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The immunomodulatory properties of *Helicobacter pylori* confer protection against allergic and chronic inflammatory disorders

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Chronic infection with the gastric bacterial pathogen *Helicobacter pylori* causes gastritis and predisposes carriers to a high risk of developing gastric and duodenal ulcers, gastric cancer, and gastric lymphoma, but has also recently been shown to protect against certain allergic and chronic inflammatory disorders. The immunomodulatory properties that allow the bacteria to persist for decades in infected individuals in the face of a vigorous, yet ultimately non-protective, innate, and adaptive immune response may at the same time confer protection against allergies, asthma, and inflammatory bowel diseases. Experimental evidence from mouse models suggests that *H. pylori* has evolved to skew the adaptive immune response toward immune tolerance rather than immunity, which promotes persistent infection on the one hand, and inhibits auto-aggressive and allergic T-cell responses on the other. Regulatory T-cells mediating peripheral immune tolerance have emerged as key cellular players in facilitating persistent infection as well as protection from allergies, in both observational studies in humans and experimental work in mice. Recent data suggest that *H. pylori* actively targets dendritic cells to promote tolerance induction. The findings discussed in this review raise the possibility of harnessing the immunomodulatory properties of *H. pylori* for the prevention and treatment of allergic and auto-immune diseases, and also provide new insights relevant for *H. pylori*-specific vaccine development.

Keywords: *Helicobacter* immunomodulation, asthma and allergies, dendritic cells and regulatory T-cells, immune tolerance

INTRODUCTION

Helicobacter pylori is the most common bacterial infection in humans worldwide. The bacteria possess the remarkable ability to persist in infected individuals for many decades and have intimately co-existed with humans at least since they first migrated out of East Africa approximately 60000 years ago (Linz et al., 2007). During this long period of co-evolution, the bacteria have acquired traits that allow them to evade and subvert both innate and adaptive branches of the immune system to ensure their persistence in the face of a vigorous, yet ultimately non-protective, local and systemic immune response (Muller et al., 2011). The evolutionary costs possibly associated with the gastric pathology induced by chronic *H. pylori* infection have been proposed to be offset by potential benefits and a selective advantage for human carriers (Blaser and Atherton, 2004). Indeed, epidemiological and experimental data now point to a strong protective effect of *H. pylori* infection on the development of many extra-gastric diseases, including gastroesophageal reflux disease and its associated sequels (Vaezi et al., 2000; Islami and Kamangar, 2008; Whiteman et al., 2010), childhood asthma and allergy (Chen and Blaser, 2008; Amberbir et al., 2011), and certain metabolic disorders (Osawa et al., 2005; Mera et al., 2006). The epidemiological and experimental evidence for possible protective properties of *H. pylori* infection, as well as the mechanistic basis underlying these effects, are the subject of this review.

H. PYLORI PROTECTS AGAINST ALLERGIC ASTHMA AND OTHER ATOPIC DISEASES

THE PATHOGENESIS OF ASTHMA

In allergic asthma, genetically susceptible individuals respond to environmental allergens with inappropriate T-cell-mediated immune responses, leading to chronic obstruction of the airways. Allergic asthma is characterized by the accumulation of inflammatory infiltrates in the lung, airway hyper-responsiveness to a variety of specific and non-specific stimuli, increased serum immunoglobulin E (IgE) levels, and mucus hypersecretion. Chronic inflammation further leads to structural changes (airway remodeling) with collagen deposits, hyperplasia, and thickening of the airway wall. In asthmatic patients, allergic episodes trigger the bronchoalveolar infiltration of various immune cell populations, mostly eosinophils, mast cells, and activated $CD4^+$ T-cells. Effector T-helper 2 (Th2) cells play a central role in orchestrating the immune response to allergens by releasing cytokines that trigger the predominant features of asthma (Robinson et al., 1992): the secretion of IL-4 and IL-13 contributes to B-cell production of IgE (Wills-Karp et al., 1998; Bacharier and Geha, 2000), the release of IL-5 drives eosinophilic inflammation (Wang et al., 1989; Rosenberg et al., 2007), and IL-9 stimulates mast cell proliferation (Renauld et al., 1995). The action of IL-4 and IL-13 on lung epithelia further induces goblet cell metaplasia, whereas IL-13 acting on smooth muscle cells promotes the development of airway

hyper-responsiveness (Wills-Karp et al., 1998). Recently, other subsets of T-helper cells have been linked to asthma pathogenesis, including Th9 (Shimbara et al., 2000; Erpenbeck et al., 2003), Th25 (Tamachi et al., 2006; Ballantyne et al., 2007), and Th22 cells (Nakagome et al., 2011). A subset of lung-infiltrating T-cells known as Th17 cells has been described to account for neutrophilic airway inflammation, but also for enhanced Th2-cell-mediated eosinophilic airway inflammation (Wakashin et al., 2008). IL-17 secretion by both Th17 cells and eosinophils was further found to be increased in asthmatic patients (Molet et al., 2001). Although asthma is generally considered to be an adaptive immune disorder, the innate arm of the immune system also contributes to the pathology through the production of pro-inflammatory mediators by bronchial epithelial cells (Kauffman et al., 2006), mast cells (Amin et al., 2005), basophils (Ono et al., 2010), natural killer T (NKT) cells (Akbari et al., 2003), and dendritic cells (DC; Lambrecht et al., 2000).

There is now ample evidence that a variety of suppressive and regulatory mechanisms are crucially involved in preventing the activation of potentially harmful effector responses in the lungs of healthy individuals (Ray et al., 2010). This task is predominantly accomplished by $CD4^+CD25^+$ regulatory T-cells (Tregs) that either develop in the thymus (natural Tregs) or are induced in the periphery in response to specific antigens (adaptive or induced Tregs). Tregs can suppress pathogenic T-cell responses through direct contact with their target cells or via the release of anti-inflammatory cytokines such as IL-10 and transforming growth factor beta (TGF-β). Both $CD25^{hi}$ (Curotto de Lafaille et al., 2008) and IL-10-producing Tregs (Akdis et al., 2004) have been implicated in preventing Th2 responses to allergens. Peripheral blood-derived $CD4^+CD25^+$ Treg subsets of healthy individuals indeed inhibit the proliferation and cytokine production of their allergen-responsive $CD4^+CD25^-$ effector counterparts *in vitro*. In contrast, this ability was reduced in Treg subsets of allergic individuals, suggesting that effective suppression of pathogenic Th2 responses might be defective or overridden in patients with allergic diseases (Robinson, 2009). In bronchoalveolar lavage fluid (BALF) from asthmatic children, both the percentage and the suppressive capacity of Tregs were reduced compared to healthy control individuals (Kay, 2001). In a mouse model of ovalbumin-induced airway inflammation, the transfer of ovalbumin-specific Tregs could prevent or reverse the development of airway hyper-responsiveness and Th2 immune responses in an IL-10-dependent manner (Boudousquie et al., 2009). Overall, these findings suggest that functional Tregs of healthy individuals shift allergen-specific immune responses toward tolerance, thereby preventing the development of asthma and other allergic disorders.

HELICOBACTER INFECTION IS INVERSELY CORRELATED WITH ALLERGIC ASTHMA IN HUMANS

Many atopic individuals never develop allergic disease manifestations in their lifetime, suggesting that the genetic background acts synergistically with environmental factors to determine individual allergy susceptibility. The influence of environmental factors is drastically illustrated by the alarming increase of asthma and associated allergic disease incidence in Western societies over the last decades, especially among children (Eder et al., 2006). A plausible explanation has been formulated in the "hygiene hypothesis," which postulates a causal inverse relationship between allergies and pediatric infectious diseases (Strachan, 1989). At the immunological level, this hypothesis proposes that early life exposure to microbial antigens is required for the normal maturation of the immune system and the generation of protective regulatory T-cell responses. This notion has recently been revisited by Blaser and Falkow (2009), who suggest that the specific loss of our ancestral indigenous microbiota due to modern hygienic practices and the widespread use of antibiotics, rather than a general decline in arbitrary childhood infections, is causally associated with the epidemic increase of asthma and other allergic diseases.

In experimental models of airway inflammation, several viral and parasitic pathogens, including influenza viruses and helminths, have been implicated in protection against asthma and allergy (Wilson et al., 2005; Kitagaki et al., 2006). In addition, the role of *H. pylori* as a protective agent against atopic disorders has been suggested by numerous cross-sectional (Matricardi et al., 2000; Kosunen et al., 2002; Linneberg et al., 2003; Jarvis et al., 2004; Radon et al., 2004; von Hertzen et al., 2006; Herbarth et al., 2007; Janson et al., 2007; Shiotani et al., 2008) and case–control studies (Bodner et al., 2000; Matricardi et al., 2000; Tsang et al., 2000; Jun et al., 2005). McCune and colleges have reported that individuals carrying *H. pylori* were 30% less likely to have concomitant allergic conditions, including asthma, eczema, and allergic rhinitis (McCune et al., 2003). Several independent studies have further suggested more pronounced protective effects of *H. pylori* in children and in individuals with early onset asthma (Chen and Blaser, 2007, 2008; Amberbir et al., 2011) and in CagA-seropositive individuals (Chen and Blaser, 2007; Reibman et al., 2008).

ASTHMA PROTECTION CONFERRED BY *H. PYLORI* IS MEDIATED BY REGULATORY T-CELLS

We have recently reported that experimental *H. pylori* infection prevents allergic asthma in a mouse model of ovalbumin- or house dust mite-induced airway inflammation (Arnold et al., 2011a). Infected mice were efficiently protected against allergen-induced airway hyper-responsiveness, tissue inflammation, and goblet cell metaplasia, and exhibited reduced pulmonary and bronchoalveolar infiltration with eosinophils, Th2 cells, and Th17 cells (Arnold et al., 2011a). The protection against asthma could be attributed to *H. pylori*-induced, highly suppressive Tregs, which accumulate in the lungs of infected mice and block pathogenic effector T-cell responses (**Figure 1**). The depletion of $CD4^+CD25^+$ Tregs by systemic administration of a CD25-neutralizing antibody led to enhanced pulmonary inflammation and abrogated the characteristic T-cell hypo-responsiveness to ovalbumin in infected mice. The adoptive transfer of Tregs purified from the mesenteric lymph nodes of infected but not naïve donors was further sufficient to transfer protection to uninfected recipients (Arnold et al., 2011a). In addition, *H. pylori*-infected animals were characterized by lung-infiltrating semi-mature DC, which might suggest that Tregs generated during infection have the ability to influence extragastric immune responses by retaining DCs in a semi-mature state (**Figure 1**). An analogous mechanism was recently proposed by Onishi et al. (2008) who found that $FoxP3^+$ Tregs form aggregates

on DCs to actively down-regulate their co-stimulatory molecules CD80 and CD86, thus competing with naïve T-cells for access to DCs and limiting their ability to activate effector T-cell responses. Our finding of the accumulation of Tregs and semi-mature DCs in the lungs of infected, but not asthmatic mice (Arnold et al., 2011a) is in line with this model of asthma prevention (summarized schematically in **Figure 1**).

ASTHMA PROTECTION CONFERRED BY *H. PYLORI* IS LINKED TO THE EXPRESSION OF SPECIFIC VIRULENCE FACTORS AND IS MOST PRONOUNCED IN YOUNG INDIVIDUALS

Although a negative association between CagA-positive *H. pylori* infection status and allergic disease manifestations has been suggested (Chen and Blaser, 2007), protection conferred by *H. pylori* infection in our model was not linked to the expression of a functional type IV secretion system (Arnold et al., 2011a). Interestingly, the mucosal or systemic administration of the *H. pylori* neutrophil-activating protein (HP-NAP) in a therapeutic model of asthma was shown to inhibit bronchial inflammation through agonistic ligation of toll-like receptor 2 (TLR2; Codolo et al., 2008). HP-NAP delivery reduced lung eosinophilia in response to repeated ovalbumin challenge and decreased the production of IL-4, IL-5, and GM–CSF in the bronchioalveolar fluid (Codolo et al., 2008). In *H. pylori*-infected individuals, stimulation of lamina propria lymphocytes with HP-NAP further increased IL-10 production compared to uninfected controls, while reducing the proliferative and IFN-γ responses of stimulated PBMC (Windle et al., 2005). Because IL-10 is a key cytokine in the resolution of asthmatic inflammation (Xystrakis et al., 2006; Ogawa et al., 2008), this raises the possibility that specific *H. pylori* virulence

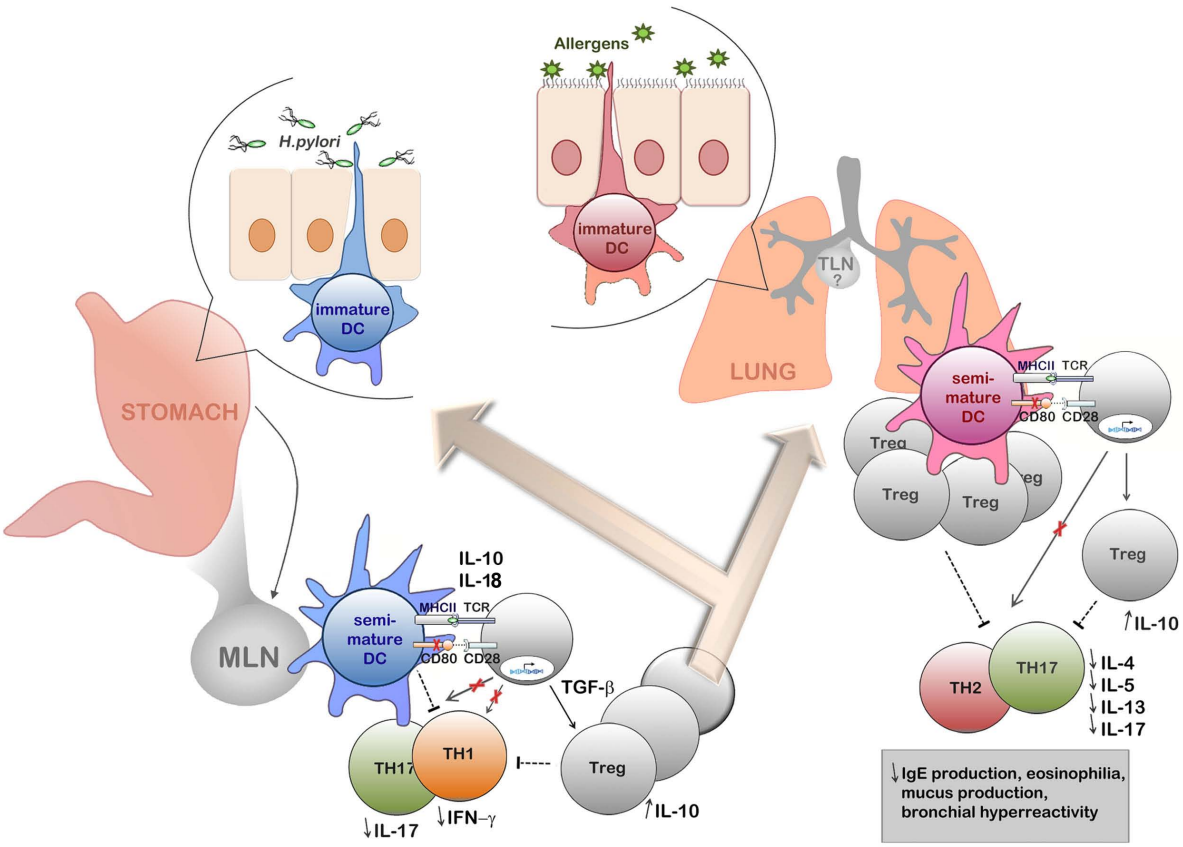

FIGURE 1 | Schematic representation of the current model of *H. pylori*-induced immune tolerance and asthma protection. Tolerogenic dendritic cells and *H. pylori*-induced regulatory T-cells act in concert to prevent adaptive Th1/Th17-driven immunity to the infection and to inhibit allergen-specific Th2 responses. In chronically infected humans, *H. pylori* resides exclusively in the gastric mucosa, where it is presumably encountered and detected by tissue-resident DC populations extending dendrites into the gastric lumen. *H. pylori*-experienced DCs migrate to the gut-draining mesenteric lymph nodes, where they act as potent inducers of TGF-β-dependent FoxP3$^+$ regulatory T-cells, but fail to prime *H. pylori*-specific Th1 and Th17 responses. Induced Tregs may further perpetuate the tolerogenic effects of *H. pylori*-experienced DCs by retaining mesenteric lymph node DCs in a semi-mature state and by directly suppressing *H. pylori*-specific gastric Th1 and Th17 responses, thereby protecting the host from excessive gastric immunopathology. Newly induced Tregs further migrate to the lung, where they suppress allergen-specific Th2 and Th17 responses involved in the pathogenesis of asthma. The generation of allergic T-cell responses may be blocked either through the tolerogenic effects of Tregs on DCs (retaining DCs in a semi-mature state) or directly through suppression of Th2 and Th17 responses via Treg/T-effector cell contact or via soluble cytokines, in particular IL-10. The ultimate outcome of gastric *H. pylori* infection on the allergen-challenged lung is reduced eosinophilia, mucus production and airway hyper-responsiveness. The involvement of the tracheal lymph nodes in *H. pylori*-induced asthma suppression is likely, but currently not well understood.

factors promote protection against allergic diseases by stimulating the Treg-specific production of IL-10.

Early onset asthma in children and adolescents is rare in the *H. pylori*-infected population (Chen and Blaser, 2008). *H. pylori*-infected children are known to preferentially launch Treg responses to the pathogen (Harris et al., 2008), which may account for the particularly beneficial effects of *H. pylori* in this population. Similarly, experimental *H. pylori* infection induces a continuum of protection against airway inflammation that is negatively correlated with age at the time of infection. Protection was most evident in neonatally infected mice, which develop *H. pylori*-specific immunological tolerance mediated by long-lived, inducible Tregs (Arnold et al., 2011b). Because the neonatal period of life is a unique developmental stage in which immune responses are highly plastic and inherently biased toward tolerance, Tregs generated during the first weeks and months of life are thought to differ qualitatively in their suppressive potential compared to their adult counterparts. Indeed, murine neonatal $CD4^+$ T-cells were shown to intrinsically differentiate into $CD4^+FoxP3^+$ Tregs in response to TCR stimulation and TGF-β signals (Wang et al., 2010). They further stably express high levels of FoxP3, which renders them particularly suppressive. It is therefore tempting to speculate that the observed inverse correlation between *H. pylori* colonization and allergic asthma is mechanistically linked to neonatally acquired immune tolerance to the bacterium (see The Beneficial Effects of *H. pylori* on Allergic and Chronic Inflammatory Disorders are Mediated by Tregs and Tolerogenic DCs).

H. PYLORI PROTECTS AGAINST INFLAMMATORY BOWEL DISEASE

THE PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE

Other immune system disorders for which inverse associations with *H. pylori* have been examined are the inflammatory bowel diseases (IBDs), chronic inflammatory conditions of unknown etiology of the gastrointestinal (GI) tract. Two main types of IBDs–Crohn's disease and ulcerative colitis are distinguished based on the affected GI region and transmural involvement. Crohn's disease is characterized by transmural inflammation of the bowel preferentially involving the terminal ileum and right colon. Ulcerative colitis manifests as a chronic inflammatory condition of the colonic mucosa; in its most limited form it may be restricted to the distal rectum, while the entire colon is involved in its most advanced form. The main symptoms of both IBDs are diarrhea, abdominal pain, and weight loss. Standard medications for both IBDs include salicylates, corticosteroids, and other immunomodulators; surgery is required for the treatment of bowel stenosis, abscesses, and internal fistulas in Crohn's disease patients. Curative treatment is currently not possible as the etiology of both IBDs is unclear.

In healthy individuals, intestinal mucosal homeostasis is controlled by $FoxP3^+CD4^+$ Tregs, which efficiently suppress pathogenic T-cell responses through IL-10 and TGF-β (Maloy et al., 2003; Kamanaka et al., 2006; Li et al., 2007a). The failure of regulatory networks to control excessive T-cell responses breaks this equilibrium and leads to chronic inflammation. In patients with ulcerative colitis, the intestinal production of IL-4 and IL-13 cytokines is reminiscent of an atypical Th2 adaptive response (Fuss et al., 1996), whereas Crohn's disease patients present a Th1-polarized cytokine profile, with production of interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and IL-12 (Fuss et al., 1996). In addition, both types of diseases are characterized by the accumulation of IL-17-producing $CD4^+$ T-cells, termed Th17 cells (Annunziato et al., 2007). These cells differentiate from naïve T-cells through the synergistic effects of IL-6 and TGF-β, IL-1, and IL-21 (Veldhoen et al., 2006; Korn et al., 2007) and require IL-23 for their maintenance and expansion (Ouyang et al., 2008). Recent work has shown that IL-23 drives chronic intestinal inflammation in a mouse model of colitis by directly targeting T-cells, and induces their proliferation and accumulation in the colon (Hue et al., 2006). IL-23 further favors the emergence of an immunogenic $IL\text{-}17A^+IFN\text{-}\gamma^+$ double-positive $CD4^+$ T-cell subset (Hue et al., 2006; Ahern et al., 2010) and inhibits the differentiation of $FoxP3^+$ Treg cells (Kullberg et al., 2006; Ahern et al., 2010), suggesting that the IL-23/Th17 axis is a major determinant in the pathogenesis of IBD. The key role of IL-23 is also supported in humans, as increased expression of IL-23 is detected in IBD patients and mutations in the *IL23R* gene increases susceptibility to both Crohn's disease and ulcerative colitis (Ahern et al., 2010). IL-23 can also drive inflammation in the absence of T-cells. In lymphocyte-deficient $Rag^{-/-}$ mice, the development of colitis following *Helicobacter hepaticus* infection or treatment with agonistic anti-CD40 antibody depended on IL-23 (Hue et al., 2006; Yen et al., 2006). This inflammation was further attributed to an IL-23-responsive innate lymphoid population that expresses IL23R, Thy1 and RORγt, and secretes IL-17 and IFN-γ (Buonocore et al., 2010). The detection of a similar innate lymphoid cell population in the inflamed intestine of patients provided evidence for a functional role of IL-23-responsive innate cells in the pathogenesis of IBD (Buonocore et al., 2010).

HELICOBACTER INFECTION IS INVERSELY CORRELATED WITH IBD

Several epidemiological studies have examined a possible inverse correlation between IBDs and *Helicobacter* infection. A Hungarian study investigating 133 IBD patients (both Crohn's and colitis patients) and similar numbers of controls found a significant inverse association with *H. pylori* infection (Pronai et al., 2004); whereas only 13% of IBD patients carried *H. pylori*, the rates ranged from 39 to 67% in various control groups (Pronai et al., 2004). This result was confirmed in a Polish study examining 94 pediatric IBD patients (both types of IBD), which revealed a lower *H. pylori* colonization rate in patients compared to healthy controls (9.6 vs. 38.4%, $p < 0.0001$; Sladek et al., 2007). A recent meta-analysis conducted by Luther et al. (2010) of 30 articles examining such a possible link confirmed that *H. pylori* infection may indeed confer some level of protection against IBD, with only 27% of IBD patients showing evidence of *H. pylori* infection compared to 41% of patients in the control group. The authors caution, however, that the heterogeneity among examined studies and the possibility of publication bias may limit the certainty of their findings. It is therefore all the more interesting that the same group has provided experimental evidence of protective effects of *H. pylori* infection on *Salmonella typhimurium*-induced colitis. Upon co-infection of both bacteria, *H. pylori* suppressed *Salmonella*-specific Th17 responses in the cecum, and reduced cecal inflammation caused by

Salmonella infection (Higgins et al., 2011). The protective effects were linked to increased levels of IL-10 in the mesenteric lymph nodes of co-infected over *Salmonella*-only infected mice, suggesting that this regulatory cytokine modulates the differentiation and/or activity of Th17 cells (Higgins et al., 2011). The same group has attributed the protective effects of *H. pylori* on colitis to the bacteria's chromosomal DNA, which appears to exhibit a high ratio of immunoregulatory to immunostimulatory sequences (Luther et al., 2011) and is by itself sufficient to prevent sodium dextran sulfate-induced colitis. In their experimental protocol, Luther et al. (2011) treated mice with one orally administered dose of 20–50 μg *H. pylori* DNA prior to subjecting them to an acute and a chronic protocol of colitis induction; in both models, administration of the DNA reduced the pathology and also attenuated other parameters of DSS-induced colitis such as bleeding and weight. The protective properties of *H. pylori* DNA were attributed to inhibition of cytokine production by DC, which upon addition of the DNA failed to produce type I interferon and IL-12 in response to *E. coli* DNA (Luther et al., 2011). Whether *H. pylori* DNA is indeed the relevant factor conferring protection against IBD in humans or mice remains to be elucidated in more detail; in fact, data showing protection by live infection in IBD models other than acute *Salmonella*-induced colitis are currently not available.

H. PYLORI MAY PROTECT AGAINST OTHER T-CELL-DRIVEN AUTO-IMMUNE DISEASES

Given the documented protective effects of *H. pylori* infection on asthma and other allergic disease manifestations on the one hand, and IBD on the other, the possibility has been raised that the presence or absence of this infection may also influence the risk of developing additional T-cell-driven immunological or metabolic disorders (Blaser and Falkow, 2009). The incidence of auto-immune diseases caused by the aberrant activation of aggressive autoreactive T-cells, such as multiple sclerosis (MS) and type I diabetes mellitus, has increased sharply in the second half of the twentieth century (Bach, 2002), i.e., in the time frame in which *H. pylori* has begun to disappear – at least in recent birth cohorts – from human populations in most developed countries (Blaser and Falkow, 2009). Socioeconomic conditions favoring lower *H. pylori* transmission and infection rates, such as frequent use of antibiotics in childhood, small family size, and non-crowded housing (Blaser and Falkow, 2009) have all also been found to be associated with a higher prevalence of allergic and auto-immune diseases (Bach, 2002). While a possible inverse correlation between *H. pylori* infection and auto-immune diseases remains largely speculative at this point in time, it is tempting to postulate that the same immunomodulatory and immunoregulatory mechanisms protecting infected individuals from allergic asthma may also be operative against excessive T-cell-driven auto-immune activation. The pathogenesis of auto-immune diseases has been studied most thoroughly in MS, an auto-immune disorder directed against the myelin sheath of neuronal axons, causing demyelination and a broad spectrum of CNS symptoms. In MS, as in IBD (see *H. pylori* Protects Against Inflammatory Bowel Disease), the Th17 subset of helper T-cells is thought to be the driving force behind the chronic (neuro-) inflammation causing disease symptoms. It is now widely accepted that Th17 cells, not Th1 cells as believed previously (Gutcher and Becher, 2007), are the main encephalitogenic population in auto-immune neuro-inflammation in experimental auto-immune encephalomyelitis (EAE), the standard mouse model of MS. Pathogenic auto-immune Th17 cells are characterized by the secretion of the cytokines IL-22, IL-21, IL-17A, IL-17F, and GM–CSF (Littman and Rudensky, 2010). A recent study has reported a dominant role for Th17-derived GM–CSF in auto-immune CNS inflammation based on the evidence that autoreactive helper T-cells specifically lacking GM–CSF failed to initiate neuro-inflammation despite expression of IL-17A and IFN-γ, whereas GM–CSF secretion by *Ifng*$^{-/-}$Il17a$^{-/-}$ helper T-cells was sufficient to induce EAE (Codarri et al., 2011).

Very little solid epidemiological data is available to date to support a protective effect of *H. pylori* on the development of MS. One study has found an inverse correlation of *H. pylori* infection with MS in the Japanese population (Li et al., 2007b), and some studies point to a higher prevalence of MS in adults with a record of having been afflicted with asthma in childhood (Ponsonby et al., 2006). In the study by Li et al. (2007b) examining 105 MS patients and 85 healthy controls, *H. pylori* seropositivity was significantly lower in patients with conventional MS (22.6%) relative to the healthy controls (42.4%). This result obviously remains to be confirmed in larger patient cohorts, and should also be experimentally examined in the EAE model of MS. In EAE, CNS inflammation and progressive paralysis of the tail and hind limbs is entirely driven by myelin-specific auto-aggressive T-cells (Codarri et al., 2011), and should therefore be susceptible to *H. pylori*-induced, Treg-mediated immunoregulation. Other experimental models of auto-immune disease, such as the non-obese diabetic model of type I diabetes (Chaparro et al., 2006) may provide informative results as well.

THE BENEFICIAL EFFECTS OF *H. PYLORI* ON ALLERGIC AND CHRONIC INFLAMMATORY DISORDERS ARE MEDIATED BY TREGS AND TOLEROGENIC DCs

TREGS PROMOTE *H. PYLORI* PERSISTENCE, LIMIT GASTRIC INFECTION-ASSOCIATED IMMUNOPATHOLOGY AND PREVENT AIRWAY HYPER-RESPONSIVENESS IN MICE

Numerous recent reports have implicated Tregs and DCs with tolerogenic activity in mediating the systemic immunomodulatory effects of *H. pylori* infection, both in human carriers, and in experimentally infected animals. In a seminal study examining human gastric T-cell responses to *H. pylori* infection, Robinson et al. (2008) showed that patients with peptic ulcer disease exhibited stronger Th1 and Th2 responses to *H. pylori* than asymptomatic carriers; conversely, the latter group predominantly mounted Treg responses to the infection. IL-10-expressing Tregs were particularly abundant in the gastric mucosa of the normal carriers compared to the peptic ulcer disease patients; interestingly, mucosal IL-10 levels were directly correlated with bacterial densities, with asymptomatic carriers showing high IL-10 expression receiving the highest colonization scores and peptic ulcer disease patients with low IL-10 expression receiving comparatively low colonization scores (Robinson et al., 2008). In a similar study conducted by Harris et al. (2008) the relatively mild gastritis typical of *H. pylori*-infected children could also be linked to Treg-predominant T-cell responses. Children with a mild form of gastritis exhibited higher

gastric mucosal Treg numbers and higher levels of the regulatory cytokines IL-10 and TGF-β than adults with more severe gastritis (Harris et al., 2008). Evidence for a functional role for Tregs and Treg-derived cytokines in promoting *H. pylori* persistence on the one hand, and in mediating *H. pylori*-induced immunomodulation on the other has been provided in experimental infection models. The earliest such evidence came from IL-10$^{-/-}$ mice, which are able to spontaneously clear *Helicobacter* infections, but suffer from – at least temporarily – strongly enhanced Th1 mediated gastritis (Ismail et al., 2003). The depletion of Tregs in mice infected with *Helicobacter* at 6 weeks of age using a CD25-specific antibody resulted in a strong reduction in colonization, and in accelerated and enhanced gastritis (Sayi et al., 2011). The depletion of Tregs in a genetic mouse model in which the diphtheria toxin receptor is expressed under the Treg-specific *foxp3* promoter (*foxp3*-DTR-transgenic mouse) also resulted in clearance of the infection and in severe gastritis, even accompanied by the development of preneoplastic gastric lesions (Arnold et al., 2011b). Mice whose CD4$^+$ T-cells cannot respond to TGF-β due to transgenic expression of a dominant-negative form of TGF-β receptor II also develop strongly enhanced pathology and spontaneously reduce bacterial burdens (Arnold et al., 2011b), indicating that TGF-β-dependent inducible Tregs, but not TGF-β-independent natural Tregs, are predominantly involved in maintaining persistence and in mediating *H. pylori*-specific immunomodulation. Interestingly, the systemic depletion of Tregs in the *foxp3*-DTR-transgenic model improved the clearance of *H. pylori* by vaccinated mice, suggesting that the efficacy of an *H. pylori* vaccine is significantly hampered by the Treg-mediated suppression of protective effector T-cell responses (Hitzler et al., 2011). The latest evidence for an important role of Tregs in the immunomodulation conferring protection against asthma was provided by the finding that the depletion of Tregs abrogates asthma protection (Arnold et al., 2011a). Conversely, as mentioned above, purified Tregs alone were sufficient to transfer protection from *H. pylori*-infected donors to uninfected recipients (Arnold et al., 2011a). Whereas as few as 100'000 Tregs isolated from neonatally infected donors were suppressive in the asthma model, Tregs from uninfected or adult-infected mice failed to confer protection (Arnold et al., 2011a). The selective suppressivity of Tregs from neonatally infected mice can be attributed to the fact that neonatal exposure to *H. pylori* induces immune tolerance to the bacteria (Arnold et al., 2011b).

H. PYLORI RE-PROGRAM DCs TOWARD TOLEROGENICITY

In contrast to natural Tregs, which originate from the thymus, inducible Tregs are generated in the periphery. Certain populations of poorly immunogenic DCs are believed to initiate and maintain peripheral immune tolerance through the induction of anergy, deletion of autoreactive T-cells and the instruction and differentiation of inducible Tregs (Maldonado and von Andrian, 2010). Such tolerogenic DCs function by converting naive T-cells into FoxP3$^+$ Tregs through antigen presentation in the absence of co-stimulatory signals or cytokines, either alone or in combination with the production of soluble and membrane-bound tolerogenic factors such as IL-10, TGF-β, retinoic acid, and programmed death ligands (PD-Ls; Kretschmer et al., 2005; Maldonado and von Andrian, 2010). DCs appear to indeed play a central role in the induction and maintenance of *H. pylori*-specific immune tolerance (**Figure 2**). The depletion of DCs impairs vaccine-induced protective immunity to a similar degree as the depletion of Tregs in the same model (Hitzler et al., 2011). In experimental infection models using adult-infected mice, the depletion of DCs improves the control of the infection and strongly enhances gastric T-cell infiltration and chronic gastritis (Hitzler et al., 2011). DCs isolated from the mesenteric lymph nodes of neonatally infected, tolerant mice exhibit tolerogenic properties *ex vivo*, i.e., they act as poor inducers of Th1 or Th17 cells, and excellent inducers of Tregs (Oertli et al., 2012). The depletion of DCs from neonatally infected, tolerant mice is consequently sufficient to break tolerance (Oertli et al., 2012). Whereas a functional role for DCs in balancing tolerance and immunity in *Helicobacter* infection is thus well established, the underlying mechanism is much less thoroughly understood. Evidence from *in vitro* infection of bone-marrow-derived DCs suggests that *H. pylori* possesses the ability to profoundly re-program DCs toward tolerogenicity (**Figure 2**; Kao et al., 2010; Oertli et al., 2012). DCs that have been exposed to *H. pylori* fail to undergo maturation upon stimulation with *E. coli* LPS; the IL-12 secretion and up-regulation of the co-stimulatory molecules CD80, CD86, and CD40 that are hallmarks of LPS-matured DCs are prevented by the infection (**Figure 2**; Oertli et al., 2012). *H. pylori*-exposed DCs further efficiently induce FoxP3 expression in co-cultured naive T-cells in a TGF-β-dependent manner, but fail to prime Th1 or Th17 cells (Kao et al., 2010; Oertli et al., 2012). The ability of *H. pylori* to re-program DCs in such a manner requires direct contact (Oertli et al., 2012), but is independent of the virulence factor CagA (Kao et al., 2010).

THE TOLEROGENICITY OF DCs REQUIRES THE SYNTHESIS, PROCESSING, AND SECRETION OF INTERLEUKIN-18

The tolerogenic activity of DCs requires the DC-intrinsic expression and processing of IL-18 (**Figure 2**), as demonstrated by the inability of IL-18$^{-/-}$ DCs to induce FoxP3 expression in co-cultured T-cells and the failure of IL-18 receptor-deficient (IL-18R$^{-/-}$) T-cells to convert to FoxP3$^+$ Tregs upon co-culturing with *H. pylori*-infected wild type DCs (Oertli et al., 2012). Indeed, IL-18$^{-/-}$ as well as IL-18R$^{-/-}$ mice exhibit significantly lower Treg numbers in their mesenteric lymph nodes than wild type mice under conditions of *Helicobacter* infection, and generate stronger Th17 responses and develop more severe infection-associated immunopathology (Oertli et al., 2012). CD4$^+$CD25$^+$ cells isolated from infected IL-18$^{-/-}$ or IL-18R$^{-/-}$ donors fail to prevent allergen-induced asthma, indicating that not only the differentiation, but also the suppressive activity of Tregs depends on IL-18 signaling (Oertli et al., 2012). The current model thus assumes that the availability of IL-18 dictates whether naive T-cells co-cultured with DCs differentiate into Th1, Th17, or Treg cells; whereas Th1 and Treg differentiation depend crucially on IL-18, Th17 cells develop under conditions where IL-18 is lacking (**Figure 2**). The results obtained in the *H. pylori* model are reminiscent of the hypersusceptibility of IL-18$^{-/-}$ animals toward experimentally induced colitis, which has been attributed to the lack of Nlrp6 inflammasome activation (Elinav et al., 2011). Which nod-like receptors are involved in the innate immune recognition of *H. pylori* leading to caspase-1 activation and IL-18 processing remains

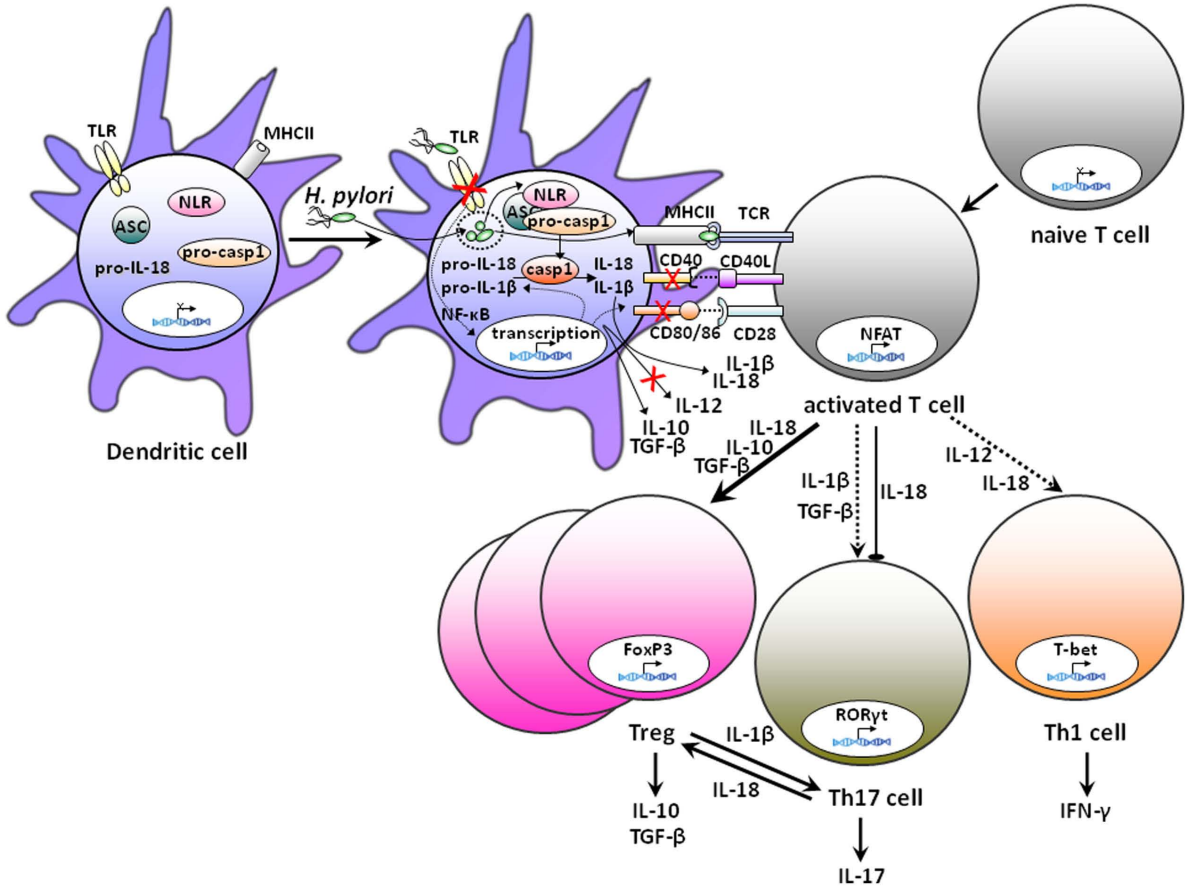

FIGURE 2 | Schematic representation of the effects of *H. pylori* exposure on DCs and the DC/T-cell interaction. Exposure to *H. pylori* induces semi-mature DCs with high expression of MHC class II, but only low to moderate expression of the co-stimulatory molecules CD40, CD80, and CD86, and of the cytokine IL-12. In contrast, IL-10 is made in large quantities by *H. pylori*-experienced DCs. Inflammasome activation by *H. pylori* through as yet uncharacterized cytoplasmic nod-like receptors (NLRs) leads to caspase-1 activation and the processing and secretion of IL-1β and IL-18. IL-1β promotes Th17 differentiation, whereas IL-18 is required for Th1 and Treg differentiation. *H. pylori*-experienced DCs actively induce the conversion of naive T-cells to FoxP3$^+$ Tregs in a process that requires IL-18, TGF-β, and possibly IL-10. In contrast, *H. pylori*-experienced DCs are poor inducers of Th17 and Th1 differentiation. The documented lack of *H. pylori* TLR ligands in conjunction with efficient inflammasome activation by the bacteria suggests that the relative availability of pro-IL-1β (low level expression due to lack of transcriptional activation) and pro-IL-18 (high levels due to constitutive expression) for caspase-1 processing may dictate the outcome of the DC/T-cell interaction.

to be determined. It is interesting to note in this context that *H. pylori* lacks many TLR ligands shared by other gram-negative, pathogenic bacteria. *H. pylori* flagellin is a poor ligand of TLR5 (Gewirtz et al., 2004) due to mutations in the TLR5 recognition site of the N-terminal D1 domain of flagellin (Andersen-Nissen et al., 2005). The bacterium's LPS consists predominantly of the tetra-acylated lipid A variety, which is known to exhibit 1000-fold reduced bioactivity as compared to *E. coli* LPS (Moran et al., 1997). While *H. pylori* harbors TLR2 ligands (Rad et al., 2009; Sayi et al., 2011), these exhibit predominantly anti-inflammatory properties *in vivo* (Sayi et al., 2011). The combined results imply that the lack of (pro-inflammatory) TLR signaling in conjunction with high level inflammasome activation and IL-18 secretion may favor Treg over Th17 differentiation during *H. pylori* infection. Our recent finding that addition of *E. coli* LPS can reverse the tolerogenic effects of *H. pylori* on DCs (Oertli et al., 2012) lends further support to this model. LPS is a strong inducer of IL-1β, which in turn is required for Th17 polarization (**Figure 2**). The relative availability of IL-1β and IL-18, which is influenced by TLR-/Myd88- and NF-κB-dependent transcriptional activation of IL-1β expression (IL-18, in contrast, is preformed and stored in granules, and not subject to extensive transcriptional regulation), thus dictates whether Tregs or Th17 cells are preferentially induced. In the context of *H. pylori* exposure of DCs, IL-18 is produced in copious amounts due to efficient inflammasome activation; in contrast, due to the concomitant lack of TLR-mediated transcriptional activation, IL-1β is not available for caspase-1-mediated processing, leading to the preferential differentiation of naive T-cells into Tregs as opposed to Th17 cells (**Figure 2**).

As Th17 cells have been implicated in adaptive immunity to *H. pylori* infection (DeLyria et al., 2009; Velin et al., 2009; Hitzler et al., 2011), the preferential induction of Tregs over Th17 cells may have conferred a selective advantage to the bacteria in the 60000 years

of co-evolution of *H. pylori* with its human host (Moodley et al., 2009) and explains why infected individuals with strong gastric Treg, but weak T-effector responses show the highest levels of colonization and the least severe gastric pathology (Robinson et al., 2008). An only recently recognized bystander effect of the strong *H. pylori*-specific Treg induction is cross-suppression of allergen- or autoantigen-specific T-cell responses (Arnold et al., 2011a), which results in the above-discussed protective effects against asthma and other allergies, as well as against IBDs.

CONCLUSION AND PERSPECTIVES

Two avenues of active research in the *Helicobacter* field will likely benefit most from integrating the concepts outlined here into current models and strategies; on the one hand, it is obvious that *H. pylori* – or at least its tolerance-promoting properties – should be harnessed for the development of new preventive or therapeutic strategies in the treatment of asthma and other allergies, and of IBDs. Whether an infection-independent strategy sometimes referred to as "tolerizing vaccination" will work in this context remains to be seen. On the other hand, vaccine development efforts directed at eradicating *H. pylori* (therapeutically or prophylactically) must take into account the need to overcome the immunomodulatory properties of this infection if sterilizing immunity is to be achieved. Finally, it will be interesting to compare the strategies that *H. pylori* has evolved to establish and maintain persistent infection to those exploited by other chronic bacteria such as mycobacteria and *Salmonella*. Overriding the immune evasion and – modulation strategies of persistent bacterial infections is a crucial first step in breaking the asymptomatic carrier state and in successfully interrupting the transmission cycle that perpetuates the worldwide public health problems associated with these persistent infections.

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