the pharmacologic blockage of this pathway inhibited IL-8 secretion. The gastric biopsy specimens from *H. pylori*-infected patients cultured with a neutralizing IL-17 antibody also decreased IL-8 secretion and ERK 1/2 MAP kinase

activation. There is also a significant association in the expression between IL-8 and IL-17 in *H. pylori* colonized biopsies.

The chronic inflammatory reaction caused by the *H. pylori* infection might be involved in the production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) that in turn may lead to oxidative DNA damage and apoptosis of gastric epithelial cells, consequently favoring gastric carcinogenesis and peptic ulcer [50–52] (Fig. 2). Robinson et al. [53] reported a significantly lower frequency of IL-10(+) Tregs and enhanced Th1 responses in the mucosa of patients with peptic ulcer disease, compared to infected asymptomatic patients. Defective regulation of T cell responses may lead to the pathogenesis of peptic ulcer disease, as mononuclear cells from these patients were shown to secrete less IL-10 compared to asymptomatic controls. Also virulence factors of *H. pylori* are involved in inducing peptic ulcers. The neutrophil-activating protein of *H. pylori* contributes to Th1 polarization by stimulating both IL-12 and IL-23 secretion from neutrophils and monocytes [19]. IL-12 production in the gastric mucosa is linked to the development of peptic ulcers in infection with *H. pylori cagA*<sup>+</sup> strains, most likely due to stimulation of Th1 responses [54]. Also several studies have associated the *cagA*<sup>+</sup> *H. pylori* strains with higher grades of gastric inflammation by stimulating the gastric epithelium to secrete higher levels of pro-inflammatory cytokines and migration and infiltration of high levels of mononuclear and neutrophil cell in the gastric mucosa [55]. These findings might indicate that Th17, Th1 populations and virulence factors be involved in inducing peptic ulcers. The number of Th17 and Th1 cells in patients with peptic ulcer disease is higher than in infected gastritis patients, also defective Treg responses may lead to the pathogenesis of peptic ulcer disease [48,53,56].

## 7. IL-17 and gastric cancer

As *H. pylori*-induced chronic gastritis plays an important role in the development of gastric cancer [57], patients with advanced cancer showed a higher proportion of Th17 cells in peripheral blood and in tumor-draining lymph nodes compared to non-cancerous subjects [58,59]. Increased concentrations of IL-17 and IL-23 were observed in the sera of patients with advanced gastric cancer. Further, the mRNA expressions of IL-17 and IL-23 p19 in tumor tissues were significantly enhanced. These findings suggest a close association of Th17 cells, IL-17, and IL-23 in gastric cancer pathogenesis. It has been shown that Th17 is infiltrated the cancer tissues; TGF- $\beta$  IL-1 $\beta$  and IL-21 are also included in gastric cancer development by promoting Th17 cell generation. This may suggest



**Fig. 2.** Role of Th17 and Th1 cells in *H. pylori*-infected patients with peptic ulcer. Activation neutrophile and macrophage can lead to important antimicrobial effects but can also result in inflammation and injury due to release of inflammatory mediators such as cytokines, reactive oxygen species (ROS), and nitric oxide (NO). Reactive oxygen or nitrogen species from neutrophils or other inflammatory cells increase the oxidative stress that together with other immune-mediated mechanisms, induce apoptosis of the epithelium. In addition, oxidative stress can damage DNA, leading to the disruption of gene function. Thus, the longer the period of exposure of a tissue to activated immune/inflammatory cells and mediators, the more cellular damage may accumulate.

Th17 cell expansion in gastric cancer which may contribute to cancer development and metastasis [50,60,61]. An increase can be seen in Th17 in *H. pylori*-infected patients as well as in human gastric tumors. It also has been shown that *H. pylori* prime GMF (gastric myofibroblast/fibroblasts) promoted differentiation of Th17. This process is dependent on TGF- $\beta$ 1, IL-6 and IL-21. *H. pylori*-exposed and gastric tumor derived MF (myofibroblast and fibroblast) produced at increased levels, maintaining a stronger ability to induce Th17 cells. These findings suggest that the enhanced Th17 promoting capacity of the GMF (gastric myofibroblast/fibroblasts), derived from gastric tumors may be among the key factors contributing to gastric tumor promoting inflammatory milieu [60]. A study on the association between gastric cancer and polymorphism of IL-17F and IL-17A genes showed that the IL-17A/-197A allele was significantly higher among Japanese patients with gastric cancer in comparison to control ones [62]. The IL-17A/-197A allele seems to be associated with the severity of mucosal atrophy of stomach leading to the development of the intestinal-type gastric cancer. The homozygote of IL-17A/-197A/A has been associated with the inflammation of gastric mucosa contributing to a small but significant risk for developing diffuse-type gastric cancer. However, IL-17F/7488C allele is not associated with gastric carcinogenesis. This allele is associated with inhibition of lymph node metastasis. An investigation in Chinese patients showed that in gastric cancer the IL-17F/7488GA and GC genotypes increase the gastric cancer risks and the IL-17A/197 polymorphism is not associated with gastric cancer susceptibility [63,64].

## 8. Conclusion

In conclusion, IL-17 may play an important role in the inflammatory response to *H. pylori* colonization, and may finally influence the outcome of *H. pylori*-associated diseases arising within the context of gastritis. In addition to its ability to enhance IL-8 production, IL-17 may modulate the expression of other molecules

relevant to the pathophysiology of gastritis, peptic ulcer and gastric cancer. Indeed, the involvement of IL-17 in *H. pylori*-related gastritis is also supported by the demonstration that this cytokine is able to stimulate both immune and non-immune cells to produce multiple inflammatory mediators, such as TNF- $\alpha$ , IL-1, IL-6 and matrix metalloproteinases [40,65–67]. This cytokines are capable of causing mucosal degradation and has been associated with gastrointestinal disease [68,69]. Study in *H. pylori*-infected patients with gastritis and peptic ulcer disease indicated that a negative correlation between the Th17 cells/FOXP3<sup>+</sup>Tregs ratio and the bacterial density was demonstrated. Tregs may reduce inflammation and tissue destruction, as indicated by the inverse correlation of their numbers and inflammation score [32]. In children with *H. pylori* infection, Tregs were found in higher frequencies, compared to adults, indicating that these cells may protect against the exaggerated inflammation resulting in peptic ulcer disease, as this complication is rare in this age group [33,37]. In this review we tried to discuss the relation between IL-17 and Th17 cells to the clinical forms of *H. pylori* infection. However, to elucidate further the signature specific of IL-17 and Th17 cells to the clinical forms of *H. pylori* infection more studies are needed.

## Acknowledgments

The authors have no conflicting financial interests. This work was supported by research deputy of Shahrekord University of Medical Sciences Grant no. 1025. The authors are grateful to the staffs of Cellular & Molecular Research Center, Shahrekord University of Medical Sciences.

## References

- [1] R.M. Peek Jr., M.J. Blaser, *Helicobacter pylori* and gastrointestinal tract adenocarcinomas, *Nat. Rev. Cancer* 2 (2002) 28–37.
- [2] R.M. Peek Jr., J.E. Crabtree, *Helicobacter* infection and gastric neoplasia, *J. Pathol.* 208 (2006) 233–248.
- [3] M.J. Blaser, D.E. Berg, *Helicobacter pylori* genetic diversity and risk of human

- disease, *J. Clin. Invest.* 107 (2001) 767–773.
- [4] L.J. van Doorn, C. Figueiredo, R. Sanna, A. Plaisier, P. Schneeberger, W. de Boer, et al., Clinical relevance of the *cagA*, *vacA*, and *iceA* status of *Helicobacter pylori*, *Gastroenterology* 115 (1998) 58–66.
- [5] M.Y. Wang, C. Chen, X.Z. Gao, J. Li, J. Yue, F. Ling, et al., Distribution of *Helicobacter pylori* virulence markers in patients with gastroduodenal diseases in a region at high risk of gastric cancer, *Microb. Pathog.* 59–60 (2013) 13–18.
- [6] A. Jafarzadeh, V. Mirzaee, H. Ahmad-Beygi, M. Nemati, M.T. Rezayati, Association of the *CagA* status of *Helicobacter pylori* and serum levels of interleukin (IL)-17 and IL-23 in duodenal ulcer patients, *J. Dig. Dis.* 10 (2009) 107–112.
- [7] L. Salimzadeh, N. Bagheri, B. Zamanzad, F. Azadegan-Dehkordi, G. Rahimian, M. Hashemzadeh-Chaleshtori, et al., Frequency of virulence factors in *Helicobacter pylori*-infected patients with gastritis, *Microb. Pathog.* 80 (2015) 67–72.
- [8] H. Umit, A. Tezel, S. Bukavaz, G. Unsal, M. Otkun, A.R. Soylu, et al., The relationship between virulence factors of *Helicobacter pylori* and severity of gastritis in infected patients, *Dig. Dis. Sci.* 54 (2009) 103–110.
- [9] L.L. Gatti, E.K. Fagundes e Souza, K.R. Leite, E.L. Bastos, L.R. Vicentini, L.C. Silva, et al., *cagA vacA* alleles and *babA2* genotypes of *Helicobacter pylori* associated with gastric disease in Brazilian adult patients, *Diagn. Microbiol. Infect. Dis.* 51 (2005) 231–235.
- [10] Y. Yamaoka, J. Soucek, S. Odenbreit, R. Haas, A. Arnqvist, T. Boren, et al., Discrimination between cases of duodenal ulcer and gastritis on the basis of putative virulence factors of *Helicobacter pylori*, *J. Clin. Microbiol.* 40 (2002) 2244–2246.
- [11] P.K. Boughan, R.H. Argent, M. Body-Malapel, J.H. Park, K.E. Ewings, A.G. Bowie, et al., Nucleotide-binding oligomerization domain-1 and epidermal growth factor receptor: critical regulators of beta-defensins during *Helicobacter pylori* infection, *J. Biol. Chem.* 281 (2006) 11637–11648.
- [12] J. Viala, C. Chaput, I.G. Boneca, A. Cardona, S.E. Girardin, A.P. Moran, et al., Nod1 responds to peptidoglycan delivered by the *Helicobacter pylori* *cag* pathogenicity island, *Nat. Immunol.* 5 (2004) 1166–1174.
- [13] S. Brandt, T. Kwok, R. Hartig, W. König, S. Backert, NF- $\kappa$ B activation and potentiation of proinflammatory responses by the *Helicobacter pylori* *CagA* protein, *Proc. Natl. Acad. Sci. U. S. A.* 102 (2005) 9300–9305.
- [14] Y. Ito, T. Azuma, S. Ito, H. Miyaji, M. Hirai, Y. Yamazaki, et al., Analysis and typing of the *vacA* gene from *cagA*-positive strains of *Helicobacter pylori* isolated in Japan, *J. Clin. Microbiol.* 35 (1997) 1710–1714.
- [15] D.A. Israel, R.M. Peek, Pathogenesis of *Helicobacter pylori*-induced gastric inflammation, *Aliment. Pharmacol. Ther.* 15 (2001) 1271–1290.
- [16] C. Pagliaccia, M. de Bernard, P. Lupetti, X. Ji, D. Burroni, T.L. Cover, et al., The m2 form of the *Helicobacter pylori* cytotoxin has cell type-specific vacuolating activity, *Proc. Natl. Acad. Sci. U. S. A.* 95 (1998) 10212–10217.
- [17] S. Maeda, K. Ogura, H. Yoshida, F. Kanai, T. Ikenoue, N. Kato, et al., Major virulence factors, *VacA* and *CagA*, are commonly positive in *Helicobacter pylori* isolates in Japan, *Gut* 42 (1998) 338–343.
- [18] Y. Yamaoka, T. Kodama, M. Kita, J. Imanishi, K. Kashima, D.Y. Graham, Relationship of *vacA* genotypes of *Helicobacter pylori* to *cagA* status, cytotoxin production, and clinical outcome, *Helicobacter* 3 (1998) 241–253.
- [19] A. Amedei, A. Cappon, G. Codolo, A. Cabrelle, A. Polenghi, M. Benagiano, et al., The neutrophil-activating protein of *Helicobacter pylori* promotes Th1 immune responses, *J. Clin. Invest.* 116 (2006) 1092–1101.
- [20] T.A. Moseley, D.R. Haudenschield, L. Rose, A.H. Reddi, Interleukin-17 family and IL-17 receptors, *Cytokine Growth Factor Rev.* 14 (2003) 155–174.
- [21] L.E. Harrington, R.D. Hatton, P.R. Mangan, H. Turner, T.L. Murphy, K.M. Murphy, et al., Interleukin 17-producing CD4<sup>+</sup> effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages, *Nat. Immunol.* 6 (2005) 1123–1132.
- [22] H. Park, Z. Li, X.O. Yang, S.H. Chang, R. Nurieva, Y.H. Wang, et al., A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17, *Nat. Immunol.* 6 (2005) 1133–1141.
- [23] Ivanov II, B.S. McKenzie, L. Zhou, C.E. Tadokoro, A. Lepelletier, J.J. Lefaille, et al., The orphan nuclear receptor ROR $\gamma$ mat directs the differentiation program of proinflammatory IL-17<sup>+</sup> T helper cells, *Cell* 126 (2006) 1121–1133.
- [24] W. Ouyang, J.K. Kolls, Y. Zheng, The biological functions of T helper 17 cell effector cytokines in inflammation, *Immunity* 28 (2008) 454–467.
- [25] S. Aggarwal, A.L. Gurney, IL-17: prototype member of an emerging cytokine family, *J. Leukoc. Biol.* 71 (2002) 1–8.
- [26] S.G. Hymowitz, E.H. Filvaroff, J.P. Yin, J. Lee, L. Cai, P. Risser, et al., IL-17s adopt a cystine knot fold: structure and activity of a novel cytokine, IL-17F, and implications for receptor binding, *EMBO J.* 20 (2001) 5332–5341.
- [27] S.C. Liang, A.J. Long, F. Bennett, M.J. Whitters, R. Karim, M. Collins, et al., An IL-17F/A heterodimer protein is produced by mouse Th17 cells and induces airway neutrophil recruitment, *J. Immunol.* 179 (2007) 7791–7799.
- [28] Y. Iwakura, H. Ishigame, The IL-23/IL-17 axis in inflammation, *J. Clin. Invest.* 116 (2006) 1218–1222.
- [29] R. Rad, L. Brenner, S. Bauer, S. Schwendy, L. Layland, C.P. da Costa, et al., CD25<sup>+</sup>/Foxp3<sup>+</sup> T cells regulate gastric inflammation and *Helicobacter pylori* colonization in vivo, *Gastroenterology* 131 (2006) 525–537.
- [30] A. Kandulski, T. Wex, D. Kuester, U. Peitz, I. Gebert, A. Roessner, et al., Naturally occurring regulatory T cells (CD4<sup>+</sup>, CD25<sup>high</sup>, FOXP3<sup>+</sup>) in the antrum and cardia are associated with higher *H. pylori* colonization and increased gene expression of TGF- $\beta$ 1, *Helicobacter* 13 (2008) 295–303.
- [31] T.J. Jang, The number of Foxp3-positive regulatory T cells is increased in *Helicobacter pylori* gastritis and gastric cancer, *Pathol. Res. Pract.* 206 (2010) 34–38.
- [32] A. Lundgren, E. Suri-Payer, K. Enarsson, A.M. Svennerholm, B.S. Lundin, *Helicobacter pylori*-specific CD4<sup>+</sup> CD25<sup>high</sup> regulatory T cells suppress memory T-cell responses to *H. pylori* in infected individuals, *Infect. Immun.* 71 (2003) 1755–1762.
- [33] P.R. Harris, S.W. Wright, C. Serrano, F. Riera, I. Duarte, J. Torres, et al., *Helicobacter pylori* gastritis in children is associated with a regulatory T-cell response, *Gastroenterology* 134 (2008) 491–499.
- [34] J.H. Gil, J.W. Seo, M.S. Cho, J.H. Ahn, H.Y. Sung, Role of Treg and TH17 cells of the gastric mucosa in children with *Helicobacter pylori* gastritis, *J. Pediatr. Gastroenterol. Nutr.* 58 (2014) 252–258.
- [35] J.Y. Kao, M. Zhang, M.J. Miller, J.C. Mills, B. Wang, M. Liu, et al., *Helicobacter pylori* immune escape is mediated by dendritic cell-induced Treg skewing and Th17 suppression in mice, *Gastroenterology* 138 (2010) 1046–1054.
- [36] M. Zhang, M. Liu, J. Luther, J.Y. Kao, *Helicobacter pylori* directs tolerogenic programming of dendritic cells, *Gut Microbes* 1 (2010) 325–329.
- [37] C. Serrano, S.W. Wright, D. Bimczok, C.L. Shaffer, T.L. Cover, A. Venegas, et al., Downregulated Th17 responses are associated with reduced gastritis in *Helicobacter pylori*-infected children, *Mucosal Immunol.* 6 (2013) 950–959.
- [38] N. Bagheri, A. Taghikhani, G. Rahimian, L. Salimzadeh, F. Azadegan Dehkordi, F. Zandi, et al., Association between virulence factors of *Helicobacter pylori* and gastric mucosal interleukin-18 mRNA expression in dyspeptic patients, *Microb. Pathog.* 65 (2013) 7–13.
- [39] N. Bagheri, F. Azadegan-Dehkordi, H. Sanei, A. Taghikhani, G. Rahimian, L. Salimzadeh, et al., Associations of a TLR4 single-nucleotide polymorphism with *H. pylori* associated gastric diseases in Iranian patients, *Clin. Res. Hepatol. Gastroenterol.* 38 (2014) 366–371.
- [40] V. Serelli-Lee, K.L. Ling, C. Ho, L.H. Yeong, G.K. Lim, B. Ho, et al., Persistent *Helicobacter pylori* specific Th17 responses in patients with past *H. pylori* infection are associated with elevated gastric mucosal IL-1 $\beta$ , *PLoS One* 7 (2012) e39199.
- [41] F. Freire de Melo, A.M. Rocha, G.A. Rocha, S.H. Pedrosa, S. de Assis Batista, L.P. Fonseca de Castro, et al., A regulatory instead of an IL-17 T response predominates in *Helicobacter pylori*-associated gastritis in children, *Microbes Infect.* 14 (2012) 341–347.
- [42] R. Caruso, D. Fina, O.A. Paoluzi, G. Del Vecchio Blanco, C. Stolfi, A. Rizzo, et al., IL-23-mediated regulation of IL-17 production in *Helicobacter pylori*-infected gastric mucosa, *Eur. J. Immunol.* 38 (2008) 470–478.
- [43] J.G. Fox, T.C. Wang, Inflammation, atrophy, and gastric cancer, *J. Clin. Invest.* 117 (2007) 60–69.
- [44] Y. Shi, X.F. Liu, Y. Zhuang, J.Y. Zhang, T. Liu, Z. Yin, et al., *Helicobacter pylori*-induced Th17 responses modulate Th1 cell responses, benefit bacterial growth, and contribute to pathology in mice, *J. Immunol.* 184 (2010) 5121–5129.
- [45] G. Rahimian, M.H. Sanei, H. Shirzad, F. Azadegan-Dehkordi, A. Taghikhani, L. Salimzadeh, et al., Virulence factors of *Helicobacter pylori vacA* increase markedly gastric mucosal TGF- $\beta$ 1 mRNA expression in gastritis patients, *Microb. Pathog.* 67–68 (2014) 1–7.
- [46] N. Bagheri, G. Rahimian, L. Salimzadeh, F. Azadegan, M. Rafeian-Kopaei, A. Taghikhani, et al., Association of the virulence factors of *Helicobacter pylori* and gastric mucosal interleukin-17/23 mRNA expression in dyspeptic patients, *Excli J.* 12 (2013) 5–14.
- [47] F. Luzzza, T. Parrello, G. Monteleone, L. Sebkova, M. Romano, R. Zarrilli, et al., Up-regulation of IL-17 is associated with bioactive IL-8 expression in *Helicobacter pylori*-infected human gastric mucosa, *J. Immunol.* 165 (2000) 5332–5337.
- [48] T. Mizuno, T. Ando, K. Nobata, T. Tsuzuki, O. Maeda, O. Watanabe, et al., Interleukin-17 levels in *Helicobacter pylori*-infected gastric mucosa and pathologic sequelae of colonization, *World J. Gastroenterol.* 11 (2005) 6305–6311.
- [49] L. Sebkova, A. Pellicano, G. Monteleone, B. Grazioli, G. Guarneri, M. Imeneo, et al., Extracellular signal-regulated protein kinase mediates interleukin 17 (IL-17)-induced IL-8 secretion in *Helicobacter pylori*-infected human gastric epithelial cells, *Infect. Immun.* 72 (2004) 5019–5026.
- [50] T. Sawa, H. Ohshima, Nitrate DNA damage in inflammation and its possible role in carcinogenesis, *Nitric Oxide: Biol. Chem./Off. J. Nitric Oxide Soc.* 14 (2006) 91–100.
- [51] A. Siomek, A. Rytarowska, A. Szafarska-Poplawska, D. Gackowski, R. Rozalski, T. Dziaman, et al., *Helicobacter pylori* infection is associated with oxidatively damaged DNA in human leukocytes and decreased level of urinary 8-oxo-7,8-dihydroguanine, *Carcinogenesis* 27 (2006) 405–408.
- [52] M.S. Ladeira, M.A. Rodrigues, D.M. Salvadori, D.M. Queiroz, D.V. Freire-Maia, DNA damage in patients infected by *Helicobacter pylori*, *Cancer Epidemiol. Biomarkers Prev.* 13 (2004) 631–637.
- [53] K. Robinson, R. Kenefack, E.L. Pidgeon, S. Shakib, S. Patel, R.J. Polson, et al., *Helicobacter pylori*-induced peptic ulcer disease is associated with inadequate regulatory T cell responses, *Gut* 57 (2008) 1375–1385.
- [54] N. Hida, T. Shimoyama Jr., P. Neville, M.F. Dixon, A.T. Axon, T. Shimoyama Sr., et al., Increased expression of IL-10 and IL-12 (p40) mRNA in *Helicobacter pylori* infected gastric mucosa: relation to bacterial *cag* status and peptic ulceration, *J. Clin. Pathol.* 52 (1999) 658–664.
- [55] N. Figura, M. Valassina, F. Roviello, F. Pinto, C. Lenzi, R. Giannace, et al., *Helicobacter pylori cagA* and *vacA* types and gastric carcinoma, *Dig. Liver Dis. Off. J. Italian Soc. Gastroenterol. Italian Assoc. Study Liver* 32 (Suppl. 3) (2000) S182–S183.

- [56] J.H. Gil, J.W. Seo, M.S. Cho, J.H. Ahn, H.Y. Sung, Role of Treg and TH17 cells of the gastric mucosa in children with *Helicobacter pylori* gastritis, *J. Pediatr. Gastroenterol. Nutr.* 58 (2014) 245–251.
- [57] B.J. Marshall, H.M. Windsor, The relation of *Helicobacter pylori* to gastric adenocarcinoma and lymphoma: pathophysiology, epidemiology, screening, clinical presentation, treatment, and prevention, *Med. Clin. North Am.* 89 (2005), 313–44, viii.
- [58] Q. Li, J. Chen, Y. Liu, X. Zhao, B. Tan, J. Ai, et al., Prevalence of Th17 and Treg cells in gastric cancer patients and its correlation with clinical parameters, *Oncol. Rep.* 30 (2013) 1215–1222.
- [59] B. Zhang, G. Rong, H. Wei, M. Zhang, J. Bi, L. Ma, et al., The prevalence of Th17 cells in patients with gastric cancer, *Biochem. Biophys. Res. Commun.* 374 (2008) 533–537.
- [60] I.V. Pinchuk, K.T. Morris, R.A. Nofchissey, R.B. Earley, J.Y. Wu, T.Y. Ma, et al., Stromal cells induce Th17 during *Helicobacter pylori* infection and in the gastric tumor microenvironment, *PLoS One* 8 (2013) e53798.
- [61] X. Wu, Z. Zeng, L. Xu, J. Yu, Q. Cao, M. Chen, et al., Increased expression of IL17A in human gastric cancer and its potential roles in gastric carcinogenesis, *Tumour Biol.* 35 (2014) 5347–5356.
- [62] T. Shibata, T. Tahara, I. Hirata, T. Arisawa, Genetic polymorphism of interleukin-17A and -17F genes in gastric carcinogenesis, *Hum. Immunol.* 70 (2009) 547–551.
- [63] Z. Qinghai, W. Yanying, C. Yunfang, Z. Xukui, Z. Xiaoqiao, Effect of interleukin-17A and interleukin-17F gene polymorphisms on the risk of gastric cancer in a Chinese population, *Gene* 537 (2014) 328–332.
- [64] X. Wu, Z. Zeng, B. Chen, J. Yu, L. Xue, Y. Hao, et al., Association between polymorphisms in interleukin-17A and interleukin-17F genes and risks of gastric cancer, *Int. J. Cancer* 127 (2010) 86–92.
- [65] D.V. Jovanovic, J.A. Di Battista, J. Martel-Pelletier, F.C. Jolicoeur, Y. He, M. Zhang, et al., IL-17 stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages, *J. Immunol.* 160 (1998) 3513–3521.
- [66] S. Bamba, A. Andoh, H. Yasui, Y. Araki, T. Bamba, Y. Fujiiyama, Matrix metalloproteinase-3 secretion from human colonic subepithelial myofibroblasts: role of interleukin-17, *J. Gastroenterol.* 38 (2003) 548–554.
- [67] S. Hasegawa, S. Nishikawa, T. Miura, Y. Saito, H. Madarame, K. Sekikawa, et al., Tumor necrosis factor-alpha is required for gastritis induced by *Helicobacter felis* infection in mice, *Microb. Pathog.* 37 (2004) 119–124.
- [68] E.M. El-Omar, The importance of interleukin 1beta in *Helicobacter pylori* associated disease, *Gut* 48 (2001) 743–747.
- [69] P.J. Bergin, E. Anders, W. Sicheng, J. Erik, A. Jennie, L. Hans, et al., Increased production of matrix metalloproteinases in *Helicobacter pylori*-associated human gastritis, *Helicobacter* 9 (2004) 201–210.