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Review

# The biological functions of IL-17 in different clinical expressions of *Helicobacter pylori*-infection

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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-1β, IL-6, tumor necrosis factor (TNF)-α, TGF-β1, 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*.



## 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 $CD4^+$ 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

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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 peptidogylcan with Nod1 leads to activation of NF-κB-dependent proinflammatory responses, such as secretion of IL-8 or β-defensin-2 [11,12]. Brandt et al. recently showed that cagA is capable of activating NF-κB, which in turn induces IL-8 expression [13]. These results show that *H. pylori* activates NF-κB through multiple distinct mechanisms. The vacuolating cytotoxin A (vagA) 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 $CD4^+$ 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 (RORγt) 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-α, 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-β 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-β increases Th17 induction and decreases Treg induction indicating a negative correlation between Th17 and Treg generation (Fig. 1). Following the depletion of $CD25^+$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-β 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-γ [44]. Gene expression of IL-6, IL-12 p35, IL-23 p19, IL-12/IL-23 p40 and transforming growth factor-β1 (TGF-β1) are all up-regulated in *H. pylori*-infected subjects [42,45,46]. IL-12 and IL-23 expressions in the stomach are also