REVIEW ARTICLE

Conventional, Regulatory, and Unconventional T Cells in the Immunologic Response to *Helicobacter pylori*

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Abstract

Infection by the gastroduodenal pathogen *Helicobacter pylori* elicits a complex immunologic response in the mucosa involving neutrophils, plasma cells, eosinophils, and lymphocytes, of which T cells are the principal orchestrators of immunity. While so-called classical T cells (e.g. T-helper cells) that are activated by peptide fragments presented on antigen-presenting cells have received much attention in *H. pylori* infection, there exists a diverse array of other T cell populations that are potentially important for the outcome of the ensuing immune response, some of which have not been extensively studied in *H. pylori* infection. Pathogen-specific regulatory T cells that control and prevent the development of immunopathology associated with *H. pylori* infection have been investigated, but these cells can also benefit the bacterium in helping to prolong the chronicity of the infection by suppressing protective immune responses. An overlooked T cell population, the more recently described Th17 cells, may play a role in *H. pylori*-induced inflammation, due to triggering responses that ultimately lead to the recruitment of polymorphs, including neutrophils. The so-called innate or unconventional T cells, that include two conserved T cell subsets expressing invariant antigen-specific receptors, the CD1d-restricted natural killer T cells which are activated by glycolipids, and the mucosal-associated invariant T cells which play a role in defense against orally acquired pathogens in the intestinal mucosa, have only begun to receive attention. A greater knowledge of the range of T cell responses induced by *H. pylori* is required for a deeper understanding of the pathogenesis of this bacterium and its ability to perpetuate chronic infection, and could reveal new strategies for therapeutic exploitation.

Helicobacter pylori is recognized as the causative agent of active chronic gastritis and is the predominant cause of peptic ulceration, i.e. gastric and duodenal ulcers [1]. Additionally, *H. pylori* is a cofactor in the development of gastric cancer, both adenocarcinoma and mucosa-associated lymphoma, and therefore has been designated as a class I carcinogen by the World Health Organization [2]. Overall, 10–15% of *H. pylori*-infected individuals develop peptic ulcers and 1–2% develop gastric adenocarcinoma [3]. Persistence of infection for years or even decades is a central hallmark of the interaction between *H. pylori* and untreated humans [1]. As there is associated gastric inflammation, the immune response to *H. pylori* can play an important role in pathogenesis. The focus of the present paper is to review the role of conventional, regulatory and unconventional T cells in the response to *H. pylori* infection, placed in the context of the overall immunologic response to this infection, and to highlight the state of knowledge as well as emerging issues on the nature of the T cell response.

Characteristics of the Immunologic Response to *H. pylori*

H. pylori colonization of the gastric mucosa elicits a complex immune response initiating innate as well as adaptive immune responses [1,4–7]. It is well-established that there is a significant influx of neutrophils, lymphocytes, plasma

cells, and eosinophils into the gastric mucosa in *H. pylori*-associated gastritis [8]. Ultimately, despite the development of a prominent localized immune response, leading to active inflammation in the gastric mucosa [3], the bacterium is rarely eliminated and infections can last for decades if left untreated [9]. It is important to note that a large proportion of infecting *H. pylori* (85%) occupy a unique ecological niche within the gastric mucus, as well as on the surface of gastric epithelial cells (10%) and at intercellular junctions (5%) [10,11]. By residing within this environment, the bacterium may minimize recognition by the innate immune system and evade phagocytosis because neutrophils and macrophages do not appear to traverse the gastric epithelium into the mucus layer [12]. On the one hand, the duration of immune recognition of *H. pylori*, but potential lifelong colonization on the other hand, demonstrate the effectiveness of the bacterium to evade, dampen or inhibit host responses contributing to immunity [13]. Importantly, among all individuals infected with *H. pylori*, 15–20% will develop more severe forms of gastric disease including peptic ulcers and cancer [14]. Thus, while the interplay between the virulence factors of *H. pylori* and the host immune responses is likely to contribute to the outcome of infection, these responses are largely ineffective in eliminating the bacterium.

Inflammatory Response to *H. pylori*

Early in infection, *H. pylori* induces production of the chemokines RANTES (Regulated on Activation, Normal T Expressed and Secreted, also called CCL5), GRO-α, MIP-1α, ENA 78, and MCP-1, as well as secretion of the cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α) [15]. The production and expression of these proinflammatory agents is controlled by the transcription factor, nuclear factor-kappaB (NF-κB), and the initial trigger is likely to be mediated by epithelial cells [16]. Several *H. pylori* membrane proteins encoded within the *cag* pathogenicity island (PAI), which also contains the cytotoxin-associated gene A (*cagA*), induce activation of NF-κB and up-regulation of mRNA of the neutrophil chemotactic chemokine IL-8 [17]. Moreover, epithelial cells infected with $CagA^+$ *H. pylori* strains activate the early transcription factor AP-1 which is known to stimulate IL-1, IL-6, and MCP-1 production [18]. Consistent with this, Masamune et al. [19] showed that direct contact of epithelial cells with *H. pylori* results in C_2-ceramide production with subsequent activation of NF-κB and IL-8. The list of *H. pylori* products which trigger or exacerbate mucosal inflammation continues to grow. Host responses to the urease molecule, lipopolysaccharide (LPS), *H. pylori* heat-shock proteins (Hsp60 and Hsp70), and the vacuolating toxin (VacA) include development of marked antral gastritis, severe mucosal damage [20,21], up-regulation of proinflammatory cytokine production [20,22], and altered epithelial barrier function [23] with changed uptake of macromolecules [24]. Therefore, *H. pylori* and its products induce a significant inflammatory response in the infected mucosa contributing to the pathology associated with infection.

Innate Immune Response to *H. pylori*

Innate immune responses against infection depend on recognition of invariant structures or so-called pathogen-associated molecular patterns (PAMPs) on microorganisms [25]. These PAMPs include microbial components such as LPS, peptidoglycan, flagellin, double-stranded RNA, and zymosan. The receptors on epithelial and innate immune cells, e.g. macrophages, neutrophils, and natural killer cells (NK cells), that recognize these PAMPs are termed pathogen-recognition molecules, examples of which are the Toll-like receptors (TLRs) [25] and the Nod proteins [26].

There have been several studies investigating innate immune responses to *H. pylori* that have focused on TLR4 [27–29], which is generally considered the pathogen-recognition molecule for Gram-negative bacterial LPS, ranging from the activation of TLR4 expression in gastric epithelial cells by *H. pylori* [29] to the role of TLR4 in the proapoptotic action of LPS [27] and the interaction of *H. pylori* LPS with TLR4 influencing superoxide metabolism in gastric pit cells [28]. More recently, studies have also focused on TLR2 and TLR5 which have been deduced to be the pathogen-recognition molecules for bacterial lipopeptides and flagellin, respectively [30]. In particular, NF-κB activation in response to *H. pylori* is decreased by transfection with dominant negative constructs for TLR2 and TLR5 [31], thus indicating the importance of these immune receptors in immune recognition. TLR4 mRNA has been detected in human gastric epithelial cell lines [29], although using these cell lines signaling through TLR4 in mediating innate responses to *H. pylori* was concluded not to be important [32]. On the other hand, such cells lines can lack MD-2 expression which is a critical cofactor for TLR4-mediated signaling [31]. This was deduced to explain the observed lack of significance of TLR4 signaling in such cell lines, and furthermore, examination of biopsy specimens showed TLR4-dependent signaling during *H. pylori*-associated infection and the essential role of MD-2 in this signaling [33]. Likewise, TLR4-dependent signaling with CD14, which has been considered important in loading LPS onto TLR4, was reported to be absent in primary human gastric epithelial cells [32]. However, LPS presentation to gastric epithelial cells would occur in a serum-free, and hence CD14-free, environment in the stomach. In contrast, other investigators found TLR4 expression on

gastric pit cells of biopsies from guinea pigs [28] and humans [33] that is capable of sampling *H. pylori* LPS in the stomach environment. Thus, in contrast to gastric cell lines in vitro, TLR4-mediated signaling can occur in vivo.

Importantly, compared to other Gram-negative bacteria, *H. pylori* LPS is a poor activator of the innate immune response [34–36]. In accord with this low activity, *H. pylori* LPS exhibits poor binding to serum-associated LPS-binding protein and CD14 [37] but also to TLR4 [38]. The predominant TLR response to *H. pylori* bacteria (but also to *Helicobacter felis* and *Helicobacter hepaticus* whole cells) is not mediated by TLR4, which contrasts with most Gram-negative bacteria that preferentially activate TLR4 by their potent LPS ligands, but rather by TLR2 [39]. Using TLR-transfected cell lines, Smith et al. [31] reported that *H. pylori* LPS was a TLR2 agonist, whose activation was enhanced by CD14, and deduced that TLR2 binding was likely based on similarities between the structure of the lipid A component of *H. pylori* LPS and that of *Porphyromonas gingivalis* lipid A whose LPS unusually is considered to be a TLR2, not a TLR4, ligand [40]. However, Mandell et al. [39] using highly pure LPS from *H. pylori* clinical isolates, that had been chemically assayed to be free of lipopeptides and other contaminants, found TLR4- but not TLR2-mediated cytokine production by TLR-transfected cell lines and macrophages from knockout mice. Likewise, another study demonstrated that *H. pylori* acted via TLR4 to stimulate reactive oxygen production from guinea pig gastric pig cells [28]. The discrepancies between these findings can be attributed to the presence of TLR2-activating contaminants in LPS test preparations [38], which have also contributed to inconsistencies in results when investigating other ligand–immune receptor interactions [41], as well as to differences in LPS dosages between the studies (nanogram [39] vs. microgram [31]). The latter has been confirmed in an independent study [42]. Hence, although the predominant TLR response to *H. pylori* is TLR2-mediated, this response is not mediated by *H. pylori* LPS, rather *H. pylori* LPS is a TLR4 agonist with low activity.

Notwithstanding this, the failure to detect TLR2 expression in the stomach (both in humans [39] and in mice [43]), compared to the detection of TLR4 on gastric pit cells (in guinea pigs [28] and humans [33]) has important implications for *H. pylori* colonization. In the absence of TLR2 in the gastric environment, the interaction of *H. pylori* LPS with TLR4 can be critical to the early detection of *H. pylori* by the innate immune system [44] and would influence colonization [45]. Accordingly, upon initial infection of the gastric mucosa, *H. pylori* may be weakly recognized by interaction of its LPS with TLR4 on gastric cells. Thus, *H. pylori* by expressing an LPS with very weak TLR4 agonist activity and colonizing a TLR2-deficient environment can escape detection and elimination by the immune response initially. Consistent with this evasion of immune detection, though functional TLR5 is expressed in the adult stomach [46], and TLR5 is considered to bind and respond to bacterial flagellins, *H. pylori* flagellins FlaA and FlaB induce a very low activation of TLR5-mediated responses [47]. Overall, although *H. pylori* molecules interact with TLR4 and TLR5 that are expressed in the stomach, these interactions are of low activity, thereby allowing initial *H. pylori* colonization. Subsequently, with the progression of longer term infection, a substantial inflammatory response to *H. pylori* can develop after the infiltration of TLR2-expressing granulocytes and monocytes into the infected gastric mucosa.

Another family of pathogen-recognition molecules, the Nod proteins, appear to have a more central role in mediating innate immunity against *H. pylori*. Two members of this protein family, Nod 1 (also called CARD4) and Nod2 (also called CARD15), are involved in the intracellular recognition of bacterial muropeptides derived from bacterial peptidoglycan but differ in their specificity; Nod1 recognizes a bacterial muramyl tripeptide [48], Nod2 a muramyl dipeptide [41]. Of particular importance, NF-κB and IL-8 production in epithelial cells has been shown to be dependent on signaling through intracytoplasmic Nod1 recognition of muropeptides from *H. pylori* peptidoglycan [49]. Thus, in innate immune recognition of *H. pylori* by gastric epithelial cells, recognition by Nod1 is likely more important than by TLRs. This is supported by a mouse model of *Helicobacter* infection where inhibition of Nod1-mediated activation of the innate immune system resulted in a significantly greater colonization density. The *H. pylori* muramyl tripeptide is delivered intracellularly by the type IV secretion system-encoding *cag* PAI [49], and this represents one mechanism by which *cag* PAI-positive strains elicit a more vigorous inflammatory response and, in part, explains why these strains are associated with more aggressive disease symptoms, e.g. gastric cancer [38].

A further PAMP recognition receptor of importance in the innate immune response to *H. pylori* is surfactant protein-D (SP-D) [12]. SP-D is a collagenous glycoprotein that contains trimeric arrays of C-type (calcium-dependent) lectin domains and which belongs to a family of proteins called the collectins [50]. Although originally identified in the lungs as a component of surfactant [51] and associated with type II cells and Clara cells [52], expression of SP-D also occurs at the gastric luminal surface and within gastric pits [53]. Infection with *H. pylori* up-regulates expression of SP-D, which colocalizes with *H. pylori* organisms, in patients with gastritis [53]. Moreover, the influence of SP-D binding on *Helicobacter* colonization has been demonstrated in a SP-D-deficient mouse model [54]. In vitro studies have shown that SP-D binds and agglutinates *H. pylori* cells in a lectin-like manner [12,53], and results in considerable

reduction in bacterial motility, as determined on the basis of curvilinear velocity in microscopic video tracking experiments [53]. Bacterial aggregation by SP-D can reduce susceptibility to infection and colonization density, as observed in the SP-D-deficient mouse model [54], by its effect on bacterial motility, as well as influencing phagocytosis and bacterial membrane permeability, and hence survival [12]. The *H. pylori* ligand for SP-D binding has been identified as LPS [53], though there is marked variation in the avidity of binding among strains and their LPSs [53,55], potentially reflecting different structural properties. Of particular interest, a single *H. pylori* strain can produce variants with modified LPS O-chain structures that escape or avoid SP-D agglutination [55]. Upon examination of gastric biopsies, SP-D-binding isolates predominate in the mucus layer compared to the tissue component [12,55]. Although the SP-D-susceptible forms have a more rapid growth kinetics, they would be more readily cleared from the mucosa, but on the other hand, the SP-D-resistant forms with a lower growth rate would have a selective advantage to avoid SP-D binding and, hence, interact with gastric tissue leading to inflammation and potential nutrient release [55]. However, reversible switching of O-chain structure occurs in the absence of SP-D selective pressure in vitro [55], suggesting that SP-D evasion is mediated by phase-variable mechanisms [56]. Thus, the ability of the bacterium to evade SP-D binding would allow interaction with the gastric epithelium and colonization to become established.

Collectively, although SP-D binding can play an important role in initial defense against the infection, once colonization becomes established and bacterial interaction occurs with gastric epithelial cells, the Nod1-mediated interaction would appear more important for the induction of the inflammatory response than TLR4- or TLR5-mediated responses.

Antigen-Presenting Cells in *H. pylori* Infection

There are several populations of immune cells localized within the gastric mucosa that through molecular cross-talk contribute to *H. pylori*–host interactions [3,7]. Thus, in addition to epithelial cells, macrophages and dendritic cells reside within the gastric mucosal layers of *H. pylori*-infected individuals. *H. pylori* infection results in up-regulation of MIP-3α gene expression in gastric epithelial cells, thus inducing an influx of mononuclear cells into the lamina propria of the mucosa [57]. Nonetheless, these cells may be functionally impaired, as *H. pylori* can inhibit phagocytosis by macrophages [58,59], though the molecular mechanism has not been elucidated to date, but ultimately results in decreased and altered processing of *H. pylori* antigens. Because the peptide-dependent activation of cells associated with the adaptive immune response (B and T cells) requires macrophage and dendritic cell presentation of *H. pylori*-processed antigens, this has major importance for the outcome of the developing immune response against the bacterium, although the responses of these cells to *H. pylori* live bacteria and *H. pylori*-derived products are complex. NF-κB activation by macrophages/monocytes, and consequently, IL-12 induction that influences T cell differentiation, appears independent of the *H. pylori cag* PAI [60] but in contrast to epithelial cells [32], it predominantly involves CD14 and TLR4 [61]. Moreover, *H. pylori* LPS stimulates NF-κB and IL-8 production by macrophages/monocytes in a CagA-independent manner [62], whereas NF-κB activation in epithelial cells by *H. pylori* is peptide-dependent [63]. Overall, activation of antigen-presenting cells not only plays a role in processing and presentation of *H. pylori* antigens to cells of the adaptive immune response but also influences their differentiation due to the release of cytokines, e.g. IL-12 induction influences T-cell differentiation.

Adaptive Immune Responses to *H. pylori*

The other main arm of immunity, the adaptive immune response is characterized by the presence of T and B cell populations which bear highly diverse antigen-specific receptors. T cells are responsible for cell-mediated immunity and, thus, are central to and promote activation of many other immune cells and killing virally infected and target tumor cells, whereas B cells produce antibodies in humoral immunity. Initially, it was assumed that a protective immune response against *H. pylori* would be predominantly mediated by antibodies, based on analogy with other mucosal infections [1] and correlations between anti-*H. pylori* antibodies in breast milk and absence of *H. pylori* in breast-fed children [64]. Consistent with this deduction, studies have shown that antibodies can influence colonization by *H. pylori* in animal experiments [65] and be bactericidal [66], and can effectively prevent infection and reduce colonization in *Helicobacter* animal models in mice [67] and gerbils [68]. Nevertheless, it has become apparent that the humoral response is only marginal for the induction of protective immunity [1], and it is cellular rather than humoral immunity that has been deduced to play the principal role in sterilizing immunity [69–72]. For example, Ermak et al. [69] reported that protection of mice against *H. pylori* infection by immunization with urease antigen is dependent on major histocompatibility complex (MHC) class II-restricted cell-medicated mechanisms and that antibody responses to urease are not required for protection. Likewise, *H. pylori* immunization had no effect on the bacterial infection level in MHC class II-deficient mice [70], but did reduce colonization in B cell-deficient mice [71]. Moreover, Eaton et al. [72] showed that enhanced cellular immune responses in recipient SCID

mice after splenocyte transfer allowed clearing of *H. pylori* infection and resolution of gastritis.

In summary, although there have been numerous investigations of the proinflammatory responses to *H. pylori*, as well as the innate and humoral immune responses to the microorganism, and which have been shown to contribute to *H. pylori* infection outcome, the remainder of this review will focus on the role of T cells and related cell lineages in immune responses to *H. pylori* to highlight their importance in the context of these other immune responses.

Classical T cell Immune Response

T cells are the principal orchestrators of adaptive immunity which undergo clonal expansion upon recognition of peptide fragments complexed with MHC class I or II molecules on antigen-presenting cells. Classically, conventional T cells have been considered to include $CD4^+$ T-helper cells that recognize peptides complexed to MHC class II molecules and, through cytokine secretion, promote the immune response including B cell differentiation, whereas $CD8^+$ T-cytotoxic cells can recognize peptides complexed to MHC class I molecules and promote killing of cells infected by intracellular pathogens [73]. Nevertheless, there are a variety of other T cell subsets that contribute to and regulate the immune response to infection. Overall, *H. pylori* is capable of stimulating T cell activity, and a variety of bacterial antigens have been implicated in the process [74,75].

In the effector phase of an immune response, different T cell subsets, called T-helper-1 (Th1) and T-helper-2 (Th2) cells, expand (Table 1). Th1 cells promote proinflammatory cell-mediated immunity through production of cytokines such as interferon-gamma (IFN-γ) and TNF-α, whereas Th2 cells promote humoral immunity by secreting IL-4, IL-5, and IL-13 that induce B cells to produce antibodies [73,76] (Fig. 1). Although Th1- and Th2-type cytokine profiles were originally identified through analysis of murine T cell clones [77], there is evidence that chronically stimulated human T-cells are polarized into Th1 or Th2 patterns of cytokine synthesis [78], the so-called Th1/Th2 paradigm. There are many genetic and environmental factors which influence the differentiation of Th1 and Th2 cells. IL-12, IL-18, and interferons favor Th1-cell development, whereas IL-4 is a potent stimulus for Th2-cell development [79].

H. pylori and the Th1/Th2-Cell Paradigm

To date, studies investigating the nature of the immune response to *H. pylori* have largely focused on classical T cells which are found in abundance in the antrum of the

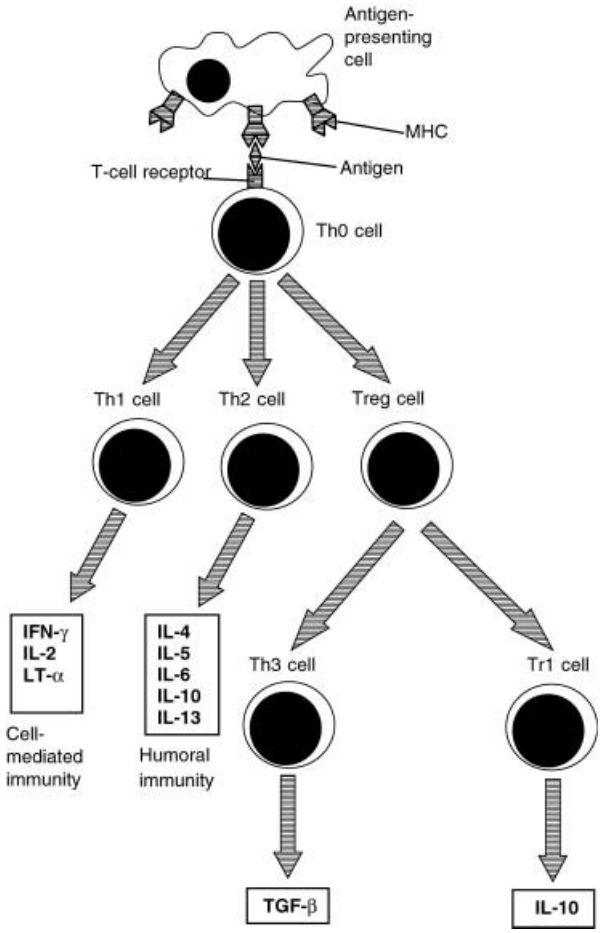

Figure 1 T-helper and regulatory T-cell differentiation with associated cytokine profiles. T-helper cells differentiate from immature T-cell populations (Th0 cells) in the thymus. Under the influence of local cytokines, a naïve Th0 cell differentiates into a T-helper-1 (Th1) cell that secretes interferon-gamma (IFN-γ), interleukin- (IL-) 2, and lymphoxin-alpha (LT-α), or a T-helper-2 (Th2) cells that secretes IL-4, IL-5, IL-6, IL-10, and IL-13, or into regulatory T cells (Treg cells) that secrete IL-10 or tumor growth factor-beta (TGF-β) (Th3 cell and Tr1 cell, respectively). Th1 cells are considered mainly proinflammatory and are central to development of cell-mediated immunity; Th2 cells promote antibody production and humoral immunity; whereas Th3 cells are mainly down-regulatory.

majority of *H. pylori*-infected donors [80]. In *H. pylori* infection, T cells participate in promoting local inflammation, can be partially protective, and/or are involved in regulating the immune response to *H. pylori*. Early studies that investigated T cell responses to *H. pylori* showed that, in healthy controls as well as in *H. pylori*-infected individuals, peripheral blood-derived T cells proliferated in response to stimulation with *H. pylori*-derived antigens, including whole bacterium [81] and crude membranes or cytoplasmic proteins [82]. However, others have shown that memory T cells derived from peripheral blood of infected individuals respond less to stimulation with *H. pylori*

Table 1 Defining features of T-helper, T-regulatory, and unconventional T cell populations

	T-helper cells		Regulatory T cells			Unconventional T cells	
	Th1 cell	Th2 cell	Th3 cell	Tr1 cell	Th17 cell	Natural killer T cell	Mucosal-associated invariant T cell
T-cell receptor α-chain	Heterogenous	Heterogenous	Heterogenous	Heterogenous	Heterogenous	Semi-invariant (Vα14/24-Jα18)	Semi-invariant (Vα7.2/19-Jα33
T-cell receptor β-chain	Heterogenous	Heterogenous	Heterogenous	Heterogenous	Heterogenous	Limited (Vβ2,7,8/11)	Limited (Vβ6/8)
Phenotype	$CD4^+$	$CD4^+$	$CD4^+$ and $CD8^+$	$CD4^+$ and $CD8^+$	$CD4^+$	$CD4^-CD8^-$or $CD4^+$	$CD4^-CD8^-$
Cytokines	IFN-γ, IL-2, & TNF-α	IL-4, IL-5, IL-9, & IL-13	TGF-β	IL-10	IL-17A, IL-17F, IL-22, IL-6, & TNF-α	IL-4 & IFN-γ	TGF-β & IFN-γ
Location	Blood, thymus, lymphoid organs, tissues	Blood, thymus, lymphoid organs, tissues	Gastric mucosa	Blood, thymus, lymphoid organs	Intestinal lamina propria	Thymus, spleen, liver, bone marrow, blood, gastric mucosa	Blood, intestinal lamina propria
Restriction	MHC class II	MHC class II	MHC class II	MHC class II	MHC class II	CD1d	MR1
Ligands	Peptide	Peptide	Peptide	Peptide	Peptide	Endogenous and exogenous lipids	Possibly peptides
Function	Immunity to intracellular bacteria and some viruses	Immunity to helminths and parasites	Immuno-regulatory, control of excessive responses to foreign antigen	Immuno-regulatory, control of excessive responses to foreign antigen	Immunity to extracellular bacteria	Anti-tumor, immuno-regulatory	Potential immunity to oral pathogens Gut IgA secretion Oral tolerance

IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; MR1, major histocompatibility complex class 1-related molecule; TGF, tumor growth factor; TNF, tumor necrosis factor.

antigens [83]. Subsequently, it was shown that removal of regulatory T cells (Treg cells, see below) restored the proliferative response to *H. pylori* [84]. In the human gastric mucosa, *H. pylori* induces recruitment of $CD4^+$ and $CD8^+$ T cells [85] and murine studies have shown that the gastric inflammation is T cell-dependent, as, experimentally, *H. pylori* does not induce gastritis in T cell-deficient mice [86]. Thus, there is evidence that T cell responses to *H. pylori* antigens are detectable in many individuals and that gastric T cell infiltration is important in disease pathogenesis.

The mucosal inflammation induced by *H. pylori* is believed caused by a polarization towards a Th1-dominated T cell response. Freshly isolated lymphocytes from *H. pylori*-infected mucosa were shown to have a Th1 cell phenotype (i.e. secreting IFN-γ) [87], and studies in IL-4- and IFN-γ-deficient mice confirmed the role of Th1 cells in perpetuating the development of inflammation associated with *H. pylori* infection [88]. Moreover, D'Elios et al. [89] showed that *H. pylori*-specific T cells with a Th1 phenotype (i.e. secreting IFN-γ) could be cloned from *H. pylori*-infected gastric mucosa and, through the production of IFN-γ, are cytotoxic to gastric epithelial cells. The production of IL-8 by infected gastric epithelial cells, which acts as a chemokine for neutrophils and an activating factor, plays a significant role in the initial response to *H. pylori* infection. Produced in response to bacterial products by phagocytic cells, such as neutrophils, the cytokine IL-12 is a potent inducer of naïve T cell conversion to the Th1 phenotype [90], and also neighbouring activated macrophages are potent producers of inflammatory IL-1, IL-6, IL-8, and TNF-α. Notably, the presence of *H. pylori* in gastric biopsies has been associated with strong production of IL-12 [91] and the concomitant presence of large numbers of Th1 cells [92]. Furthermore, increased levels of IL-17 [93] and IL-18 [94] have been found in the *H. pylori*-infected gastric mucosa. IL-18 is considered a strong promoter of Th1-cell proliferation by induction of IFN-γ secretion [95], and IL-17 can act as a potent inducer of neutrophil-recruiting IL-8 secretion during *H. pylori* infection [93]. Interestingly, the neutrophil-activating protein of *H. pylori* promotes the expansion of IFN-γ-producing cells (i.e. the Th1 phenotype) in antigen-stimulated T cell cultures, while decreasing the number of IL-4-secreting cells (i.e. the Th2 phenotype) [96]. Thus, the secretion of all of these inflammatory mediators creates a cytokine milieu that facilitates the polarization of the T cell response to a Th1 phenotype. The antigenic specificities of the T cell clones isolated from the *H. pylori*-infected mucosa have been extensively studied, and have revealed that CagA and *H. pylori* urease are the immunodominant antigens. Indeed, the majority of Th1 cell clones isolated from *H. pylori*-infected mucosa are specific for CagA with prominent production of IFN-γ, but not IL-4 [89]. Therefore, overall, there is an abundance of evidence confirming the presence and pathogenic potential of Th1 cells in *H. pylori* infection.

Polarization towards a Th1 cell cytokine profile can contribute to development of peptic ulcers and more severe mucosal pathology, while on the other hand, activation of a Th2 cell response results in amelioration of the dyspeptic symptoms. In particular, it has been suggested that the concomitant production of Th2 cell cytokines like IL-4 is protective against severe pathology, and curbs the detrimental effects of the Th1-related cytokines [80]. Consistent with this, T cells cloned from antral biopsies of patients with peptic ulcers associated with *H. pylori* infection produced large amounts of IL-12, IFN-γ, and TNF-α in vitro, but not IL-4 [97], whereas both IFN-γ and IL-4 were secreted by T cells from patients with nonulcer gastritis [89,98]. Moreover, in renal transplant patients receiving Th1 cell immunosuppression, it has been reported that peptic ulcers are absent from the gastric mucosa despite the presence of colonization with *H. pylori* [99]. Therefore, it has been deduced that an uncontrolled Th1 cell response to *H. pylori* infection results in persistence of inflammation and disease, whereas in contrast, a Th2-mediated response reduces the proinflammatory immune effects. Furthermore, it is now generally accepted that development of *H. pylori*-induced pathology largely depends on Th1 cell-mediated responses and Th1 cytokines [88,100–105]. This has been established in animal models using $IL\text{-}4^{-/-}$ and $IFN\text{-}\gamma^{-/-}$ mice [88], IFN-γ neutralization in a mouse model [100], adoptive transfer experiments in IL-4-deficient mice [101] and mice defective in Th1-cell development [103], as well as genetic evidence from human populations [104] and experiments on the modulation of the Th1 response from concurrent helminthic infection [102] and *Toxoplasma* infection [105]. Nonetheless, although a Th2-polarized response protects against such pathology, this does not imply that Th2 cells are responsible for protection against *H. pylori* infection after immunization [1]. Instead, Th1-polarized, rather than Th2-polarized, *H. pylori*-specific T cells recruit monocytes that can lead to elimination of *H. pylori* locally in the gastric mucosa and be protective against infection [106–108]. Akhiani et al. [106] observed in animal models that protection following immunization with *H. pylori* lysate was IL-12 dependent and mediated by Th1 cells. Similarly, Hafsi et al. [107] found that membrane preparations of *H. pylori* induced the Th1-polarized response and could account for the specific adaptive immune response. Nevertheless, although reducing the bacterial load, the induced Th1 cells can play a role in post-immunization gastritis [108].

Details of an important mechanism controlling Th1/Th2 polarization in *H. pylori* infection, and based on bacterial variation, have emerged more recently. The dendritic

cell-specific surface receptor, ICAM-3 grabbing nonintegrin (DC-SIGN, CD209), a C-type lectin, is found in gastric lamina propria or close to the gastric lumen during *H. pylori* infection [109] and can act as a ligand for the bacterium [110]. *H. pylori* activates dendritic cells and promotes their maturation in a *cag* PAI- and VacA-independent manner [111]. *H. pylori*-activated dendritic cells preferentially produce IL-12, and lesser amounts of IL-6 and IL-10, in contrast to most other extracellular bacteria [112]. The secreted IL-12, as well as *H. pylori* antigens [113], promotes NK-cell activation and induces a Th1 cell response [107]. *H. pylori* variants that express Lewis blood group antigens, which occur within the O-chain moiety of LPS [56], can bind to DC-SIGN and enhance the production of IL-10 which promotes a Th2 cell response and blocking of Th1 cell activation [110]. Since Lewis antigen expression is subject to phase variation [114], a significant proportion of Lewis-negative variants can occur within an isolate population of bacteria. Thus, a polarized Th1-effect can change to a mixed Th1–Th2 cell response through the extent of Lewis antigen–DC–SIGN interaction [110], thereby modulating the host response, and allowing a switch from an acute infection response to one that will allow chronic infection.

In summary, there is significant evidence that suggests that infection with *H. pylori* is associated with a polarized T cell response. Upon recognition of *H. pylori* antigens, the development of an uncontrolled Th1 cell response with the secretion of proinflammatory cytokines is centrally involved in promoting the chronicity of infection and associated with development of the more severe *H. pylori*-related pathologies. On the other hand, a Th2-mediated response reduces the proinflammatory immune effects. However, although inducing a post-immunization gastritis [108] because of a local delayed-type hypersensitivity response [100], evidence indicates that Th1 cells play a protective role against *H. pylori* infection.

Th17 Cells

More recently, a novel subset of effector T cells, called Th17cells because of their production of IL-17 [115], has been deduced to play a prominent role in the development of chronic inflammation associated with inflammatory [116] and autoimmune disorders [117]. Th17 cells are a distinct population of T cells (Table 1) that are induced under the influence of IL-23 (a cytokine that shares homology with IL-12) [118], as well as IL-6 and tumor growth factor beta (TGF-β) [119]. Th17 cells are a subset of $CD4^+$ T cells but differ from Th1 and Th2 cells by not expressing the Th1 transcription factor T-bet nor the Th2 transcription factor GATA-3 [120]. Nevertheless, Gocke et al. [121] showed that administration of interfering RNA specific for T-bet suppressed both Th1 and Th17 cells, thereby implying some role for T-bet in Th17 cell differentiation.

The production of IL-17 by these T cells stimulates a variety of cells including fibroblasts, endothelial cells, epithelial cells, and macrophages to secrete chemokines ultimately resulting in the recruitment of polymorphs, including neutrophils [122]. Therefore, while IL-17 is produced by cells of the adaptive response, this cytokine can function as a potent activator of innate immunity, and may participate in protective immunity against largely noninvasive bacteria, such as *H. pylori*. Such a role for IL-17 has been demonstrated in host defense against other bacteria, e.g. *Klebsiella pneumoniae* [123]. Likewise, human and murine T cells produce IL-17 upon stimulation with *Borrelia burgdorferi* [124] and *Mycobacterium tuberculosis* [125].

The emerging evidence also indicates a significant role for IL-17 in the development of inflammation [116], specifically, IL-17 induces expression of inflammatory mediators like IL-6 and prostaglandins [126], and Th17 cells have been implicated in the immunopathology associated with chronic inflammation [127]. Notwithstanding that the Th1-cytokine IFN-γ and the Th2-cytokine IL-4 inhibit the development of Th17 cells [128], Th17 cells, and Treg cells are likely to play antagonistic roles in chronic inflammation in the gut, including that induced by *H. pylori*, although TGF-β can induce the development of both populations [119]. Nevertheless, the interrelationship between Th17 cells and other effector T cell populations and Treg cell populations remains to be fully elucidated. Given the growing reports of the prominent association of IL-17 with a variety of other bacterial infections, it is likely that Th17 cells are involved in the response to *H. pylori*. Furthermore, due to the secondary impact of IL-17 from Th17 cells on neutrophil recruitment and the role of Th17 cells in chronic inflammation, it is apparent that Th17 cells have a potential role to play in *H. pylori*-induced inflammation, particularly because neutrophil influx and inflammation chronicity are both hallmarks of this infection. Clearly, however, a great deal further study is required to elucidate the mechanisms of *H. pylori* interaction with Th17 cells and the influence of these cells on the *H. pylori*-associated immune response.

Regulatory T Cells

Notably, while there is evidence of an infiltration of IFN-γ-producing cells into the infected gastric mucosa in *H. pylori* infection, this is also accompanied by infiltration of TGF-β-producing cells, thus suggesting that regulatory cytokines secreted by regulatory cells may counteract the effects of Th1 cells (i.e. IFN-γ producing) [129] (Fig. 1). In general, effector mechanisms and the development of inflammation in response to infection are controlled by a variety

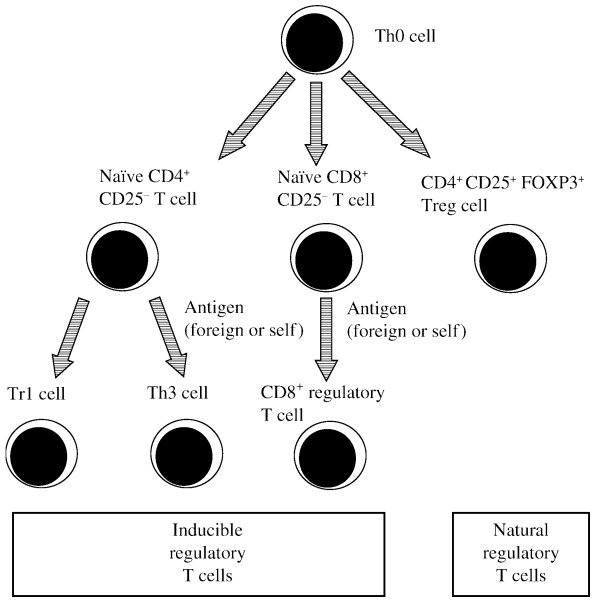

Figure 2 Natural and inducible regulatory T cells. The markers CD25 and Foxp3 (forkhead box P3) are expressed on natural regulatory T cell (Treg cells) that matures from a precursor T-helper cell (Th0 cell) in the thymus. Inducible regulatory T cells are generated in the periphery upon stimulation of naïve $CD4^+CD25^-$ and $CD8^+CD25^-$ with antigen. These inducible cell populations include Tr1 cells that secrete interleukin-10 (IL-10), Th3 cells that secrete tumor growth factor-beta, and IL-10-secreting $CD8^+$ regulatory T cells.

of different host suppressor mechanisms, including the generation of antigen specific regulatory T cells, the Treg cells (Table 1), whose existence has been the subject of much debate for many decades, and which have been reviewed extensively [130–133].

Phenotype and Function of Treg Cells

Treg cells can be isolated from mice and humans, and these cells have the capacity to suppress the activation of $CD4^+$ and $CD8^+$ T cells, NK cells, and B cells in vivo and in vitro. Treg cells are crucial for the maintenance of tolerance to self-antigens, food antigens, and normal intestinal flora, and for preventing the development of autoimmune diseases, enhancing antitumor responses and controlling infections (see reviews [130–133]).

Two major subpopulations of Treg cells, the so-called natural and inducible populations, exist [134] (Fig. 2). Natural Treg cells originate in the thymus and exit to the periphery constituting between 5% and 10% of all T cells [133,134]. On the other hand, Treg cells may be induced or generated in the periphery upon antigenic stimulation and under the influence of cytokines secreted by dendritic cells [134]. Naturally occurring Treg cells were first identified by Sakaguchi et al. in 1995 [135] as a population of $CD4^+$ T cells constitutively expressing the surface marker CD25 (i.e. $CD4^+CD25^+$ T cells), and that suppressed and prevented the development of T cell-mediated autoimmune disease in mice. Subsequently, other investigators identified additional markers associated with naturally occurring Treg cells and these include low expression of CD45RB [136], and expression of GITR [137] and CD134 (OX40) [138]. Notwithstanding this, many of these markers are not exclusively found on Treg cells. The expression of the transcription factor forkhead box P3 (Foxp3) is considered the most promising marker of natural Treg cells since transfection of T cells with the *foxp3* gene confers them with intracellular regulatory activity [139].

The suppressive function of Treg cells is mediated via the production of IL-10 as in the case of Treg cells named Tr1 cells [140], or TGF-β in the case of cells termed Th3 cells [141] (Fig. 1). The properties of Tr1 and Th3 cells are listed in Table 1. While Th2 cells also secrete IL-10 and may have regulatory function, they are distinguishable from Tr1 cells that do not secrete the characteristic Th2 cell cytokine, IL-4 [141]. Also, populations of $CD4^+$ Treg cells, $CD8^+$ γδ T cells [142], and NKT cells that are capable of secreting IL-10 [143] may also be categorized as Treg cells.

H. pylori and Treg Cells

As *H. pylori* colonization provokes a state of lifelong chronic infection [9], the concept that Treg cells are involved in actively suppressing the host immune response to *H. pylori* has been explored [84]. In support of this concept, *H. pylori* [144] and the related *H. felis* [145] are unable to persist in IL-10 knockout mice, and mice lacking Treg cells, $CD4^+CD25^+$ [146], and $CD25^+Foxp3^+$ [147] cells develop more severe gastritis while possessing reduced *H. pylori* bacterial loads in the gastric mucosa. Initial studies investigating the role of Treg cells in *H. pylori* infection have focused on T cells isolated from peripheral blood. Lundgren et al. [84] demonstrated that although stimulation of peripheral blood $CD4^+$ T cells from infected and noninfected humans occurred with an antigenic preparation of *H. pylori* in vitro, the memory T cells from infected subjects responded less compared than those of noninfected controls. Importantly, this nonresponsiveness to *H. pylori* was abolished upon removal of $CD4^+CD25^+$ Treg cells, indicating the relevance of these Treg cells in suppressing the proliferative response.

While these findings suggest an important role for Treg cells in responsiveness to *H. pylori*, investigations at the site of infection within the gastric mucosa are certainly of more importance pathophysiologically. To address the role of Treg cells at the site of *H. pylori* infection, Lundgren et al. [148] later demonstrated the presence of Treg cells that expressed the characteristic $CD4^+CD25^+$ T cell phenotype

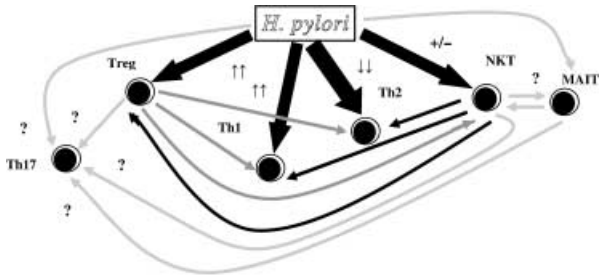

Figure 3 Potential complex interactions in the gastric mucosa of effector T cells, regulatory T cells, unconventional T cells, and *Helicobacter pylori*. *Key*: ↑↑, expansion; ↓↓, inhibition; +/–, activation or inhibition; black arrow, positive effect; gray arrow, negative effect, light grey arrow, effect unclear. *H. pylori* activates T-helper-1 (Th1) cell proliferation, promotes, and expands the numbers of regulatory T cells (Treg) cells, and inhibits T-helper-2 (Th2) cells. Certain populations of natural killer T (NKT) cells are activated in response to *H. pylori*-derived molecules, whereas others are inhibited. In turn activated NKT cells promote the expansion of Treg cells, while activated Treg cells suppress the functional activities of Th1, Th2, and NKT cells. Other interactions may exist. These include the responses of the mucosal invariant T cell (MAIT) and Th17 cells (Th17) to *H. pylori* and potential interrelationships between these populations and Th1, Th2, and Treg cells. For example, the Th1-cytokine interferon-gamma and the Th2-cytokine interleukin-4 inhibit the development of Th17 cells, whereas tumor growth factor-beta (a Treg cell differentiator) promotes their development.

and coexpressed high levels of Foxp3 mRNA. Moreover, $CD4^+CD25^+$ Treg cells have been shown to home and accumulate in the *H. pylori*-infected gastric mucosa [149], particularly in tumor compared to tumor-free gastric mucosa [150]. Hence, these pathogen-specific Treg cells have been associated with chronic infections by *H. pylori* and postulated to control the development of immunopathology [150]. Notwithstanding that the precise mechanisms of suppression have to be defined, suppression of local immune responses to *H. pylori* in the gastric mucosa may account for the persistence of the bacterial load and chronicity of infection (Fig. 3). Duodenal ulcers are considered to develop as a result of an increase in gastric acid production in response to *H. pylori* antral infection [151], ultimately leading to ulceration, whereas in contrast, adenocarcinoma develops after pangastritis and potent proinflammatory cytokine suppression of acid secretion [152] leading to atrophy and intestinal metaplasia with progression to malignant transformation [153]. It is likely that alterations in local suppressor cells, such as Treg cells, which control and regulate inflammation [133], as well as bacterial colonization [130], are central to the development of both of these diseases, and represents a hypothesis worthy of further investigation.

Thus, while it has been postulated that pathogen-specific Treg cells control and prevent the development of immunopathology associated with infection [132], these cells also may benefit the pathogen in helping to prolong the chronicity of the infection by suppressing protective immune responses. Such a phenomenon is seen in other bacterial infections (e.g. *Bordatella pertussis*) where pathogen-specific Treg cells suppress Th1 cell responses resulting in persistence of infection [154]. A similar phenomenon may also operate in other *Helicobacter* infections where Treg cells were reported to be expanded in numbers during *H. hepaticus* experimental infection but inhibited the development of intestinal inflammation [155]. In the case of *H. pylori*, the presence and activities of local gastric Treg cell populations may have implications in the suppression of protective immune responses and, thereby, contribute to maintenance of a chronic state of infection (Fig. 3).

Unconventional or Innate T Cells

Despite studies to date having focused largely on analysis of the response of classical T cells to *H. pylori* infection, the extent and the effectiveness of the so-called unconventional T cells within the gastric mucosa is likely to have an equally important role in determining clinical outcome. Besides conventional T cells that express T cell receptors (TCRs) with a very diverse repertoire, there are two evolutionarily conserved T cell subsets expressing invariant antigen-specific TCRs which are generated by a particular variable-joining (V-J) gene segment combination during ontogeny. These are the CD1d-restricted NKT cells and the mucosal-associated invariant T (MAIT) cells [156] (Table 1). These invariant T cell populations are often classified as innate cells because they display a memory T cell phenotype in the absence of antigenic stimulation and they respond rapidly to challenge [157].

NKT Cells and Microbial Immunity

The discovery of innate lymphocyte populations which share the characteristics of NK cells and classical T cells has generated great anticipation for better understanding early responses of the immune system [158]. Like conventional T cells, these NKT cells express a TCR but also coexpress cell-surface receptors that are characteristic of the NK cell lineage. In contrast to T cells, the majority of NKT cells express an invariant TCR alpha chain, encoded by *Vα14* and *Jα18* genes paired with variable *Vβ8*, *Vβ7*, or *Vβ2* genes [159] (Table 1). Furthermore, NKT cells recognize glycolipid antigens presented by CD1d [160] which is expressed on cells of hemopoietic origin (dendritic cells, B cells, and T cells) as well as on gastrointestinal epithelial cells [161]. With regard to function, NKT cells are activated very early in an immune response and are capable of activating a variety of cell types [162]. Upon stimulation they rapidly produce both IL-4 and IFN-γ and, thereby, influence the differentiation of T cells into either a Th1- or

a Th2-cytokine phenotype [163]. NKT cells display diverse effector mechanisms participating in tumor surveillance, regulation of autoimmune diseases, and in host defense against bacteria, viruses and protozoa [164]. Defects in the numbers and function of NKT cells have been reported in a variety of human diseases including advanced cancer [165], autoimmunity [166], and microbial infection [167].

NKT cells are activated by lipids such as α-galactosylceramide (α-GalCer) [160], a marine sponge-derived glycosphingolipid that has been used for anticancer therapeutic purposes. Injection of mice with α-GalCer can result in tumor rejection by a mechanism that is dependent on IFN-γ production and/or antitumor cytotoxicity by NKT cells [168]. An endogenous glycosphingolipid, isoglobotrihexosylceramide (iGB3) [169], is also capable of activating NKT cells.

In addition to an antitumor role, NKT cells have been shown to play a protective role in immunity to several different bacterial infections. The mechanisms of how this is achieved remain an open, but central, question. In some cases, mice lacking NKT cells or CD1d are more susceptible to certain pathogens. For example, Kumar et al. [170] showed that a deficiency of NKT cells results in an impaired immune response to *B. burgdorferi*. In other studies, NKT-cell activation was shown to ameliorate disease as in the case of lung infection with *Pseudomonas aeruginosa* [171] or *M. tuberculosis* [172]. The target microbial lipid antigens presented by CD1d to NKT cells have been the subject of close scrutiny, and bacterially derived glycosylceramides have been identified that can activate NKT cells. Mattner et al. [173] reported evidence for antigen-specific activation of NKT cells by glycosylceramides from Gram-negative, LPS-negative alpha-proteobacteria such as *Ehrlichia muris* and *Sphingomonas capsulate*, and Kinjo et al. [174] showed that glycosphingolipids from *Sphingomonas* served as targets for activation of NKT cells. Moreover, activation of NKT cells by Gram-negative, LPS-positive *Salmonella typhimurium* was mediated through an endogenous lysosomal glycosphingolipid, iGB3 presented by dendritic cells [169]. Though not identical, this bears some resemblance to T cell CD1d-restricted recognition of self-glycolipids presented on dendritic cells that have been stimulated by a range of bacterial products, including LPS [175].

H. pylori and NKT Cells

Novel populations of T cells expressing the NK cell markers CD56, CD161, and CD94 have been observed in antral biopsy specimens from adult human gastric mucosa [176,177]. These NKT cells account for 14–35% of the T-cell population in the epithelial layer and for 16–25% of T cells in the lamina propria of the gastric mucosa [176]. This represents a sizeable T-cell subset suggesting a function for these cells in local immunity. Of note, marked differences in the frequencies of NKT-cell populations occur in *H. pylori*-infected individuals when compared with noninfected controls [177,178]. The numbers of these cells expressing CD56 and CD94 in both the epithelium and the lamina propria layers of the mucosa were reduced in infected individuals, whereas cells expressing CD161 were increased [177], indicating potential functional differences between these NKT cells in response to *H. pylori* infection. Moreover, in vitro stimulation with differing *H. pylori* LPS preparations can result in expansion or reduction in these NKT populations [178], further emphasizing differing functional roles.

Given the abundance of NKT cell populations in the normal antral mucosa, the observed changes in the frequencies of NKT cell subsets in *H. pylori* infection, and the central role of these T cells in antitumor immunity [179], changes in the number and/or the functional responses of NKT cells to *H. pylori* may influence the development of localized malignancy in the gastric mucosa. Nonetheless, as a T cell population in the gastric niche of *H. pylori,* NKT cells are likely involved in the initial cellular response to *H. pylori* and may play an important role in the outcome of bacterial colonization [167] as seen with infections at other body sites, such as the lungs [171].

As Treg cells and NKT cells are central to the immunoregulation required for controlling pathogenic autoreactivity and for maintaining homeostasis following infection, their interactions also raise issues pertinent in *H. pylori* infection. These populations of T cells share some similarities, but are phenotypically and functionally different (Table 1). Nevertheless, there are reports highlighting potential cross-talk between these cells [180]. Specifically, NKT cells have the potential to regulate the functional activities of Treg cells through IL-2-dependent mechanisms [181]; the IL-2 produced by activated NKT cells can promote proliferation and expansion of Treg cells, whilst having no effect on the suppressive activities of these cells. On the other hand, activation of NKT cells has been demonstrated to control Treg cell function in autoimmunity [182]. Conversely, Treg cells can control the functional activities of NKT cells by suppressing the proliferation, cytokine secretion, and cytotoxic activities of these cells [183]. Thus, it can be speculated that NKT cells and Treg cells reciprocally regulate each other in *H. pylori*-infected mucosa (Fig. 3). Bearing in mind that Treg cells have a suppressive role in antitumor immunity [184] and NKT cells promote tumor surveillance [185], the direct effects, as well as the interactions between these T cells, may greatly influence the development of *H. pylori*-associated gastric cancer. Hence, investigations examining the local activities of NKT cells and Treg cells and their responses to infection

with *H. pylori* would greatly enhance our understanding of immunity to this gastric pathogen and infection outcome.

MAIT Cells

MAIT cells are another group of phylogenetically conserved T cells [186] (Table 1). They were first described by Porcelli et al. [187], who found T-cells expressing another invariant TCR alpha-chain, Vα7.2-Jα33, among human peripheral blood T cells. MAIT cells are most abundant in the intestinal mucosa, specifically in the lamina propria, and are virtually absent from the intestinal epithelium [188]. The restricting element for MAIT cells has been identified as the monomorphic MHC class 1-related (MR1) molecule [189]. MAIT cells are absent in mice deficient for this molecule, but are present in mice deficient for MHC class I and class II molecules and in CD1d-deficient mice [190]. The function of MAIT cells is unknown, but their preferential localization in the intestinal lamina propria suggests that they are involved in host defense mechanisms [188]. In particular, MAIT cells can have a role in defence against orally acquired pathogens and in oral tolerance [186]. Moreover, their interaction with other immune cells in the gut could result in the polarization of the immune response to a Th1, Th2, or a Th3 phenotype or in controlling local IgA production [191], and would have importance in influencing both the cellular and the humoral responses in *H. pylori* infection. Importantly, the high numbers of MAIT cells occurring in the human gut and the invariance of their TCR alpha-chain suggests that these cells have such important roles [188]. Though not yet defined, a dysfunction of MAIT cells would affect disease development, including those associated with *H. pylori* infection.

One study has shown that α-mannosylceramide-activated these cells [192], but the antigen-binding groove appears unsuitable for binding hydrophobic lipids or glycolipids, and is more likely suitable for binding hydrophilic peptides [189]. Compared with colonized mice, MAIT cells are undetectable in germ-free animals, indicating that the presence of commensal bacteria appears to be essential for the expansion of MAIT cells in the intestine after birth [191]. Since commensal bacteria and those causing chronic infections share properties [38] and mechanisms [193] to subvert and modulate the immune response and aid longterm colonization, whether infection with *H. pylori* influences proliferation of MAIT cells remains an open question (Fig. 3).

Concluding Remarks

In summary, infection with *H. pylori* results in the development of robust innate and adaptive host immune responses characterized by a marked inflammatory response with an influx of neutrophils and lymphocytes [3,8]. However, this response seldom results in natural clearance of infection. Moreover, it can be argued that much of the pathology associated with *H. pylori* infection results from the host's immune response rather than the direct action of the bacterium or its pathogenic factors. The innate response towards *H. pylori* infection is an initial, rapid response involving recognition of various PAMPs. SP-D binding can play an important role in initial defense against the infection, but once colonization becomes established and bacterial interaction occurs with gastric epithelial cells, the Nod1-mediated interaction would appear more important for the induction of the inflammatory response than TLR4- or TLR5-mediated responses. Although *H. pylori* molecules interact with TLR4 and TLR5 that are expressed in the stomach, these interactions are of low activity, thereby allowing *H. pylori* colonization. Subsequently, with infection progression, a substantial inflammatory response to *H. pylori* can develop after the infiltration of TLR2-expressing granulocytes and monocytes into the infected gastric mucosa.

The adaptive immune response to *H. pylori* is delayed, antigen-specific, and leads to the activation of T, B, and memory cells, but is influenced by the innate immune response. The humoral response is characterized by the presence of large numbers of antibody-producing cells and the T cell response is skewed toward Th1 cells. This adaptive immune response is initiated and maintained by monocytes and related cells because of their production of IL-12 which induces differentiation of naïve T cells to Th1 cells. Nevertheless, *H. pylori* neutrophil-activating protein [96] and outer membrane preparations [194] are capable of inducing this Th1-polarization, and there are concomitant increases in the Th1-promoting cytokines, IL-12, IL-17, and IL-18 during infection. The development of an uncontrolled Th1 cell response with the secretion of proinflammatory cytokines is centrally involved in promoting the chronicity of *H. pylori* infection and is associated with development of the more severe *H. pylori*-related pathologies. Induction of a Th2-mediated response reduces the proinflammatory immune effects. Though inducing a postimmunization gastritis [108] because of a local delayed-type hypersensitivity response [100], evidence indicates that Th1 cells play a protective role against *H. pylori* infection. As systemic adjuvants commonly used in human vaccines, such as aluminium hydroxide, induce Th2-type immune responses preferentially [195], for successful vaccine development a challenge exists to utilize new adjuvants and develop immunization protocols that would promote a Th1-type immune response toward *H. pylori* infection in humans [196].

On the one hand, the ubiquity and duration of immune recognition of *H. pylori*, but potential lifelong colonization on the other hand, demonstrate the effectiveness of the bacterium to evade, dampen, or inhibit host responses contributing to immunity [13,38]. One such mechanism of the bacterium is the secretion of a low-molecular-weight protein from *H. pylori* which, although allowing antigen-specific activation of T cells, is capable of inducing cell cycle arrest of such cells [197]. Also, the inability to clear *H. pylori* infection may be linked to the activation of Treg cells which have the capacity to inhibit activation of Th1 cells, thereby limiting mucosal damage but at the same time prolonging the persistence of the pathogen. Consistent with this hypothesis, increased numbers of gastric $CD4^+Foxp3^+$ Treg cells have been found in the *H. pylori*-infected mucosa and are capable of suppressing *H. pylori*-induced Th1 cell proliferation and IFN-γ production [150]. Thus, pathogen-specific regulatory T cells can control and prevent the development of immunopathology associated with *H. pylori* infection, but these cells can also benefit the bacterium in helping to prolong the chronicity of the infection by suppressing protective immune responses. Given that *H. pylori* is a pathogen that possesses several evasion strategies [13], the responses of the selected T cell populations and subsets which recognize *H. pylori* will determine the outcome of infection and which other immune cells and mechanisms are mobilized into defense.

Overall, there are a number of outstanding questions concerning the interrelationships between the various T-cell populations and their responses to *H. pylori* (Fig. 3). As a T-cell population Th17 cells have be classified as part of adaptive immunity, but they play an important role in mobilization of acute inflammation and neutrophilic responses to extracellular bacteria, as well as in maintenance of epithelial layer barrier integrity [120]. Already, Th17 cells have been implicated in defense against extracellular bacteria such as *Klebsiella* [123] and *Citrobacter* [198]. Since IL-17 induces a neutrophilic influx [122] and contributes to the development of chronic inflammation [127] but also induces growth, differentiation, and junctional integrity of epithelial cells, the potential role of this cytokine and Th17 cells in response to *H. pylori* needs to be explored, particularly in a defensive role at the epithelium and in maintaining epithelial barrier integrity.

NKT cells are well-recognized cells of the immune system through their capacity to rapidly kill targets and by potent cytokine secretion without prior need for extensive cell division. Through their invariant TCRs, NKT cells preferentially recognize glycolipids and these cells have been implicated in protective roles in a number of bacterial infections [170–172]. It is likely that they play an important role in *H. pylori* infection and that modulation of acyl chain expression in *H. pylori* lipids could influence NKT cell recognition or activation. Nonetheless, the relationship between NKT cells and Treg cells in the gastric mucosa requires examination. Since NKT cells promote cancer surveillance [185], whereas Treg cells have a suppressive role in such immunity [184], the possibility of interaction between these T cells during *H. pylori* infection and their influence on infection outcome remains an open question. What possible roles do other innate T cells, such as MAIT cells, have in the gastric mucosa? Are they involved in maintenance of tolerance or do they contribute to the development of pathology? Collectively, the intimate links between Th1, Th2, and these other T-cell populations remain to be defined. A clear understanding of the mechanisms that *H. pylori* may use to suppress these interactions would give valuable insights into how this bacterium counteracts the host immune responses to perpetuate chronic infection and could reveal new strategies for therapeutic exploitation.

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