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REVIEW ARTICLE

Role of Regulatory T-cells in Different Clinical Expressions of *Helicobacter pylori* Infection

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Helicobacter pylori (*H. pylori*) colonization induces vigorous innate and specific immune responses; however, the infection does not disappear and a chronic active gastritis continues if left untreated. It has been shown that the topographical pattern and immune response of gastritis are the main reasons for the bacteria persistence and the clinical outcome. Gastritis due to *H. pylori* is caused by a complicated interaction among a variety of T cell subsets. Regulatory T (Treg) cells suppressing the immune response of antigen-specific T-cells have recently been demonstrated to play a key role in chronic inflammation by immunologic tolerance. Treg cells have been identified as the major regulatory component of the adaptive immune response and being involved in *H. pylori*-related inflammation and bacterial persistence. There have been many controversies over the role of Treg cells in *H. pylori* infection. Many studies have shown that the local Treg response protects the gastric mucosa from intensified inflammation and tissue damage, and the risk of *H. pylori*-associated diseases has an inverse correlation with Treg accumulation, even if the decrease in the inflammatory response is recognized by Treg it causes increase in bacterial density. This paper reviews the role of Treg in different clinical expressions of *H. pylori* infection.

Key Words: Helicobacter pylori, Regulatory T-cells, Gastritis, Peptic ulcer, Gastric cancer.

Introduction

Helicobacter pylori (*H. pylori*) is a helical, microaerophilic, gram-negative, and flagellated bacteria. This bacterium is one of the most important human pathogens, affecting >50% of humans. *H. pylori* and mankind have had an ancient relationship for at least 58,000 years (1,2). *H. pylori* infection commonly happens in early childhood and, if left untreated, the host may carry the bacterium during their entire lifetime (3). *H. pylori* colonization is usually asymptomatic (4). However, carriage of *H. pylori* for long terms considerably increases the risk of acquiring site-specific diseases. Of the infected population, ~10% develop peptic ulcer disease, 0.1% develop mucosa-associated lymphoid tissue lymphoma (MALT), and 1–3% develop gastric adenocarcinoma, (5–8). The variable outcomes in *H. pylori*-infected patients may depend on various factors such as *H. pylori* virulence factors, inflammatory responses influenced by host genetic diversity, or environmental factors (such as smoking, malnutrition, high salt intake, vitamin and antioxidant deficiency), which ultimately affect the interactions between pathogen and host (9). *H. pylori* colonization causes a powerful and complicated immune response in the gastric mucosa, which is not adequate to eliminate the pathogen and may even have a contribution to chronic infection or other complications (7,10,11). The exact mechanisms by which the *H. pylori*-induced immune response contributes to gastrointestinal mucosal damage have not yet been explained adequately. However, many studies have demonstrated that immune response and cytokines contribute to controlling the infection and sustaining the development of the chronic inflammation (12–15). In this review, we seek to discuss the role of regulatory T-cells

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and their signature cytokines in different clinical expressions of *H. pylori* infection.

Bacterial Virulence Factors

Chronic inflammation caused by *H. pylori* in the gastric mucosa plays a major role in the development of gastric cancer (16). Several bacterial virulence factors contribute to the inflammatory response towards *H. pylori* by either altering host-signaling pathways important for maintaining tissue homeostasis in epithelial cells or stimulating innate immune cells differentially. Of these, the best-characterized ones are cag pathogenicity island (PAI), CagA, and VacA. However, some bacterial determinants such as γ-glutamyltranspeptidase (γGT), urease or peptidoglycan have been demonstrated to be significant inducers of gastric inflammation.

CagPAI

Cag PAI is an approximate 40-kb locus composed of 27–31 genes. Several genes within this island encode the cag type IV secretion system (T4SS) and the CagA protein (17). The T4SS forms a syringe-like pilus structure through which CagA can be ''injected'' into the target cells. Binding to the ectodomain of α5β1 integrin is a very important step for the translocation of CagA into the host cells (18). After assembly of the T4SS and pilus formation, CagA is translocated into host cells where it can phosphorylate at EPIYA sites (19) by SRC and ABL. Several studies have demonstrated that CagA can directly activate NF-κB and induce IL-8 release (20,21). CagA is injected into not only gastric epithelial cells but also B lymphoid cells (22) and murine and human dendritic cells (DCs) (23,24). Notably, CagA translocation into DCs suppresses host immune response through declining pro-inflammatory cytokine secretion such as IL-12p40 and increasing the expression of the suppressive cytokine IL-10 (24), suggesting pro- and anti-inflammatory property of CagA throughout *H. pylori* infection, which depends on the cellular context. In addition, the study of Cook et al. demonstrated that the concentration of the chemokine CCL20 is dramatically increased in the gastric mucosa of patients infected by *H. pylori* and the vast majority of mucosal Tregs express its receptor CCR6. Gastric biopsy samples from patients infected with cag+ strains contain higher concentrations of CCL20. CCL20 expression is induced in gastric epithelial cells in a cag type IV secretion system-dependent manner. Recombinant CCL20 induces the migration of Tregs *in vitro*, demonstrating its importance as a chemoattractant for these cells (25).

VacA

All *H. pylori* strains carry *VacA* gene, which codes for the secreted pore-forming protein VacA. Cell type-specific toxicity, expression levels, and disease severity are associated with sequence variation in VacA different domains (26). The VacA gene is present in all strains. Initial studies on VacA detected two main polymorphic regions, the signal sequence (s1 and s2) and two types of mid-region (m1 and m2), and the more recently identified intermediate (i1 and i2) region, which is located between the s and m regions (27,28). The mosaic combination of the VacA s and m region alleles can give rise to s1/m1, s1/m2, s2/m1 and s2/m2 type strains. VacA s1/m1 chimeric strains induce greater vacuolation than s1/m2 strains, and there is typically no vacuolating activity in s2/m2 strains (29). The i region plays a functional role in vacuolating activity because VacA s1/i1/m2 strains are vacuolating types and VacA s1/i2/m2 strains do not induce vacuolation. All s1/m1 VacA alleles are type i1, all s2/m2 alleles are type i2, and s1/m2 alleles can be either i1 or i2 (30). VacA is secreted by the bacterium via a type V autotransport secretion system and enters the host cells by endocytosis. When it is internalized, VacA accumulates in different cellular compartments and induces apoptosis (31). Moreover, VacA disrupts tight connections of epithelial cell and is distributed in the lamina propria where it faces T-cells recruited to the infection sites. Therefore, T cell proliferation and effector functions are inhibited, which allows persistence of the bacterium (32). VacA has also been reported to affect T-cells indirectly; however, the mechanisms are still unknown. VacA can induce DC tolerance and regulatory T cell induction, but this effect has not yet been demonstrated in human cells (33). Although VacA affects the host inflammatory response mainly by suppressing activation of T cells, the toxin induces a pro-inflammatory effect on T-cells mediated by NF-κB activation and leads to IL-8 upregulation (34). Moreover, VacA-elicited disruption of autophagy is another mechanism by which gastric inflammation may occur (35). Another distinct VacA effect is its role in persistent *H. pylori* infection by inhibiting T-cells immune response and proliferation (28). During *H. pylori* infection, T-cells are virtually hyporesponsive, which is attributed to transforming growth factor-β (TGF-β), which exerts a suppressive effect on T-cells. Moreover, the mucosal TGF-β1 expression levels were shown to be dependent on VacA genotypes, with a positive correlation between secreted VacA s1 (or s1 m1) types and increase in mucosal TGF-β1 mRNA activity and increased mucosal TGF-β1 mRNA levels, hence contributing to persistent infection. VacA-exposed dendritic cells produce IL-10 and induce the FOXP3 and contact-dependent differentiation of T-cells into $CD4^{+}CD25^{+}FOXP3^{+}$ regulatory T (Treg) cells while simultaneously preventing T helper 1 (Th1) and Th17 differentiation (33). A study by Fassi Fehri et al. indicated that miR-155 was commonly regulated by *H. pylori* in different cell lineages (epithelial and hematopoietic). Bacterial miRNA inducers were identified (VacA, GGT and LPS) and shown to be activators of cAMP. In turn, cAMP was found

to be necessary for Foxp3 induction. Eventually, miR-155 was shown to repress the protein kinase A (PKA) inhibitor (PKIa) protein expression in order to facilitate continuous intracellular cyclic adenosine monophosphate (cAMP) production. These results established a direct link between Foxp3 and miR-155 in human T-cells and highlight the importance of cAMP in the miR-155 induction cascade elicited by *H. pylori* infection (36). Other studies have suggested the sequential induction of Foxp3 and miR-155 by *H. pylori* keeps the cAMP pathway functional in order to achieve a long-lasting modulation of the immune system (36,37).

γGT

γGT is constitutively expressed by all *H. pylori* strains and its presence was shown to be essential for establishment of infection in mice (38). It has been shown that an *H. pylori*-secreted low molecular weight protein suppresses T-cell proliferation (39). This inhibitory factor was then identified as γGT and disruption of the Ras signaling pathway was shown as the molecular mechanism used by γGT to induce T-cell cycle arrest (40). Recent data on murine models of infection indicate that γGT contributes to DC polarization, which leads to skewing the T-cell response towards a regulatory phenotype (33). Nevertheless, further studies are required to clarify how γGT induces DC tolerance. In addition, γGT contributes to subsequent activation of NF-κB, gastric inflammation via generation of H_2O_2, and upregulation of IL-8 in primary gastric epithelial cells (41). GGT exposed dendritic cells produce IL-10 and induce the FOXP3 and contact-dependent differentiation of T-cells into $CD4^+CD25^+FOXP3^+$ regulatory T-cells while simultaneously preventing T helper 1 (Th1) and Th17 differentiation (33).

Urease and LPS

H. pylori express many proteins that are important in the pathogenesis of the bacterium. These proteins not only facilitate the survival of the bacterium in the gastric mucosa but also induce a vigorous innate and adaptive immune response. Of these factors, urease represents a critical virulence determinant for this species as it protects the bacteria from gastric acidity by generating ammonia from the urea in host tissues (42). In addition, urease is one of the most abundant proteins produced by *H. pylori*, representing 5% of the total bacterial cell protein. It consists of two subunits, subunit A (UreA) and subunit B (UreB), UreB is a major target for immune recognition in patients with *H. pylori*-induced gastroduodenal diseases and host immune response to UreB contribute to inflammation (42). *H. pylori* LPS and the urease B subunit (UreB) promote NLRP3 inflammasome and caspase-1 activation as well as IL-1β and IL-18 processing and secretion. *H. pylori* LPS activates IL-1β expression via TLR4, MyD88 and NF-kB, whereas UreB signals via TLR2, MyD88 and NF-kB to activate NLRP3 transcription. The assembly of NLRP3, ASC and pro-caspase-1 leads to caspase-1 activation and to the processing of pro-IL-1β and pro-IL-18. Mature cytokines are released, bind to their receptors on naive T-cells and promote Th1 differentiation and *H. pylori* control in the case of IL-1β, and Treg differentiation, immune tolerance and persistence in the case of IL-18 (43). Interestingly, *H. pylori* infection of $TLR2^{-/-}$ and $NLRP3^{-/-}$ mice phenocopied the effects of caspase-1 or IL-18 gene deletion. These mice were able to control the bacteria more efficiently and exhibited more pronounced Th1 (and Th17) responses upon infection (44). In contrast, $FoxP3^+$ Treg frequencies in the stomach-draining mesenteric lymph nodes were lower in $TLR2^{-/-}$ mice, presumably due to their inability to produce bioactive IL-18. Indeed, a defect in any of the factors of the TLR2/NLRP3/caspase-1/IL-18 axis produces a phenotype reminiscent of Treg or DC depletion, which leads to better infection control and more pronounced chronic inflammation and immunopathology (45–47).

Subpopulations of Regulatory T-cells

There are several different types of Treg cells, commonly characterized as $CD4^+$, $FOXP3^+$, $CD127^{low}$, and expressing high levels of CD25 (48). Treg cells can be divided into two subgroups, natural Treg cells (nTreg) and inducible Treg cells (iTreg), based on their maturation site (Figure 1). A major breakthrough was the report by Miyara et al. demonstrating that, by combining FOXP3 with CD45RA, Treg cells were classified as either resting ($FOXP3^{dim}$ $CD45RA^+$) or activated ($FOXP3^{high}$ $CD45RA^-$), while at the same time $FOXP3^{dim}$ $CD45RA^-$ cells were classified as activated non-suppressive T-cells ('false positive' FOXP3 expression) and therefore correctly excluded from the Treg cell enumeration (49). Infection of C57BL/6 mice with *H. pylori* demonstrated that different subpopulations of $CD4^+$ T lymphocytes play distinct roles in mediating and regulating *H. pylori*-induced gastritis. For example, adoptive transfer of $CD4^+CD45RB^{high}$ effector T-cells from naive donors to immunodeficient recipients causes severe gastritis in *H. pylori*-infected recipients, whereas cotransfer of $CD4^+CD45RB^{low}$ regulatory T-cells (known as ''Treg'') protects against gastritis (50).

Natural Treg Cells

nTreg cells develop during normal T-cell maturation in the thymus and enter peripheral tissues where they suppress the activation of self-reactive T-cells (51). nTreg cells as a distinct lineage are released from the thymus with already expressed FoxP3. They are antigen-specific and survive as a long-lived population in the periphery (52). IL-2 is required for their generation and expansion, together with stimulation of the TCR/CD3 complex and co-stimulation

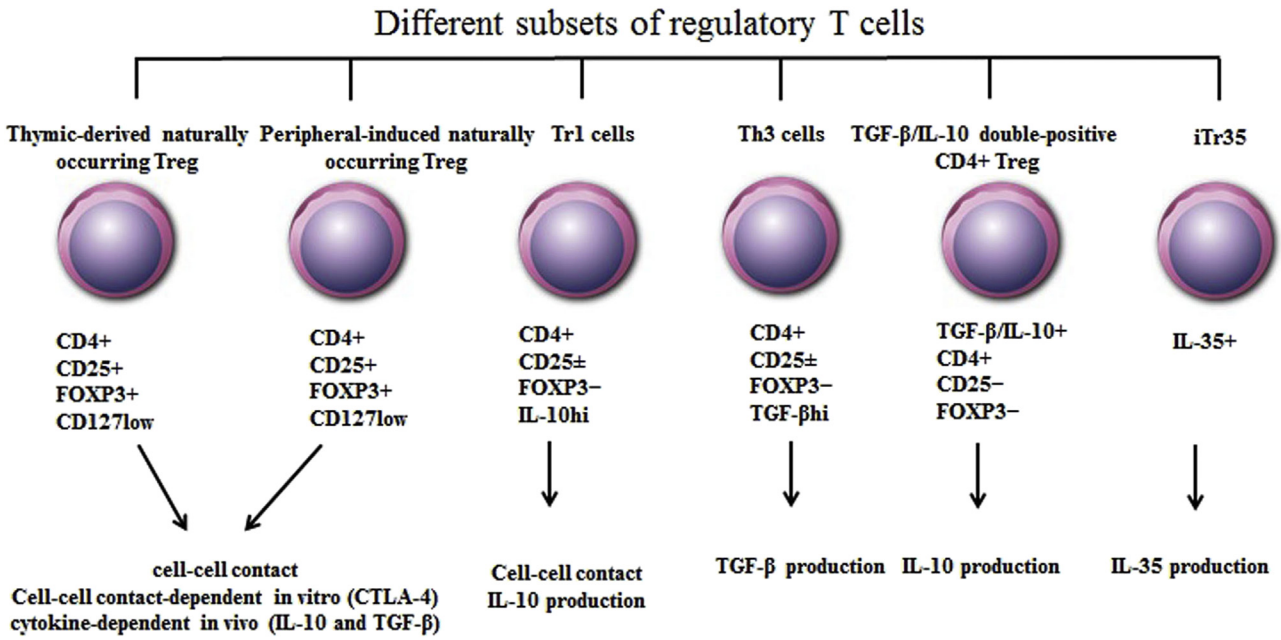

Figure 1. Subpopulations of regulatory T-cells and suggested immunosuppressive mechanism: Thymus-derived Treg (nTreg) and induced or adaptive Treg (iTreg). nTreg cells develop during normal T-cell maturation in the thymus and enter peripheral tissues where they suppress the activation of self-reactive T-cells. The iTreg cells directly develop in the peripheral lymphoid organs from naive T-cells after antigen priming. (A color figure can be found in the online version of this article.)

via CD28 (53,54). TGF-β is required to maintain nTreg cells after their emigration from the thymus (55).

Inducible Treg Cells

iTreg cells directly develop in the peripheral lymphoid organs from naive T-cells after antigen priming. iTreg cells are $FoxP3^{+}CD4^{+}CD25^{+}$ cells, which mediate their inhibitory activities by production of immunosuppressive cytokines such as IL-10 and TGF-β (51). The main factors detected as vital for inducing FoxP3 expression in $CD4^{+}CD25^{-}$ cells are IL-2 and TGF-β (55). After interacting with TCR, FoxP3 is induced downstream to TGF-β signaling (52) and is required for complete differentiation of iTreg cells. The two best-characterized iTreg types are FoxP3(+)iTreg and $FoxP3^{-}$ IL-10-producing so-called type 1 regulatory T cells (Tr1 cells). In addition, a population of TGF-producing Th3 cells has been described with regard to intestinal antigen-induced tolerance (56). Tr1 cells are defined as regulatory T-cells that are induced when antigen and IL-10 are present and are, in turn, able to produce large amounts of IL-10 (57). They were first found in the gut where they effectively suppress colitis (58). Depending on the conditions during generation, Tr1 cells usually display a high TGF-β production and lower or remove IFN-γ, IL-2, and IL-4 secretion. Both types of induced Tregs equally suppress $Th1^{-}$ as well as $Th2^{-}$ mediated immune responses. Tr1 and Th3 have been shown to originate from naive resting T-cells after stimulation with dendritic cells (DCs) (59), depending on DC type and activation status. In addition, naturally occurring Tregs are also involved in the generation of induced Tregs, a mechanism proposed as infectious tolerance. Whereas the Tr1 and Th3 populations of iTregs were long considered to be the only defined induced regulatory populations, research has identified another population of induced Tregs that can are potent mediators of suppression as well as in the propagation of infectious tolerance: iTr35 regulatory cells. These inducible regulatory cells were identified by Vignali et al. and mediate suppression primarily through the expression of the regulatory cytokine IL-35 (60).

Regulatory T-cells in H. pylori *Infection*

During acute infections, a prompt and robust immune response is needed to eradicate the infectious organisms. However, if eradication fails, a continued and strong but unsuccessful immune response would be detrimental, leading to severe tissue damage. Therefore, during chronic inflammatory states several immunomodulatory mechanisms are involved. One of these mechanisms is iTreg activation and expansion. iTreg accumulates in *H. pylori*-induced diseases and chronically infected mucosal tissues (61). It has not yet been established whether the pathogens induce iTreg responses as a strategy for increase in survival or whether the chronic inflammation results in iTreg induction. However, different pathogens' purified antigens have been demonstrated to enhance the induction of Treg *in vitro*, which makes the former alternative more likely. *H. pylori* is able to skew the DC responses towards a

Treg-inducing IL-10-secreting phenotype (62), which is often concurrent with decreased IL-12 secretion and Treg induction during *H. pylori* antigen presentation. This effect can be mediated by both CagA phosphorylation in DC and Toll-like receptor 2 ligands (24,63). Studies on *H. pylori*-infected children and adults have shown that children possess reduced gastric inflammation in comparison to infected adults, despite similarity in mean levels of *H. pylori* colonization. More importantly, inflammation in the children has been shown to be less at each level of bacterial colonization in comparison to that of adults, indicating an overall down-regulation of the immune response to *H. pylori* in children (64). Studies on *H. pylori*-infected children and adults have demonstrated that *H. pylori*-induced gastritis in adults is derived from involvement of both Th1 and Th17 immune-mediated inflammatory pathway and that both pathways are likely to down-regulate in the gastric mucosa of infected children. As a result, TGF-β gastric levels, IL-10 and gastric number of Treg Foxp3^{+} cells are higher in children than in adults in *H. pylori*-positive populations (64–66). In this regard, the predominant Treg differentiation in *H. pylori*-infected children might explain more susceptibility of children to the *H. pylori* infection and the bacterium persistence. A study in mice infected with *H. pylori* indicated that transfer of T-cells after removal of Treg to immune-deficient hosts and subsequent infection with *H. pylori* were shown to result in enhanced inflammation in the stomach and increased IFN-γ production compared to transferred T-cells containing Treg in mice (67). Further studies have shown an accumulation of Treg in the stomach of *H. pylori*-infected mice and that depletion of Treg in C57BL/6 (H2b) mice using CD25 antibody *in vivo* followed by challenge with *H. pylori* bacteria results in enhanced inflammation and recruitment of T-cells, macrophages, and B cells to the stomach compared to untreated infected wild-type mice (68,69). The events described above could explain the state of tolerance implemented by the bacterium and are summarized in Figure 2.

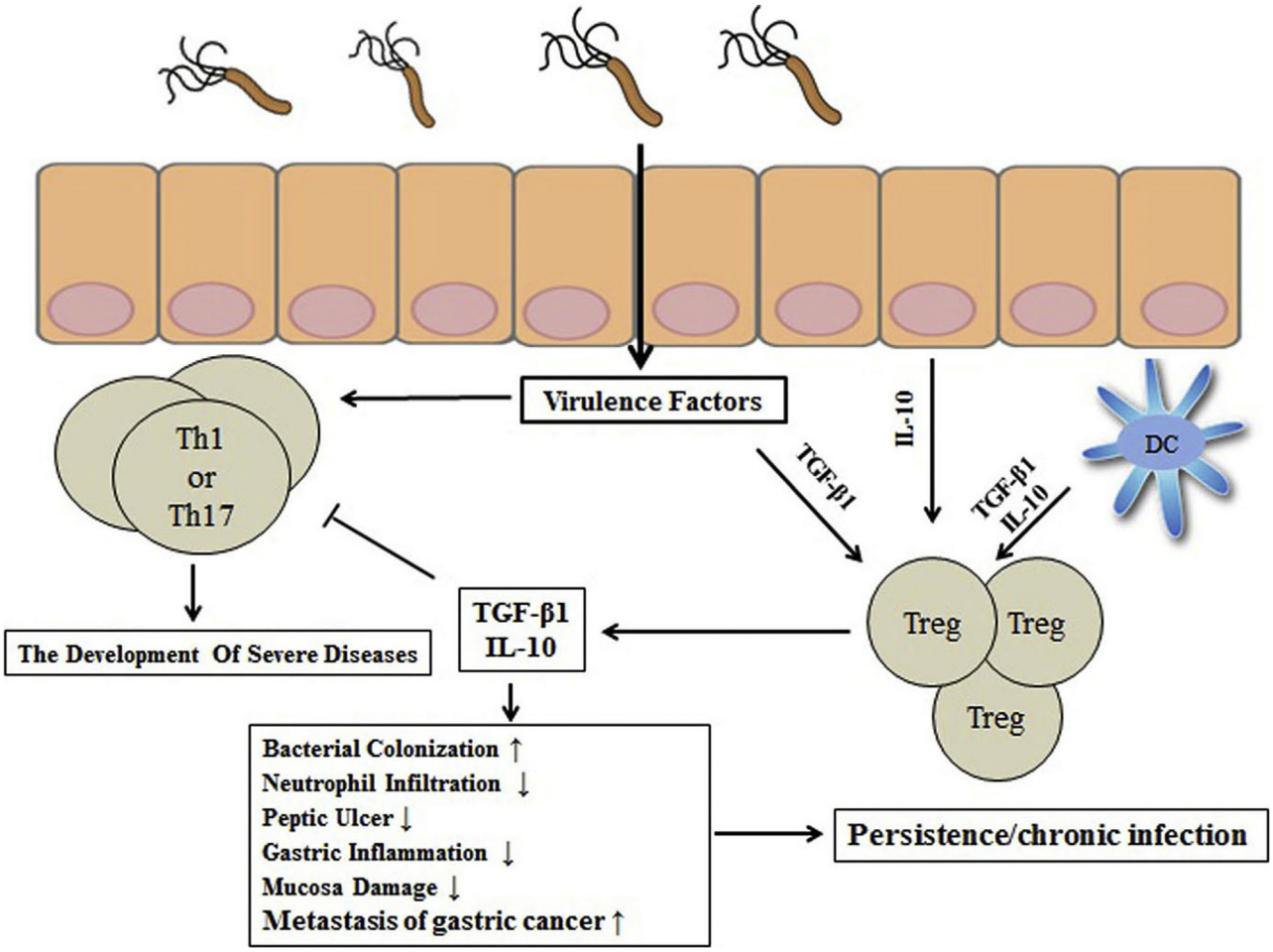

Figure 2. Role of Treg and *H. pylori* infection: *H. pylori*-induced gastritis is characterized by a predominant Th1/Th17 response that is regulated by Treg cells. The various T-cell lineages secrete different cytokines that modulate further the immune response that is a critical factor for the development of severe diseases such as peptic ulcer or gastric cancer. (A color figure can be found in the online version of this article.)

Regulatory T-cells and Gastritis

Human-based studies have shown that the degree of active *H. pylori*-induced inflammation is negatively correlated with Treg cells number in periphery or gastric mucosa (70–73). Interestingly, a similar activity was reported for peripheral Treg cells towards *H. pylori*-stimulated AGS cells showing impairment in IL-8 secretion compared to those cultivated with Treg cells (71). Lundgren et al. isolated peripheral $CD4^+CD25^{high}$T-cells from *H. pylori*-infected individuals and demonstrated their immune suppressive activity towards the CD4 cells primed by *H. pylori*-presenting DCs (71). Consistently, increased numbers of Treg cells were shown in the gastric mucosa in *H. pylori*-infected patients (71–74). Treg cells were found to be associated with increasing bacterial colonization (72), chronic inflammatory changes and the expression of immune suppressive cytokines (74,75). Eradication therapy of the infection causes a significant decrease in Treg cells and corresponding cytokine levels of gastroduodenal mucosa (74). Although *H. pylori* infection tends to transmit within a family in early childhood, interestingly a strong correlation could exist among increased numbers of mucosal Treg cells, lower inflammatory scores and elevated cytokine levels (IL-10, TGF-β1) characteristic of the functional importance of Treg cell activity in early stages of the acute infection (64,76). Although there is limited knowledge of the interaction between Treg response and *H. pylori* infection from acute childhood infection, Treg cell activity could sensibly explain a more moderate acute phase of infection resulting in the persistence of the bacteria and chronic changes in an inflammatory equilibrium between *H. pylori* and the host immune system (77). In a functional assay, Robinson et al. isolated mucosal T-cells from biopsies and stimulated those with *H. pylori* antigens (75). Compared to uninfected donors, the stimulated cells presented a predominant $CD4^+IL\text{-}10^+$ response characterized by a 36-fold increase in IL-10 production. Moreover, patients with peptic ulcer disease were characterized by remarkably reduced amounts of IL-10 and decreased Treg cell activity, indicating that a low expression of IL-10 by Treg cells is very likely to cause immune-mediated cell damage and acute inflammatory changes leading to peptic ulceration. Consistent with Strömberg et al. (78), IL-10 was shown to be able to down-regulate epithelial cells (AGS) inflammatory response through interfering with the NF-κB signal pathway, which results in a decrease in IL-8 secretion after *H. pylori* stimulation (75).

Regulatory T-cells and Peptic Ulcer

H. pylori-infected patients with duodenal ulcer have, on average, higher acid secretion than normal, healthy individuals, which results in development of areas with gastric metaplasia in the duodenum where *H. pylori* preferentially colonize (79,80). Interestingly, a decreased cytokine secretion has been reported in these areas of duodenal metaplasia compared to asymptomatic carriers, indicating that an active suppression of epithelial responses in the duodenum of duodenal ulcer patients (81) could contribute to the bacteria persistence and subsequent development of duodenal ulcers (Figure 2). The reduced duodenal cytokine response to *H. pylori* infection could be as a result of host-derived or bacterial factors and perhaps to Treg accumulation at the infection site in an effort to control tissue damage. Indeed, $Foxp3^+$ T-cells have been found to preferentially localize to areas of gastric metaplasia in duodenum of patients with duodenal ulcer (74). Unfortunately, there has been very little research on the Treg response in the stomach of *H. pylori*-infected individuals with peptic ulcers. The study by Robinson et al. found a 2.5-fold lower $IL\text{-}10^+$Treg frequency but increased Th1 and Th2 response in the mucosa of peptic ulcers patients compared to infected asymptomatic volunteers (75). In addition, stimulation of peripheral blood mononuclear cells with *H. pylori* antigens showed that mononuclear cells from peptic ulcer patients secreted much less IL-10 than cells from asymptomatic controls, indicating that defective regulation of T-cell responses to *H. pylori* may lead to peptic ulcer diseases (75).

Regulatory T-cells and Gastric Cancer

As with *H. pylori* infection, several studies demonstrated escalated numbers of Treg cells in patients with gastric cancer (82–84). The study by Wang et al. of *H. pylori*-infected patients including patients with gastric cancer showed increased number of Treg cells in the peripheral mononuclear cell population in addition to the local mucosal changes (84). Interestingly, Th1/Th2-derived cytokines was found to decline, starting from asymptomatic gastritis to gastric atrophy, intestinal metaplasia and intraepithelial neoplasia to gastric cancer. The steady decline was associated with a parallel increase in the Treg cell compartment in peripheral blood and the presence of $CagA^+$ *H. pylori* strains, which favored a Treg cell-mediated chronic inflammation and $CagA^+$ strain persistence (84). Wang et al. (84) and Jang et al. (73) reported increased numbers of mucosal Tregs in *H. pylori*-associated gastritis where they were positively correlated with a chronic grade of gastritis. Mucosal Treg cells were found to increase further in patients with dysplastic changes and at the highest density for gastric cancer (73). Data also demonstrated elevated levels of peripheral blood FOXP3-expressing $CD4^+CD25^+CD127^{low}$Treg cells in patients with gastric cancer. The increased numbers of $FOXP3^+$ $CD4^+CD25^+CD127^{low}$Treg in the tumor tissue, the mucosal microenvironment and the adjacent lymph nodes and the ascitic fluid of advanced tumor stages have been noted. A positive correlation has been found with the tumor-node-metastasis (TNM) stage and particularly high numbers in advanced tumor stages. Additional data on the functional

activity were demonstrated via Treg cell-mediated antiproliferative effect on T effector cells (83). A retrospective immunohistochemical study showed increased numbers of Treg cells were associated with vascular, perineural and lymphatic invasion of gastric tumor cells. Higher numbers of Treg cells were correlated with advanced tumor stage and negatively correlated with the total survival of 110 patients (85), proposing $FOXP3^+$Treg cells as an additional marker to identify high-risk gastric cancer patients that need further therapy after R0 resection (85). The pattern of mucosal infiltration and the total number of Treg cells were immunohistochemically characterized with regard to TNM tumor stage and survival, exhibiting a more diffuse pattern of Treg cell infiltration, which correlated with poor prognosis and survival (86).

Regulatory T-cells and MALT

More than 5% of all gastric malignancies are primary gastric lymphoma. MALT lymphoma emerges from the extranodal sites and is initiated in response to chronic antigenic stimulation caused by *H. pylori* antigen and is the best example for the malignant transformation caused by the pathogen (87). Neoplastic B cells have been proposed to arise in MALT from the marginal zone of lymphoid follicles (88). It has been suggested that persistent *H. pylori* infection may induce chronic inflammatory responses, contributing to DNA damage in lymphocytes. Genetic abnormalities subsequently increase the neoplastic B-cell clone (87). It has been suggested that neoplastic B-cell proliferation is antigen dependent and functions similar to ordinary immune response and therefore needs T-cells specifically activated by *H. pylori* antigens (89). Regression of ~75% of lymphoma cases after *H. pylori* eradication by antibiotics is the significance of this stimulation (90). The other patients who do not respond to *H. pylori* therapy may indicate that initiation of neoplastic lymphocytes in these subjects is not dependent on *H. pylori* infection (87). Many investigations proposed the hypothesis that the gastric MALT homeostasis in lymphoma is the same as chronic gastritis but not similar to the regulatory mechanisms that assume control over the actions leading to progression (91,92). Current investigations showed that patients with gastric MALT lymphoma with a high number of tumor infiltrating $FOXP3^+$ cells usually show better response to eradication therapy (Table 1) (91). Among the *H. pylori*-positive MALT lymphoma patients who received *H. pylori* eradication therapy, a significantly higher number of $FOXP3^+$ Treg cells among $CD4^+$ T-cells (the $FOXP3^+/CD4^+$ cell ratio) were seen in responders compared with non-responders. This may indicate that the ratio can predict responsiveness to *H. pylori* eradication therapy. Furthermore, this investigation showed that the $FOXP3^+/CD4^+$ ratio in gastric MALT lymphoma is nearly three times larger than that of chronic active gastritis (83). In contrast to immune effector cells and regulators (Treg cells) that are induced in inflamed areas, the immune responses in the nonresponder group are highly divergent from normal inflammation. This may suggest that, in the nonresponder group, the possible driving force of the tumor is more pronounced (Table 1) (92). To demonstrate the precise biological significance of Treg cells in MALT lymphomas, additional studies should be carried out.

Table 1. Schematic representation of potential mechanism behind the context of Treg cells and response to *H. pylori* eradication treatment (92)

	Eradication responders	**Eradication non-responders**
Driving force of tumor	+	+++
Immune response to *H. pylori*	Similar to normal inflammation	Deviated from normal inflammation
Number of Tregs cells	+++	+

Regulatory T-cells and Allergic Diseases

An inverse association between *H. pylori* and asthma is postulated. It has been shown that the high level of Tregs is seen in *H. pylori* infection. According to this hypothesis, *H. pylori* infection may contribute to allergic disease prevention, and *H. pylori*-free individuals are more susceptible to allergic disease. Additionally, a higher level of gastric Tregs in *H. pylori*-positive individuals has been reported in comparison to individuals without the organism (75,93). Interestingly, circulating Tregs are also increased in number in *H. pylori*-positive individuals (84). Furthermore, in mice experimentally infected with *H. pylori*, the systemic Tregs are elevated. Suppression of the immune responses by Tregs facilitates *H. pylori* colonization (68). The increased number of Tregs may also have immunosuppressive effect in humans. Hence, *H. pylori*-positive subjects with lower Tregs are more likely to develop peptic ulcer (75) and supposedly have more severe gastritis. Mucosal Tregs may be more elevated in $CagA^+$ *H. pylori* colonization, and the immunomodulatory cytokines such as IL-10 at mucosal levels may be more elevated than in $CagA^-$ colonization (76). If such phenomenon applies to circulating Tregs, it could potentially explain the stronger, negative association with childhood asthma of $CagA^+$ strains (94,95). Cross-sectional studies have documented that the two phenomena are inversely correlated, with *H. pylori* carriers having a decreased risk of developing childhood or early-onset allergic asthma, rhinitis and atopic dermatitis than the non-infected population (94,96). However, for more verification of the hypothesis, further studies are recommended.

Conclusion

Recent data obtained from animal and human studies are indicative of an important contribution of regulatory T-cells

to *H. pylori* infection and associated complications. A predominant Th1/Th17 immune response against *H. pylori* infection suggests a relatively mild chronic inflammation that contributes to the lifelong persistence of bacteria. The role of Treg in dampening *H. pylori*-induced inflammation at the site of infection and maintaining chronicity of the infection has already been confirmed in several studies of both mouse models and humans. Thus, it can be hypothesized that, in peptic ulcer, Treg suppresses the epithelial cell-initiated inflammatory response, which leads to bacterial overgrowth and ulcers. For gastric cancer, accumulation of Treg in *H. pylori*-induced gastritis may prevent carcinogenesis but may contribute tumor progression and metastasis in already established tumors. Interventional studies to target Treg in animal models of *H. pylori*-associated peptic ulcers and gastric cancer could remarkably enhance knowledge of specific therapies for fighting *H. pylori* infection and associated diseases. The events described above are summarized in Figure 2.

Conflict of Interest

The authors declare no conflict of interest.

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