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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