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***Helicobacter pylori* Deregulates T and B Cell Signaling to Trigger Immune Evasion**

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Abstract

Helicobacter pylori is a prevalent human pathogen that successfully establishes chronic infection, which leads to clinically significant gastric diseases including chronic gastritis, peptic ulcer disease (PUD), and gastric cancer (GC). *H. pylori* is able to produce a persistent infection due in large part to its ability to hijack the host immune response. The host adaptive immune response is activated to strategically and specifically attack pathogens and normally clears them from the infected host. Since B and T lymphocytes are central mediators of adaptive immunity, in this chapter we review their development and the fundamental mechanisms regulating their activation in order to understand how some of the normal processes are subverted by *H. pylori*. In this review, we place particular emphasis on the CD4⁺ T cell responses, their subtypes, and regulatory mechanisms because of the expanding literature in this area related to *H. pylori*. T lymphocyte differentiation and function are finely orchestrated through a series of cell–cell interactions, which include immune checkpoint receptors. Among the immune checkpoint receptor family, there are some with inhibitory properties that are exploited by tumor cells to facilitate their immune evasion. Gastric epithelial cells (GECs), which act as antigen-presenting cells (APCs) in the gastric mucosa, are induced by *H. pylori* to express immune checkpoint receptors known to sway T lymphocyte function and thus circumvent effective T effector lymphocyte responses. This chapter reviews these and other mechanisms used by *H. pylori* to interfere with host immunity in order to persist.

1 Introduction

Helicobacter pylori is a Gram-negative bacterium within the class of ϵ -proteobacteria, Campylobacterales order, and is a primary constituent of the human gastric microbiome. *H. pylori* is an important human pathogen that frequently infects during childhood and successfully establishes chronic infection in >66% of the world's population (www.CDC.gov). *H. pylori* is involved in significant clinical gastroduodenal disorders that include chronic gastritis, peptic ulcer disease (PUD), and two malignancies: gastric adenocarcinoma (GC) and mucosa-associated lymphoid tissue (MALT) lymphoma. GC remains as the third deadliest cancer worldwide with a five-year survival rate of 14% and accounts for approximately one million deaths (www.who.int; 2017 Fact Sheet).

Important to *H. pylori*'s capacity to establish chronic infection is its ability to evade or subvert innate and adaptive immune responses via multiple mechanisms. One of the earliest clues that *H. pylori* subverts the adaptive host response was the observation that CD4⁺ T cell responses in the infected gastric mucosa were polarized to T helper (Th) 1 cells (Bamford et al. 1998b; Amedei et al. 2006), which are not optimal for extracellular bacteria as *H. pylori*. As we have studied in detail the mucosal immunity to *H. pylori*, we have gained insights that helped us to better understand how *H. pylori* induces a diverse T cell response that includes Th1, Th17, and T regulatory (Treg) cell responses. In this chapter, we will examine the following:

- A comprehensive background on the adaptive immune response. To better appreciate how those responses are altered during *H. pylori* infection, we will start by discussing the normal development of B and T lymphocytes and their activation processes and provide a brief description of the various CD4⁺ T cell subsets.
- Extracellular receptor–ligand interactions and intracellular signal involvement.
- Finally, we will examine how these cells are affected by *H. pylori* infection, either directly or indirectly, by other cells affected by the infection—including the gastric epithelium. Most of the discussion will be on T cell activation, as another chapter in this book (Chapter “MALT Lymphoma as a Model of Chronic Inflammation-Induced Gastric Tumor Development”) will provide a rich discussion of B cells, as they are the target in mucosal-associated lymphoid tissue (MALT) lymphoma.

2 B and T Lymphocyte Development

Lymphocytes are central players in the adaptive immune response, and, as are all other blood cells, they emerge during hematopoiesis from pluripotent hematopoietic stem cells (HSCs) that reside in bone marrow (Fig. 1). Hematopoiesis is a unidirectional process in which all immune cell types are generated from multipotent HSCs. Immune cells must be continuously replaced because of their limited life span, but also in response to infectious and inflammatory stimuli, by using receptors for cytokines and chemokines, as well as pathogen-associated molecular pattern (PAMP) recognition receptors (Chiba et al. 2018; Pachathundikandi et al. 2013). HSCs reside in the bone marrow microenvironment composed by osteoblasts, perivascular cells, endothelial cells, and immune cells, all of which promote HSCs proliferation through an array of cytokines like CXCL12 and stem cell factor (SCF). The differentiation of lymphocytes follows a tightly regulated process that initially transits through common lymphoid progenitor (CLP) cells (Kondo et al. 1997) that are CD34⁺, CD10⁺, CD45RA⁺, and CD24[−] and are devoid of surface markers characteristic of T-, B-, or NK cells. CLP cells also contribute to the development of NK cells and subsets of dendritic cells (DCs). As B and T lymphocytes develop in the bone marrow and thymus, respectively, under the influence of local interactions and cytokines, they start to express distinctive surface markers, as detailed below for each lymphocyte population.

2.1 B Lymphocyte

B cells differentiate from CLPs in the bone marrow through a series of closely controlled stages, initially as progenitor B (pro-B) cells ($CD34^+ CD19^+ CD10^+ TdT^+ CD38^{++} CD20^-$) when heavy chain immunoglobulin (Ig) V(D)J DNA rearrangement begins with a process that involves the recombination-activating genes (RAG) 1 and 2, as well as terminal deoxynucleotidyl transferase (TdT) enzymes. Once successfully rearranged, the Ig heavy chain forms a complex with surrogate light chains to give rise to a pre-B cell receptor in precursor B (or pre-B) cells ($CD34^- CD19^+ CD10^+ CD38^+ \text{cytIgM}^+ CD20^\pm$). Signaling through this pre-B cell receptor induces light chain DNA rearrangement which induces membrane-bound Ig. Once B cells express surface IgM, they are known as immature B cells ($CD34^- CD19^+ CD20^+ CD38^+ CD40^+ \text{sIgM}^+$) and subsequently express IgD, and are regarded as naïve mature B cells in the periphery. The final differentiation of B cells into Ig-secreting plasma cells occurs in the lymph nodes and other secondary lymphoid organs after activation by engagement of the surface Ig also known as (aka) B cell receptor (BCR) with antigen and the interaction of CD40 on their surface with CD154 on Th cells (Lou et al. 2015).

2.2 T Lymphocyte

As with B lymphocytes, T cells have their origin in the bone marrow and share the CLP precursor, but their development occurs within the thymus following migration of CLP cells to this organ. Thymocyte precursors ($CD4^- CD8^- CD7^+ CD45^+$) interact with stromal cells in the thymic cortex, where most thymocytes begin to rearrange their T cell receptor (TCR) β chain loci. After the β chain locus is productively rearranged and the corresponding protein expressed, this protein forms a complex with a surrogate α chain (pre-T α) and creates a complex with CD3 (von Boehmer 2005). When this complex is formed, the cells differentiate into double positive (DP, $CD4^+ CD8^+$) thymocytes and rearrange their α chain loci to eventually express TCR $\alpha\beta$ on their surface. In addition to the α and β chain loci, there are γ and δ TCR loci, but only about 3–10% of thymocytes rearrange their $\gamma\delta$ TCR loci (Weiss et al. 1986). Once thymocytes express their TCR, they undergo positive selection in the thymic cortex where the cells that recognize antigen with the corresponding class I or II human leukocyte antigen (HLA aka major histocompatibility complex, MHC) molecules with appropriate affinity survive, while those that fail to recognize antigen die by apoptosis. The surviving cells migrate to the thymic medulla where they experience another selection step. In the medulla, thymocytes interact with antigen-presenting cells (APCs: DCs and macrophages) which present self-antigens bound by (HLA) molecules and those thymocytes with a very strong affinity die by apoptosis, while those that survive downregulate either their CD4 or CD8 co-receptor to become single positive T cells (for a review see Takaba and Takayanagi 2017). The cells that emerge from the thymus into the periphery are naïve T cells that will differentiate further into distinct subsets following activation, as described below.

Although the role of the thymus in T cell differentiation, maturation, and expansion has long been recognized, extrathymic T cell differentiation and maturation have been reported in mice and humans (Lefrancois and Puddington 1995; Bandeira et al. 1991; Howie et al. 1998). Sites that have been shown to support extrathymic T cell differentiation include the

gut and tonsils (Howie et al. 1998; McClory et al. 2012). It is important to bear in mind that the gut harbors the largest number of T cells in the body, where they are exposed to the largest possible antigenic challenge that includes dietary antigens and the gut microbiome. Interestingly, the gastrointestinal tract also holds unconventional populations of T cells such as intraepithelial lymphocytes (IEL), which represent an effector T cell population reported to develop extrathymically (Fichtelius 1967), as supported by their presence in athymic mice (Bandeira et al. 1991). The gastric epithelium has 5–8 IEL cells per 100 epithelial cells, and these numbers increase up to sixfold during disease states, such as gastritis (Feeley et al. 1998; Hayat et al. 1999). These cells express a CD8 $\alpha\alpha$ homodimer, rather than the conventional CD8 $\alpha\beta$ heterodimer expressed by peripheral T cells selected in the thymus (Ruscher et al. 2017).

After their selection in the thymus, T lymphocytes enter the circulation and travel to secondary lymphoid organs. Migration of lymphocytes to those secondary lymphoid organs hinge on their surface expression of L-selectin (CD62L), the integrin leukocyte function antigen-1 (LFA-1, $\alpha\text{L}\beta\text{2}$), and the CC chemokine receptor (CCR)7 (von Andrian and Mackay 2000), which permit rolling, adhesion, and extravasation of T cells through high endothelial venules in secondary lymphoid organs (lymph nodes and mucosal lymphoid organs). In those secondary lymphoid organs, they may become activated by APCs. Activated T cells expand and become either effector or memory T cells. Newly activated T cells may migrate to other tissues and specific adhesion molecules, and chemokine receptors enable them to home and bind the corresponding ligands in those tissues. For instance, T cells that migrate to the gastrointestinal mucosa require the integrin $\alpha\text{4}\beta\text{7}$, LFA-1, and CCR9 (Michetti et al. 2000; Quiding-Jarbrink et al. 2001; Berlin et al. 1993; Zabel et al. 1999; Johansson-Lindbom et al. 2003). An important factor that determines what adhesion molecules are expressed by activated T cells is the site where they encounter antigen (Stagg et al. 2002). For instance, $\alpha\text{4}\beta\text{7}$ expression by gastric and intestinal T cells allows them to home and bind to mucosal addressin cell adhesion molecule 1 (MAdCAM-1) expressed by high endothelial venules in the Peyer's patches and gut lamina propria (Michetti et al. 2000; Williams and Butcher 1997; Hatanaka et al. 2002).

3 B and T Lymphocyte Activation

B and T lymphocytes perform a daunting mission of recognizing from a vast universe of antigens those that are foreign to us and respond to them rapidly and specifically in spite of a very noisy background of self-antigens. The events that lead to their activation are carefully orchestrated and involve a series of extracellular signals provided via cell–cell interactions and cytokines that in turn activate intracellular signals leading to activated B and T lymphocytes. Because the events that lead to fully functional B and T lymphocytes are critical in adaptive immune responses, we will review those events below with a particular emphasis on T lymphocytes, since B lymphocytes are discussed in more detail in Chapter “MALT Lymphoma as a Model of Chronic Inflammation-Induced Gastric Tumor Development” of this book.

3.1 B Lymphocyte

Naive B lymphocytes have approximately 1.5×10^5 membrane-bound antibodies (IgM and/or IgD) that serve as B cell receptors (BCRs) to bind soluble antigens (Maddaly et al. 2010). Activation requires cross-linking of multiple monomer membrane-bound antibodies (Harwood and Batista 2010). The activation of B cells varies depending on the type of antigen and interaction with T cells. Some antigens do not require contact with T helper cells and are thus referred to as T-independent antigens. An example of these antigens is bacterial lipopolysaccharides (LPS), which at high concentrations may activate mature and immature B cells. However, the characteristic response to these antigens is “weak” in terms of antibody production and memory response and frequently results only in IgM secretion. The lack of co-stimulation (CD40L) is thought to be the reason why these antigens fail to induce class switching and increased antibody affinity (Maddaly et al. 2010). Other antigens require interaction of co-stimulatory receptors and cytokines from Th cells with B cells (acting as APCs). The co-stimulation between these cells typically occurs in secondary lymphoid organs. The binding of antigen by B cells leads to clustering of membrane-bound antibodies, and their subsequent dimerization and internalization into endosomal vesicles. Then, those B cells present peptide-laden HLA class II complexes to T cell receptors (TCRs) on antigen-specific T cells. This interaction promotes expression by B cells of the co-stimulatory molecules B7-1 (CD80) and B7-2 (CD86) which facilitate differentiation of Th cells. Activation of T cells leads to their expression CD40L which interact with CD40 on the B cells to promote their entry into the S phase. In addition, cytokines such as IL-2 and IFN- γ (Th1), and IL-4, IL-5, IL-6, IL-10, IL-13 (Th2) promote clonal expansion, antibody production, and isotype switching (from IgM to IgG) followed by differentiation into plasma cells and memory B cells (Harwood and Batista 2010).

3.2 T Lymphocyte

3.2.1 Antigen Presentation—Presentation of foreign antigens refers to the display of antigens to T cells by antigen-presenting molecules [human leukocyte antigen (HLA) class I, HLA class II or CD1] after those antigens have been appropriately processed by APCs. Antigen processing and presentation provide the host with a mechanism to constantly survey the cellular internal and external environments for the presence of potential pathogens. There are four possible pathways involved in the processing of protein antigens for presentation by either class I or class II HLA molecules. Classical antigen processing pathways include the exogenous and endogenous pathways, but autophagy and cross-presentation have expanded the possible pathways whereby antigens are processed. The location of the antigens or, in the case of replicating pathogens, the life cycle of a given pathogen determines which pathway is needed for appropriate presentation to the appropriate T cell type (CD4⁺ versus CD8⁺). In the case of pathogens that replicate within the cell, and whose antigens are thus synthesized endogenously, they are degraded in the cytosol into small peptides, 8–10 amino acids long, by the proteasome complex and are delivered to the lumen of the endoplasmic reticulum (ER), where nascent HLA class I molecules bind them for eventual presentation to cytotoxic CD8⁺ T cells. In contrast, pathogens such as *H. pylori*, that replicate in the extracellular milieu, or are exogenous to the APCs, have to be endocytosed and their protein antigens processed by thiol proteases in endocytic compartments to generate peptides that will bind to

HLA class II molecules for presentation to CD4⁺ T cells (for a review, see Blum et al. 2013). More recently, autophagy and cross-presentation have been described as alternative pathways that break away from the classical pathways since autophagy captures endogenously produced antigens and delivers them to endocytic compartments where exogenous antigens are processed. Recent studies have reported that highly virulent strains of *H. pylori* noticeably affect autophagy in host GECs and macrophages (Castano-Rodriguez et al. 2015). On the other hand, cross-presentation results from the delivery of exogenously acquired antigens into the cytosol where they are processed by the proteasome and the resulting peptides are delivered to the ER lumen where they bind newly formed HLA class I (Van Kaer et al. 2017; Joffre et al. 2012).

CD1 molecules represent another group of relatively non-polymorphic antigen-presenting proteins whose genes are not present within the MHC region. In fact, CD1 are encoded in an entirely different chromosome. While human HLA genes are encoded in chromosome 6, human CD1 genes are encoded in chromosome 1. There are four human CD1 proteins (CD1a to CD1d) that also associate with β 2-microglobulin. These molecules are expressed by classical APCs, and CD1d is strongly expressed by GECs. Although CD1 molecules also present antigens and their crystal structure resembles that of class I HLA molecules (Blumberg et al. 1995), they differ from class I and II HLA molecules in that they do not bind peptide antigens. Instead, CD1 molecules bind and present lipids, because their antigen binding pocket has a narrow opening, is deep, and is lined by hydrophobic residues (Ly and Moody 2014). CD1 molecules may present lipid antigens to a diverse group of T cells that include $\gamma\delta$ TCR or $\alpha\beta$ TCR expressing T cells, as well as invariant NK T cells (iNKT) (Adams 2014). A study by Ito et al. (2013) showed that *H. pylori* cholesteryl α -glucosides are recognized by iNKT in the stomach, which contributes to the inflammatory response that limits *H. pylori* infection (see also Chapter “The Sweeping Role of Cholesterol Depletion in the Persistence of *Helicobacter Pylori* Infections” of this book).

3.2.2 Antigen-Presenting Cells—T cells are activated by APCs able to internalize foreign antigens and process them for presentation to the T cells. Because of their role in T cell activation, APCs are crucial in orchestrating the adaptive immune response. While most nucleated cells express HLA class I molecules, the cells that are classically referred to as professional APCs are those that express HLA class II and include DCs, macrophages, and B cells. In addition to expressing class II HLA, another important feature of these cells is their expression of the co-stimulatory molecules CD80 and CD86, whose engagement of CD28 on T cells is vital for activation of naïve T cells. Interestingly, in the gastric environment, GECs represent a non-classical APC-type, as they constitutively express class II HLA, CD80, CD86, CD74, the antigen processing cathepsins, and newer members of the B7 family, as described below (Ye et al. 1997; Fan et al. 1998, 2000; Barrera et al. 2001, 2002, 2005; Beswick et al. 2004, 2007a; Das et al. 2006). The expression by GECs of class II HLA, CD80, CD86, and CD74 increases during infection with *H. pylori* (Ye et al. 1997; Fan et al. 1998, 2000; Beswick et al. 2004, 2005). Furthermore, a recent study showed that GECs express retinoic acid, which is responsible in the induction of $\alpha_4\beta_7$ integrin and the CCR9 chemokine receptor on both CD4⁺ and CD8⁺ T cells, which in turn facilitates their homing to the gastrointestinal mucosa (Bimczok et al. 2015). It is worth noting that retinoic

acid also influences the homing to the gastrointestinal mucosa of IgA-secreting B cells (Mora and von Andrian 2009).

3.2.3 T Cell Receptor Signaling—The recognition by the TCR of antigen-laden MHC molecules on the surface of APCs leads to the formation of an immunological synapse between both cell types (Huppa et al. 2003), but this interaction alone is insufficient to lead to T cell activation since the short cytoplasmic tail of TCRs does not allow them to deliver intracellular signals. TCR interacts closely with a complex of other membrane proteins on T cells, that are collectively referred to as CD3 (including γ -, δ -, ϵ -, and ζ -subunits). After TCR engagement of peptide-laden MHC molecules, the cytoplasmic domains of CD3 subunits are responsible for delivering intracellular signals. Further, CD4 and CD8 bind to conserved membrane proximal domains on the β 2-domain of MHC class II (Cammarota et al. 1992) and α 3 of class I MHC molecules (Devine et al. 1999), respectively. The cytoplasmic domains of CD4 and CD8 bind the Src family kinase LCK (lymphocyte-specific protein tyrosine kinase), which in turn phosphorylates the immunoreceptor tyrosine-based activation motifs (ITAMs) within the cytoplasmic domains of CD3 subunits (Love and Hayes 2010). Phosphorylation of CD3 subunits directs the recruitment of zeta-chain-associated protein kinase of 70 kDa (ZAP70). After ZAP70 is activated, it phosphorylates the linker for activation of T cells (LAT) and Src homology 2 domain-containing 76 kDa leukocyte protein (SLP76). A series of signaling proteins are recruited, leading to calcium mobilization, actin cytoskeleton reorganization, and activation of Ras guanosine triphosphate hydrolases (GTPases). As a consequence of these signaling processes, various transcription factors are activated, including nuclear factor- κ B (NF- κ B), activator protein 1 (AP-1), and nuclear factor of activated T cells (NFAT), which aid in directing T cell responses.

3.2.4 Co-stimulation/Co-inhibition—In addition to the signals delivered by the CD3 complex after TCR recognition of antigen, T cells must receive co-stimulation via engagement of CD28 on their surface with CD80 or CD86, also, respectively, known as B7-1 and B7-2, on the surface of APCs. Engagement of CD28 on T cells is essential for T cell activation since in the absence of the signals delivered via CD28 after binding its ligand on APCs T cells become anergic, as shown in experiments with anti-CD28 blocking antibodies (Harding et al. 1992). The intracellular signals delivered by CD28 prevent this anergic state, and they include the Tec family kinases ITK/EMT, Rlk, and Itk, as well as phosphatidylinositol 3-kinase (PI3K) (August et al. 1994; Schaeffer et al. 1999; Pages et al. 1994). The signals delivered via CD28 affect crucial events in T cells, such as transcriptional signaling, post-translational protein modifications, cytokine synthesis, and epigenetic changes that ultimately affect their phenotype and function. The ligands for CD28, CD80, and CD86 vary in their expression pattern. CD86 is constitutively expressed on APCs and is upregulated quickly during immune responses, whereas CD80 is slower in its upregulation (Lenschow et al. 1994). Both of these receptors are expressed by GECs and are upregulated during *H. pylori* infection (Ye et al. 1997). The studies by Ye et al. showed that CD86 expression was higher on GECs from *H. pylori*-infected gastric biopsy tissues compared with those from uninfected subjects (Ye et al. 1997). Another member of this family of receptors and ligands is the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) which is

expressed on activated T cells and acts as an immune checkpoint inhibitor. CTLA-4 competes for the same receptors, CD80 and CD86, and binds with higher affinity to antagonize CD28, and thus acts to provide inhibitory signals (Walunas et al. 1994). Furthermore, CTLA-4 is a key mediator of Treg function (Friedline et al. 2009). The next members of this family of immunoregulatory receptors identified, that are not constitutively expressed on resting T cells, but are induced following activation, include inducible co-stimulator (ICOS, CD278) and programmed death-1 receptor (PD-1, CD279), which provide co-stimulatory or co-inhibitory signals, respectively. The corresponding co-receptor for ICOS is ICOS-L (aka B7-H2, CD275), while PD-1 may bind two separate co-receptors: programmed death ligand-1 (PD-L1) (aka B7-H1, CD274) and PD-L2 (aka B7-DC, CD273) (Fig. 2). Interestingly, PD-L1 may also bind CD80 to deliver inhibitory signals (Park et al. 2010). PD-1 binding to any of its co-receptors results in dephosphorylation and inactivation of ZAP70 and the recruitment of Src homology 2 domain-containing tyrosine phosphatase 2 (SHP2) (Yokosuka et al. 2012), which in turn causes dephosphorylation of PI3K leading to activation of Akt (Boussiotis et al. 2014). Ligation of PD-1 may also prevent extracellular-signal-regulated kinase (ERK) activation, which may be rescued via signaling activated by exogenous IL-2, IL-7, and IL-15 (Bennett et al. 2003). The engagement of PD-1 on T cells also inhibits their cell-cycle progression and proliferation via suppression of cell-cycle regulatory genes. Additional data collected on the functions of the PD-1/PD-L1 and PD-L2 axis suggest that the role of these receptors on T cell biology extends beyond suppression of effector T cells. Studies by Allison and colleagues highlighted that not only the expression of PD-L1 and PD-L2 on APCs is differentially upregulated, but also PD-L1 and PD-L2 may have different roles affecting Th1 and Th2 responses (Loke and Allison 2003). The interaction of PD-1 with PD-L1 may also reprogram human Th1 cells into Treg cells (Amarnath et al. 2011), and this interaction may also affect diverse CD4⁺ T cell subsets differently (McAlee et al. 2015).

The B7 family of proteins with either co-stimulatory or co-inhibitory properties has expanded in recent years and is now collectively referred to as “immune checkpoint regulators” (Ceeraz et al. 2013), which now include ten reported members (Xu et al. 2016). This family of receptors currently includes B7-1, B7-2, B7-DC, PD-L1, ICOS-L, B7-H3, B7-H4, B7-H5, B7-H6, and B7-H7 (Fig. 2). Various members of this family of receptors are overexpressed by various forms of cancer, including GC, possibly as a mechanism of evasion of tumor immune surveillance (Cimino-Mathews et al. 2016; Chen et al. 2015; Hou et al. 2014). These observations together with their known T cell regulatory activity made these proteins attractive as targets for oncologic immunotherapy with some successes (La-Beck et al. 2015).

4 T Cell Subsets and Reprogramming

4.1 T Cell Subsets

We discussed earlier thymic selection and the emergence of single positive CD4⁺ and CD8⁺ T cells, which migrate to the periphery and the majority (90–95%) of which express the TCR $\alpha\beta$, while the remainder express TCR $\gamma\delta$. Also, we referred to extrathymically differentiated T cells, which are largely CD8 $\alpha\alpha$ with a large proportion of TCR $\gamma\delta$, and

double-negative CD4⁻CD8⁻ cells. CD8⁺ T cells, also known as cytotoxic T cells, after activation in the periphery may exert their cytotoxic role and then become memory T cells. CD4⁺ T cells represent a more diverse subset after they are activated. Depending on the cytokine milieu to which they are exposed during their activation by APCs, CD4⁺ T cells are programmed into distinct subsets with the expression of characteristic transcription factors and cytokine profiles, which in turn allow them to exert distinct functions. Currently, the CD4⁺ T cell subsets that have been defined include Th1, Th2, Th3, Th9, Th17, Th22, Th25, follicle helper T cells (Tfh), and Treg (Fig. 3). Interestingly, the literature on the immune response to *H. pylori* has been inclusive of most of these subsets.

4.1.1 Th1 Cells—The first subsets of T lymphocytes studied in the context of the host response to *H. pylori* were Th1 and Th2 (Karttunen et al. 1990; Bamford et al. 1998b). Each CD4⁺ T cell subset is characterized by the expression of a specialized cytokine gene under regulation by subset-defining transcription factors. Th1 is induced to differentiate by IL-12 from APCs (Hsieh et al. 1993), which induce signal transducers and the activator of transcription 4 (STAT4) or STAT1. These STATs lead to the expression of the transcription factor T-bet, regarded as the master regulator of Th1 cells (Szabo et al. 2000), and synthesis of IFN- γ , although neither of them is unique to Th1 cells. T-bet activates the *ifn- γ* gene by binding directly to its promoter (Jenner et al. 2009) and silences *il4* gene expression (Djuretic et al. 2007). It is widely accepted that the role of Th1 cells is to foster cell-mediated immunity against intracellular pathogens.

4.1.2 Th2 and Th25 Cells—Th2 cells are induced to differentiate in the presence of IL-4, which induces STAT6 phosphorylation. Phospho-STAT6 promotes the expression of the transcription factor GATA3, which in turn leads Th2 cells to produce IL-4, IL-5, and IL-13 (Scheinman and Avni 2009). GATA3 directly represses the *ifn- γ* gene (Chang and Aune 2007; Djuretic et al. 2007). Further proof of the importance of GATA3 in Th2 cell development was obtained in studies in which GATA3 was deleted from T cells and those cells failed to differentiate into the Th2 lineage, while its overexpression in Th1 cells caused them to reprogram into Th2 cells (Pai et al. 2004; Zhang et al. 1997). Th2 cells are central in humoral immunity and host responses to helminth infections; however, they are chief contributors to the pathogenesis of allergic inflammatory diseases (Nakayama et al. 2017). The literature suggests the existence of a novel IL-25-producing T cell subset designated as Th25 cells, which seem to be closely related to the Th2 cell lineage (Swaidani et al. 2011), as both cell types need IL-4 for cytokine production and IL-25 (also known as IL-17E) enhances cytokine production (Fort et al. 2001). These cells are regulated by the transcription factor Act1 and were shown to induce non-lymphoid cells to synthesize Th2 cytokines during infection with helminths (Swaidani et al. 2011; Fallon et al. 2006), and possibly to extracellular pathogens, in general, as suggested by a recent study (de Sousa and Quaresma 2018). Fallon et al. (2006) reported that *il25*^{-/-} mice were inefficient at eliminating the gastrointestinal nematode *Nippostrongylus brasiliensis*. To date, there are no studies demonstrating the involvement of Th25 cells in *H. pylori* gastric inflammation, as might be expected given their linkage to Th2 cell lineage and recent emergence of Th25 cells.

4.1.3 Th17—Th17 was initially described as a distinct Th subset in the last decade (Harrington et al. 2005; Park et al. 2005), and this lineage of Th cells has the retinoic acid receptor-related orphan receptor- γ t (ROR γ t) as their master regulator (Ivanov et al. 2006). Their differentiation involves either IL-1 β (Sutton et al. 2006; Pachathundikandi et al. 2016), IL-23 (Harrington et al. 2005), or the combination of IL-6 and TGF- β (Mangan et al. 2006). Th17 cells acquired their designation because of their ability to synthesize IL-17, both IL-17A and IL-17F (Harrington et al. 2005). IL-17 is a pro-inflammatory cytokine which acts both on hematopoietic and non-hematopoietic cells and induces antibacterial peptides, pro-inflammatory cytokines, chemokines, and prostaglandins. Among the chemokines induced by IL-17 are CXCL1, CXCL2, CXCL5, and IL-8, which promote neutrophil recruitment (Laan et al. 1999; Delyria et al. 2009), as well as CCL20, a chemokine important in cell recruitment to mucosal surfaces (Acosta-Rodriguez et al. 2007). These cells are linked to inflammation and autoimmunity (Langrish et al. 2005), as well as immunity to extracellular microbes, such as *H. pylori*, and their importance in immunity to mucosal pathogens has been highlighted in published studies (Khader et al. 2009). The differentiation of Th17 cells is inhibited by IL-27 (Hirahara et al. 2012), which also promotes Th1 cell differentiation (Yoshida et al. 2001).

4.1.4 Th22 and Th9 Cells—Th22 and Th9 cells are recently characterized CD4⁺ Th subsets. Akin to Th17, which was so designated because of their production of IL-17, Th22 produces IL-22, whose expression was previously linked to Th17 cells, but now it is accepted that Th17 (Liang et al. 2006; Kreymborg et al. 2007) and NK cells (Cupedo et al. 2009; Crellin et al. 2010), in addition to Th22, produce IL-22, although the latter secrete the highest levels. In contrast to Th17 cells, which produce both cytokines, Th22 cells do not secrete IL-17A (Eyerich et al. 2009). Though they have been found within infected tissues and multiple inflammatory states, their role in immunity has not been well characterized due to the difficulty in culturing them in vitro, but that may change soon after a recent report described their generation in vitro in the absence of Th17 cells (Plank et al. 2017). IL-22 aids in the control of mucosal infections through the induction of inflammatory mediators and antimicrobial peptides (Rutz et al. 2013). A recent report correlated IL-22-induced antimicrobial peptides with vaccine-induced protection against *H. pylori* in mice (Moyat et al. 2017). As noted above, Th9 cells also represent a recently described subset of effector T cells whose differentiation from naïve T cells depends on transforming TGF- β and IL-4 (Dardalhon et al. 2008). This subset of effector T cells has a complex requirement of different transcription factors that include STAT6, PU.1, IRF4, and GATA3 (Chang et al. 2010; Staudt et al. 2010; Goswami et al. 2012). While their function in vivo is not clearly outlined, the available data suggest their involvement in atopy, as IL-9 promotes mast cell growth and induces changes in mast cell gene expression (Brough et al. 2014; Kearley et al. 2011). Though a proteomic study showed that IL-9 was elevated in the mucosa of *H. pylori*-positive GC samples (Ellmark et al. 2006), the role of Th9 in protection against *H. pylori* or associated pathogenesis is not clear. However, it has been suggested that IL-9 could be limiting the pro-inflammatory activity of Th17 cells since IL9-deficient Th17 cells induce more severe autoimmune gastritis (Stephens et al. 2011). Interestingly, Th9 cells have recently been implicated in inflammatory bowel disease—more specifically in ulcerative colitis (Gerlach et al. 2015).

4.1.5 Tfh Cells—Tfh cells are a CD4⁺ subset specialized in providing B cell help while sustaining enduring antibody responses in germinal centers of secondary lymphoid organs. Tfh cells are distinct from other CD4⁺ T cell subsets by the expression of their hallmark CXCR5, and the transcription factor essential for their differentiation, B cell lymphoma-6 (BCL-6). Newly activated CD4⁺ T cells when exposed to IL-6 are induced to differentiate into Tfh by signaling through the IL-6 receptor (IL-6R/gp130), which elicits Bcl6 expression (Nurieva et al. 2009). In turn, Bcl6 elicits early CXCR5 expression and the Tfh migrates to the B cell follicle border (Choi et al. 2011). Initially, these Tfh cells are induced by DCs and macrophages, but eventually the main APCs that they encounter are antigen-specific B cells in the follicle, interfollicular zone, and the T-B border. Their interaction with B cells is significant since B cells express ICOS-L, which provides co-stimulatory signals via ICOS on Tfh cells, which are essential for their complete differentiation (Choi et al. 2011). These T cells are important in immunity against infectious agents as antibody responses are critical in immune responses to most pathogens.

4.1.6 Treg Cells—Treg cells are CD4⁺ T cells characterized by a high surface expression of CD25 (IL-2 receptor α chain), in addition to the expression of the transcription factor forkhead box P3 (FoxP3) (Hori et al. 2003). They represent about 5–15% of all CD4⁺ T cells in the body, and there are two populations of Treg cells, which develop in different sites. Natural Treg (nTreg) cells undergo thymic maturation while induced Treg (iTreg) cells mature post-thymically (Rodriguez-Perea et al. 2016). The latter population, iTreg, is represented by two subsets that include Tr1, which lack FoxP3 and secrete IL-10 (Vieira et al. 2004), and Th3 that are FoxP3⁺ and secrete TGF- β (Weiner 2001). Their foremost function is to suppress immunity by limiting extent and intensity of an immune response, and to maintain peripheral self-tolerance. This became evident by an experiment of nature in which humans with dysfunctional FoxP3 develop a condition known as immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome. This syndrome is characterized by a series of autoimmune disorders in various parts of the body such as the intestines, skin, and endocrine glands. Treg cells inhibit effector T cells through cell–cell contact and through the cytokines that they produce, which include IL-10, TGF- β and IL-35 (Rodriguez-Perea et al. 2016; Jafarzadeh et al. 2015). The gastrointestinal mucosa is a body site where Treg cells are found at a high frequency as they aid in maintaining immune tolerance and are important in preventing intestinal inflammation (Izcue et al. 2009).

5 Reprogramming and Plasticity

Since the original definition of Th1 or Th2 effector cells was based on their cytokine production profiles, Th effector subsets were regarded as being terminally differentiated following a linear and unalterable process—each subset with a distinctive cytokine profile. However, studies in vitro initially suggested that those Th1 and Th2 cells could be induced to produce cytokines characteristic of the other subset when cultured under conditions that would promote the opposite subset. For instance, Th1 cells secreted IL-4 when they were cultured under Th2 culture conditions (Zhu et al. 2004). Similar observations were made with Th17 and Treg cells. Treg were reported to produce IL-17 after culture with IL-6, and

they also upregulated ROR γ t expression (Yang et al. 2008). Furthermore, Treg cells may self-induce into IL-17-producing cells in the presence of IL-6 if TGF- β is absent (Xu et al. 2007) and Th17 may revert in vivo and in vitro into Th1 cells, as demonstrated by various independent groups (Martin-Orozco et al. 2009; Bending et al. 2009). These and similar observations uncovered the ability of “differentiated” T cells to convert to another phenotype leading to the hypothesis that T cells have phenotypic plasticity that is influenced by environmental cues. Thus, this ability of CD4⁺ T cells to become reprogrammed and acquire features of other T cell subsets is now referred to as T cell plasticity. CD4⁺ T cell plasticity can be modulated by a combination of extracellular and intracellular signals (DuPage and Bluestone 2016). The extracellular cues that may influence plasticity of CD4⁺ T cells include the available cytokine milieu with the signaling that is activated, intensity of the TCR signaling, and signals activated by co-stimulator/co-inhibitor receptors. Plasticity may also be influenced intracellularly by signaling cascades, cell metabolism, and transcription factor (i.e., master regulators: FoxP3, ROR γ , etc.) regulation. During infection with *H. pylori*, most of these extracellular and intracellular regulators are altered or used by the bacterium. For instance, our studies showed that infection with *H. pylori* results in the induction of the co-stimulatory molecules CD80, CD86, as well as the co-inhibitory receptor PD-L1 on GECs (Beswick et al. 2007b; Das et al. 2006; Ye et al. 1997), which not only influence the activation of T cells, but also promote their reprogramming (Beswick et al. 2007a). TGF- β , which stimulates both Th17 and Treg cells, is also produced by *H. pylori*-infected GECs, in a response that is dependent on the virulence genes *vacA* and *cagA* (Beswick et al. 2011).

6 *H. pylori* Induction and Evasion of the Host Immune Response

Pathogens that establish infections for life possess characteristics in their interactions with the human host that permit prolonged colonization periods, even in the presence of immune responses. In the case of *H. pylori*, the bacteria are adapted to colonize a distinctive niche that is hostile to most other microorganisms. Its ability to establish persistent infection with associated chronic inflammation predisposes the host to develop clinically significant gastric diseases, such as PUD and GC. The inflammatory response reflects the induction of host immunity, but *H. pylori* has an arsenal of mechanisms that enable successful evasion of innate and adaptive immunity in order to persist within the human gastric mucosa. Because the adaptive immune response is highly specific and is responsible for lasting immunity, we will focus the discussion on the adaptive immune response with an emphasis on how *H. pylori* subverts lymphocytes. Since T cells are activated by their interactions with APCs, to better understand how T cell responses are affected, we will also discuss the influence of *H. pylori* on classical APCs and the epithelium in their interactions with T cells.

Macrophages, DCs, B cells, and GECs are influenced during infection by *H. pylori*, and, in turn, they contribute to the mucosal response that takes place. Although *H. pylori* is not invasive, the bacterium and its products come in contact with cells in the lamina propria. Thus, the infected gastric mucosa has a significant influx of immune cells that include macrophages, DCs, and lymphocytes. Macrophages are recruited to the *H. pylori*-infected gastric mucosa and aid in the production of pro-inflammatory cytokines and chemokines (Dzierzanowska-Fangrat et al. 2008). Depending on how macrophages are activated they are

functionally polarized as either M1 (classically activated by IFN γ and bacterial products and are pro-inflammatory), or M2 (alternatively activated by IL-4, IL-10, or IL-13 and are associated with wound healing and tissue repair) (Murray 2017). Analysis of gastric macrophages in *H. pylori*-infected mice showed that they were polarized to M1, and in humans, they showed a mixed M1/M2 phenotype, but in atrophic gastritis macrophages, they were also M1 (Quiding-Jarbrink et al. 2010). However, the work by Wilson's group has shown that macrophages in *H. pylori*-infected mice show activation of the arginase/ornithine decarboxylase pathway (Lewis et al. 2011), which is a feature associated with M2 macrophages. Further, another group reported the presence of CD68⁺CD163⁺Stabilin-1⁺ (M2) macrophages in the lamina propria of *H. pylori*-infected patients (Fehlings et al. 2012). Wilson's group also showed that *H. pylori* induces the heme oxygenase-1 (HO-1) gene in macrophages. HO-1 is an anti-inflammatory and antioxidant enzyme. This response was elicited by phosphorylated CagA and signaling that involves the activation of p38 and NF (erythroid-derived 2)-like 2 (NRF2) (Gobert et al. 2014). The activation of HO-1 in *H. pylori*-infected macrophages fosters a switch to regulatory macrophages able to dampen immune responses. Macrophages are also considered as key promoters in the differentiation of Th17 cells within the *H. pylori*-infected mucosa. Macrophages exposed to *H. pylori* or urease secrete pro-Th17 cytokines (Zhuang et al. 2011). Furthermore, two independent studies using two different mouse models of autoimmune disease identified B cell activating factor (BAFF aka B-lymphocyte stimulator, BLyS, and TNF-superfamily member 13B) of the TNF- α family as a promoter for Th17 responses (Zhou et al. 2011; Lai Kwan et al. 2008). One report suggested that BAFF was directly involved in these responses, while the other report suggested that BAFF acts as a modulator of the cytokine milieu that would, in turn, affect the induction and function of Th17 cells. Munari et al. (2014) showed that IL-17 and BAFF levels are elevated in the mucosa of *H. pylori*-infected patients, and the increase of these two cytokines hinges on the presence of *H. pylori*. Macrophages in the gastric mucosa of patients are a major source of BAFF, which causes pro-Th17 cytokine production in a reactive oxygen species (ROS)-dependent manner. Taken together, all these reported observations suggest that *H. pylori* may affect macrophage polarity in multiple ways, and these macrophages may in turn contribute to the diverse Th cell responses reported during the infection. However, an important property for macrophages to affect T cells directly is by being able to phagocytose and process *H. pylori* antigens for presentation of the antigens to CD4⁺ T cells.

Macrophages readily internalize *H. pylori*, but the bacteria avoid phagocytic killing. Virulent type 1 strains of *H. pylori* were found to disturb phagosome maturation and induce formation of anomalous vacuoles referred to as megasomes (Allen et al. 2000; Zheng and Jones 2003). Normal maturation of phagosomes occurs in stepwise fashion in which phagosomes fuse with early endosomes, late endosomes, and lysosomes. The intravacuolar pH decreases with each stage in order to allow for activation of the lysosomal proteases needed for antigen processing (Desjardins et al. 1994). However, *H. pylori* stops phagosome maturation, preventing it from attaining its full degradative capacity, which in turn allows for extended *H. pylori* intracellular survival (Allen 1999). Experiments with isogenic *vacA* and urease mutant strains to infect murine macrophages and macrophage cell lines pointed to their role in extending the survival of *H. pylori* (Zheng and Jones 2003; Schwartz and Allen

2006). The ability of *H. pylori* VacA to perturb the endocytic traffic at a late stage was initially described by Rappuoli's and Montecucco's groups using elegant cell biology methods (Papini et al. 1994).

DCs are robust APCs and a major immune cell type connecting both innate and adaptive immune responses. DCs are also among the cell types affected by *H. pylori* during infection and thus represent an important tool in the arsenal used by *H. pylori* to subvert host immunity since DCs may also function as different subsets that differentially regulate T cell functions. Among the various effects that *H. pylori* has on DCs include the induction of cytokines, such as IL-12, IL-23, and TNF- α , which are associated with Th1 responses (Amedei et al. 2006), in addition to a panel of other pro-inflammatory cytokines and chemokines (Kranzer et al. 2004). *H. pylori* has also been reported to promote monocyte maturation into DCs with increased HLA class II expression. An important virulence factor in promoting these responses is the neutrophil-activating protein NapA (Pachathundikandi et al. 2015). As the name implies, it also affects neutrophils and was initially labeled as such because it was reported to induce a high production of oxygen radicals from neutrophils (Evans et al. 1995a, b). In vitro studies showed that NapA alone, added to in vitro cultures, could significantly limit development of Th2 clones to antigens such as tetanus toxoid (TT) and mite allergen. Interestingly, in those studies, most (89%) of the allergen-specific Th clones were Th2 clones in the absence of NapA, but in its presence their frequency decreased to only a small fraction (29%), while Th1 clones increased considerably (D'Elios et al. 2007). Because of NapA's potential to reprogram antigen-specific Th2 cell responses to polarized Th1, its possible use as an immunomodulator in Th2 diseases, such as atopy, has been suggested (Reyes and Beswick 2007). As discussed below, among the subsets of CD4⁺ T cells that have been found to infiltrate the *H. pylori*-infected gastric mucosa are Treg and Th17 cells, but their balance is skewed toward a regulatory response. The effect that *H. pylori* has on the Treg/Th17 balance appears to be exerted via DCs (Kao et al. 2010). Studies conducted by Anne Muller's group using bone marrow-derived DCs exposed to *H. pylori* and co-cultured with CD4⁺ T cells and a cocktail of anti-CD3, IL-2, and TGF- β showed that they induced more CD25⁺FoxP3⁺CD4⁺ T cells than naïve DCs (not exposed to *H. pylori*) as determined by flow cytometry (Oertli et al. 2012). Interestingly, mesenteric lymph node (MLN)-DCs that were immunomagnetically isolated from *H. pylori*-infected mice also promoted the development of a large percentage of CD25⁺FoxP3⁺CD4⁺ T cells in co-cultures with naïve CD4⁺ T cells (Oertli et al. 2012). These and other similar observations suggest that *H. pylori* induces tolerogenic properties in DCs.

Presentation of *H. pylori* antigens by DCs not only activates T cells, but also indirectly promotes B cell activation through CD40-CD40L interactions between lymphocytes (Guindi 2000). The exact role of B lymphocytes in the development of anti-*H. pylori* immunity remains ill-defined, although *H. pylori*-carriers are known to develop strong local and systemic *H. pylori*-specific IgA and IgG antibody production (Futagami et al. 1998; Nurgalieva et al. 2005; Portal-Celhay and Perez-Perez 2006). Since infected individuals have elevated serum Ig titers to *H. pylori*, this response has been used to detect *H. pylori* infection, although IgG antibodies are not considered reliable indicators of current infection. The elicited antibodies fail to control *H. pylori* (Ermak et al. 1998). Early studies with a murine model of *H. pylori* infection examined the protective role of B cells by intragastric

administration of *H. pylori*-specific IgA antibodies simultaneously with *Helicobacter felis* bacteria into germ-free mice. After infection with *H. felis*, the investigators observed a reduction of 70% of the number of colonized mice at 4 weeks post-infection (Czinn et al. 1993). In addition, experiments using mice deficient in IgA or immunoglobulin (μ MT) that were immunized with urease and lysates of *H. pylori* or *H. felis*, later challenged with *H. pylori*, showed no differences in gastric colonization by *H. pylori* during the acute phase of infection (Ermak et al. 1998; Blanchard et al. 1999; Pappo et al. 1999; Akhiani et al. 2004, 2005). However, analysis of the chronic phase of infection (>8 wk p.i.) showed that μ MT mice were able to clear the *H. pylori* infection with signs of severe gastritis, whereas the wild-type mice presented extensive *H. pylori* colonization with mild gastric inflammation (Blanchard et al. 1999). Overall, these reports showed that vaccine-induced immunity is elicited in comparable levels in wild-type and antibody- or B-lymphocyte-deficient mice. Interestingly, T cells from wild-type, IgA- and μ MT-deficient mice produced comparably high levels of IFN- γ , whereas the levels of IL-10 produced were significantly higher in wild-type mice than in the deficient mice (Akhiani et al. 2004, 2005). The use of IL-10/IgA double knockout mice helped to further examine the role of inflammation in controlling *H. pylori* colonization. These double knockout mice were 1.2-log significantly less colonized by *H. pylori* than mice deficient only in IL-10, which in turn were less colonized than wild-type mice. These observations led to the view that B cells and/or antibodies may have a pathological effect by promoting chronic inflammation.

IL-10 is among the immune signaling molecules made by B cells and has been linked with downregulation of protective T cell responses. IL-10 is significantly elevated in the gastric mucosa of patients and mice infected with *H. pylori* (Bodger et al. 2001). This cytokine is used by regulatory T and B cells to limit the inflammatory response. Mice deficient in IL-10 had a 100-fold reduction of *H. pylori* colonization in comparison with wild-type mice (Chen et al. 2001; Ismail et al. 2003). B cells can be activated directly by other mechanisms, including TLR, BCR, and cytokines receptors. BCR and TLR7/9 activation by nucleic acid-protein complexes, originating from chronic infection, and associated inflammation, initiates B cell activation via MyD88/NF- κ B (Farinha and Gascoyne 2005; Fukata et al. 2008). Interestingly, experiments with murine B cells exposed to *H. pylori* extracts upregulated CD80 and IL-10 production via TLR2/MyD88 activation and promoted differentiation of naïve CD4⁺ T cells into IL-10-producing CD4⁺CD25⁺ Treg cells, with suppressive activity in vitro through CD40/CD40L (Sayi et al. 2011; Smith 2014) (Fig. 4). Therefore, B cells can be activated pro-regulatory (IL-10 production) cooperating with T cells in the suppression of immunopathological inflammation associated with *H. pylori* infection. IFN- α is another cytokine made by plasmacytoid DC antigen-1 (PDCA-1)⁺ B cells and found to suppress *H. pylori*-induced gastritis, and downregulate Th1-type cytokines (Otani et al. 2012). Interestingly, IFN- α administration to *H. pylori*-infected mice reduced neutrophil infiltration and levels of TNF- α and IFN- γ (Otani et al. 2012). Gastric samples from *H. pylori*-infected patients showed significantly increased IFN- α and IgM in their sera, as well as PDCA-1⁺ B cells compared to controls (Ma et al. 2016). In addition, PDCA-1⁺ B cells were more frequent in *H. pylori*-infected patients suffering from atrophic gastritis or peptic ulcers in comparison with non-atrophic gastritis patients (Ma et al. 2016).

The cellular infiltrate within the *H. pylori*-infected gastric mucosa includes both CD4⁺ and CD8⁺ T cells, which are significantly increased in the neck, pit, and gland regions, as noted in gastric biopsy sections (Nurgalieva et al. 2005; Bamford et al. 1998a). In early studies, we and others reported that the response is polarized to Th1 cells (Haeberle et al. 1997; Bamford et al. 1998a; Karttunen et al. 1990), which was an early indication that the immune response to *H. pylori* is misguided since Th1 cells influence cell-mediated immunity, which is inadequate against extracellular pathogens, such as *H. pylori*. In fact, Th1 cells seem to aid in pathogenesis, as supported by observations in human carriers, suggesting Th1 participation in *H. pylori*-associated lesions (Robinson et al. 2008). The presence of Th17 and Treg cells in the infected gastric mucosa has been reported by various independent groups (Jang 2010; Shi et al. 2010; Zhang et al. 2008; Lundgren et al. 2003, 2005). Further, in the *H. pylori*-infected gastric mucosa there is a marked infiltration of CD4⁺ T cells with abnormal Th17/Treg cell ratios (Gil et al. 2014; Lundgren et al. 2003, 2005). CD25⁺/CD4⁺ versus FoxP3⁺/CD4⁺ cells frequencies vary significantly depending on the type of disease and severity (Cheng et al. 2012). FoxP3 is a master regulator of Treg cells whose frequency is significantly higher in GC patients than in patients with other *H. pylori*-related gastric diseases (Cheng et al. 2012). An increase in Treg cells leads to higher bacterial density and contributes to the development of atrophic gastritis and GC progression by suppressing anti-tumor effector T cells. Treg cells in the gastric mucosa helped explain earlier reports of T cell hyporesponsiveness of T cells from *H. pylori*-infected subjects when restimulated with *H. pylori* antigens, as compared to T cells from uninfected individuals (Fan et al. 1994; Karttunen et al. 1990). As Th17 cells are important in immune-mediated clearance of extracellular bacteria, their presence in the *H. pylori*-infected mucosa is expected. In fact, mouse immunization studies reported the contribution of Th17 cells, and a robust IL-17 secretion in protection against *H. pylori* (Delyria et al. 2009), but in those studies, the vaccinated mice were challenged with the *H. pylori* SS1 strain, which is defective in the type 4 secretion system. As explained below in some detail, our studies showed that a functional type 4 secretion system is important in *H. pylori*'s ability to evade Th17 cell responses (Lina et al. 2013). In infected mice fully virulent *H. pylori* inhibits Th17 and tips the balance to Treg cells (Kao et al. 2010). The Treg/Th17 balance is essential to immune homeostasis.

T cell activity is also shaped by immune checkpoint receptors expressed on immune cells that deliver inhibitory signals (Ceeraz et al. 2013). As mentioned earlier, the B7 family of co-stimulatory/co-inhibitory receptors has emerged as central in immune regulation, keeping a subtle balance between immune potency and suppression of autoimmunity (reviewed in (Francisco et al. 2010; Ceeraz et al. 2013)). We showed that *H. pylori* regulates GEC expression of various B7 immune checkpoints, which in turn impact local T cell development and function (Lina et al. 2013, 2015). These proteins perform as ON/OFF switches for T cell activity, and recent studies suggest their role in influencing T cell differentiation or phenotype. For example, in studies using co-cultures of naïve CD4⁺ T cells with *H. pylori*-infected GECs, we noted that PD-L1 (aka CD274, B7-H1) promoted the development of Treg from those naïve CD4⁺ T cells (Beswick et al. 2007b), and a separate report demonstrated that PD-L1 converted T-bet⁺ Th1 cells into FoxP3⁺ Treg cells in vivo (Amarnath et al. 2011). During infection with *H. pylori*, PD-L1 expression is increased by GECs (Das et al. 2006). We reported that epithelial cells from biopsy specimens of *H.*

pylori-infected patients had an elevated expression of PD-L1 when compared to epithelial cells from uninfected subjects, and this was confirmed by infecting GECs in the absence of cytokines that are present in the infected gastric mucosa, which could induce that expression (Das et al. 2006). These results, regarding gastric epithelial PD-L1 expression during *H. pylori* infection, were confirmed by Wu et al. 2010). In subsequent studies, we observed that *H. pylori* infection, besides eliciting increased expression of PD-L1, also leads to a reduced expression of ICOS-L, which is the only positive co-stimulator known to act on activated or memory T cells (Lina et al. 2013). These findings suggested that *H. pylori* uses the epithelium to create a prime inhibitory scenario for Th effector cells by altering the expression of these proteins with profound immunomodulatory effects. These responses are partially dependent on *H. pylori* CagA and peptidoglycan translocated by the type IV secretion system (Posselt et al. 2013; Backert et al. 2015; Zhang et al. 2015) (Fig. 5). CagA was found to reduce ICOS-L expression by activating the p70 S6 kinase pathway. CagA contributes to the *H. pylori*-mediated activation of the mTOR/p70 S6 kinase pathway. The serine/threonine protein kinase mTOR acts downstream from PI3K/Akt and controls activation of p70 S6 kinase. The role of p70 S6 in downregulation of ICOS-L by the *cagA*⁺ *H. pylori* strains was confirmed by adding to the cultures rapamycin, a specific inhibitor of p70 S6 kinase/mTOR. Because the ICOS-L–ICOS interaction is critical for Th17 cell development, maintenance, and function (Paulos et al. 2010), *H. pylori* is able to evade Th17 cell-mediated clearance by modifying ICOS-L expression as demonstrated in in vivo studies (Lina et al. 2013). The B7 family of “checkpoint regulators” (Ceeraz et al. 2013) affect adaptive immunity beyond T cell activation, as described above. They impact T cell differentiation, cytokine production, and reprogramming (Kuang et al. 2014; Lee et al. 2013; Ishiwata et al. 2010). As T lymphocytes play a key role in adaptive immunity, *H. pylori*’s influence on the expression of immune checkpoints may be pivotal in persistent infection and pathogenicity. It is worth noting that tumor cell expression of checkpoint inhibitors promotes tumor immune evasion and growth by inducing “exhaustion” of effector T cells (Wherry 2011), and the ability of *H. pylori* to alter the expression of these molecules may allow *H. pylori* to aid developing neoplastic cells to escape immune surveillance mechanisms.

Besides altering the local mucosal environment by modulating the expression of key immunoregulatory molecules or production of cytokines by the gastric epithelium and immune cells, *H. pylori* is also able to directly inhibit CD4⁺ T cells. *H. pylori*’s VacA toxin and γ -glutamyl-transpeptidase (GGT) have been reported to hinder T cell activation (Sundrud et al. 2004; Boncristiano et al. 2003). Both of these toxins are secreted products of *H. pylori*. VacA uses CD18 (β 2-integrin) as a receptor on T cells (Sewald et al. 2008). VacA is internalized after the cytoplasmic domain of CD18 is phosphorylated by protein kinase C (Sewald et al. 2011). *H. pylori* VacA impedes T cell signaling and proliferation by promoting the arrest of the cells cycle at G1/S. *H. pylori* VacA mediates this effect by interfering with the TCR and IL-2 signaling pathways at the level of the Ca₂⁺/calmodulin-dependent phosphatase calcineurin. By this mechanism *H. pylori* VacA prevents translocation of the important T cell transcription factor NFAT (nuclear factor of activated T cells) into the nucleus of T cells leading to the suppression of *il-2* gene transcription (Gebert et al. 2003). Studies by Cover’s group showed that *H. pylori* VacA constrains IL-2-induced

cell-cycle progression and proliferation of T cells without altering IL-2-dependent survival, but through its N-terminal hydrophobic region needed for the creation of anion-selective membrane channels averting clonal expansion of T cells activated by *H. pylori* antigens (Sundrud et al. 2004).

The GGT enzyme from *H. pylori* has also been found to contribute to PUD and GC (Gong et al. 2010; Rimbara et al. 2013). GGT is a threonine N-terminal nucleophile hydrolase that catalyzes transpeptidation and hydrolysis of the gamma-glutamyl group of glutathione and converts glutamine resulting in the secretion of glutamate and ammonia into the periplasm and local milieu. Among the multiple effects that *H. pylori* GGT has, it has been reported to inhibit T cell proliferation and DC differentiation (Gerhard et al. 2005; Oertli et al. 2013; Schmees et al. 2007). Gerhard and colleagues showed that *H. pylori* GGT induces cell-cycle arrest in T cells at the G1 phase and thus suppresses their proliferation (Schmees et al. 2007). They reported that *H. pylori* GGT causes G1 arrest by disrupting Ras- and not PI3 K-dependent signaling (Schmees et al. 2007). *H. pylori* GGT also induces Cox2, which paradoxically may also suppress the Th1 polarization (Meyer et al. 2003). Both *H. pylori* GGT and VacA may also thwart T cell activity indirectly by reprogramming DCs into “tolerogenic” DCs, which foster the differentiation of naïve T cells into Treg cells (Oertli et al. 2013). Muller and colleagues reported that those DCs foster the expression of the FoxP3, CD25 and IL-10, characteristic markers of Treg cells, in naïve T cells (Oertli et al. 2013).

7 Concluding Remarks

Although the incidence of *H. pylori* infection has been decreasing due to enhancements in living conditions, the global prevalence of *H. pylori* remains high. In North America, approximately one-third of all adults are infected, while in developing regions, almost half of the population carries *H. pylori* (Eusebi et al. 2014). Thus, *H. pylori* remains an important human pathogen associated with significant clinical disease. Over the last few years, we have learned substantially regarding its diverse mechanisms to surreptitiously maneuver the host immune response in order to maintain persistent infection that may last a lifetime. Because the diseases associated with its infection remain a significant public health concern, due to their associated morbidity and mortality, and because of the increasing incidence of antibiotic resistance, there is a clear need for an effective vaccine that allows the host to surmount the multiple strategies used by *H. pylori* to thwart the host adaptive responses reviewed in this chapter. Since T lymphocytes are arguably the most essential cells in adaptive immunity, *H. pylori*'s impact on the expression of crucial receptors that control T lymphocyte function or tolerance is decisive in bacterial persistence and pathogenesis. Thus, in order to reduce the incidence of this important human pathogen through vaccination, we clearly need to better understand how it manipulates the host immune armamentarium in order to effectively and appropriately steer it in directions that favor the host over the pathogen.

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Fig.1.

Schematic representation of lymphocyte differentiation and migration to gastric tissue. Bone marrow host hematopoietic stem cells (HSC) that progressively differentiate to rise to common lymphoid progenitors (CLP). CLPs differentiate into progenitor B cells (Pro-B cells) and double-negative (DN) thymocyte progenitors. Pro-B cells remain in bone marrow and differentiate into immature B cells that turn into mature B cells once they migrate to secondary lymphoid organs (i.e., lymph nodes and spleen). The CLP that migrate to the thymus commit to either natural killer (NK) cells or T lymphocyte lineage becoming $\gamma\delta$ T lymphocytes or double-negative DN thymocytes. DN thymocytes undergo negative selection and only immature single positive cells survive to become CD4⁺ or CD8⁺ T lymphocytes capable of migrating to secondary lymphoid organs. Lymphoid cells are eventually recruited

to gastric infected tissue where they become antibody-producing cells (B cells, plasmocytes) and CD4⁺ T lymphocytes differentiate into subsets depending on environmental cues

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Fig. 2. Co-stimulatory and co-inhibitory receptors and their ligands. These molecules are also known as members of the B7-CD28 superfamily or immune checkpoint regulators because they affect T cell activity

Fig. 3. CD4⁺ T cell subsets. Upon activation, naïve CD4⁺ T cells differentiate following specific paths depending on environmental cues, which include distinct cytokines. As part of their differentiation, they express characteristic transcription factors or “master regulators” that determine their respective phenotypic differences and the cytokines that they produce

Fig. 4.
H. pylori upregulate the expression of CD80 and IL-10 production via TLRs on B cells. B cells exposed to *H. pylori* upregulate receptors and cytokines that then promote Treg cell differentiation

Fig. 5.

H. pylori CagA and peptidoglycan translocated by the type IV secretion system into GECs promote a suppressive environment. *H. pylori* CagA and peptidoglycan injected into GECs lead to a reduction of B7-H2 expression by activating the p70 S6 kinase pathway. *H. pylori* CagA also promotes PD-L1 (B7-H1) expression by GECs. Both of these responses combined promote a suppressive environment because the ICOS-L–ICOS interaction is critical for Th17 cell development, maintenance, and function and in the absence of the interaction Th17 cells fail to develop. PD-L1 provides inhibitory signals for effector Th cells and promotes differentiation of Treg cells (Lina et al. 2013)