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The role of Th cell subsets in the control of Helicobacter infections and in T cell-driven gastric immunopathology

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INTRODUCTION
Persistent colonization of the human gastric mucosa with the Gram-negative bacterial pathogen Helicobacter pylori causes gastritis (Marshall and Warren, 1984) and predisposes carriers to a high risk of developing gastric and duodenal ulcers, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma (Parsonnet et al., 1991, 1994; Parsonnet and Isaacson, 1995; Parsonnet and Isaacson, 1996; Personnet et al., 2011; Personnet and Isaacson, 2005; Pritchard and Crabtree, 2006). H. pylori infection–associated gastric cancer develops via a sequence of histologically defined preneoplastic lesions, all of which have been linked independently to gastric cancer risk (Correa, 1995; Fox and Wang, 2007). Experimental infection of Mongolian gerbils (Rieder et al., 2005; Weidemann et al., 2009) or C57BL/6 mice with Helicobacter species recapitulates the sequential development of chronic gastritis, atrophic gastritis, epithelial hyperplasia, and intestinal metaplasia, all of which are hallmark lesions in a subset of particularly susceptible human H. pylori carriers (Correa, 1995; Fox and Wang, 2007). H. pylori patient isolates and the closely related species H. felis have been used successfully to induce gastric preneoplastic lesions in mice (Fox et al., 2002, 2003; Sayi et al., 2009; Arnold et al., 2011). Several lines of experimental evidence suggest that precancerous lesions in the infected stomach are immunopathological in origin, i.e., they arise as a consequence of T cell-driven adaptive immune responses to the infection. (1) Mice lacking a B and/or T lymphocyte compartment (Rag-1−/−, TCR-β−/−) are resistant to gastritis induced by Helicobacter infection, and the adoptive transfer of CD4+ T effector T cells from infected wild type (WT) donors to infected Rag-1−/− recipients is in itself sufficient to restore the full range of gastritis and preneoplastic pathology (Buch et al., 1999; Smythies et al., 2000; Sayi et al., 2009, 2011; Arnold et al., 2012). (2) Prior immunization with a cholera toxin-adjuvanted, whole cell vaccine aggravates, rather than prevents, infection-induced preneoplastic pathology (Mueller et al., 2009; Sayi et al., 2009). (3) Finally, mice that have been infected during the neonatal period, i.e., at a time when their immune system is not yet fully developed and inherently biased toward immune tolerance rather than immunity, are largely protected against infection-associated pathology (Arnold et al., 2011). Observational studies in human carriers support the view that pathogenic T cells are instrumental in inducing H. pylori-associated lesions: Robinson et al. (2008) showed for instance that patients with peptic ulcer disease exhibited stronger Th1 and Th2-
responses to H. pylori than asymptomatic carriers. Conversely, the asymptomatic carriers were characterized by a regulatory T cell (Treg)-predominant response to the infection. Tregs expressing the anti-inflammatory cytokine interleukin (IL)-10 were particularly abundant in the gastric mucosa of the normal carriers compared to the peptic ulcer disease patients (Robinson et al., 2009). 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 and higher levels of IL-10 and TGF-β.

Whereas a causal role for T cells in H. pylori infection-associated pathology has thus been rather well established, the contribution of the various T helper-cell subsets (defined by their cytokine profiles and lineage-determining transcription factors) is less thoroughly understood. Th1 and Th17 cell subsets have both been alternatively implicated in infection control on the one hand, and preneoplasia on the other (Aligood et al., 2009; Otani et al., 2009; Sayi et al., 2009; Stoico et al., 2009; Sheh et al., 2010; Shi et al., 2010). However, most of these studies examined one Th1 or Th17 cytokine in isolation, rather than analyzing mice that have defects in generating both Th1 and/or Th17 subsets. We have recently exploited mouse strains with targeted deletions of H. pylori and H. felis disease pathways (Hitzler et al., 2011). p19 and p35 represent the unique subunit of the Th17- and Th1-inducing cytokines IL-23 and IL-12, respectively, covalently linked heterodimers which are each composed of a unique (p19 or p35) chain and the shared p40 chain (Oppmann et al., 2000). IL-23p19 was alone responsible for either of the two processes under our surprise, we found that, despite the fact that T cells express-
STATISTICAL ANALYSIS
All P-values were calculated using Graph Pad prism 5.0 or R software. The significance of categorical differences in histopathology scores was calculated by Mann–Whitney test and the significance of numerical differences was calculated by Student’s t-test. In all graphs showing colonization data and histopathology scores, the medians are indicated by horizontal bars. In column bar graphs, standard errors of the mean are indicated by vertical bars. n.a. denotes “not applicable,” and n.s. stands for “not significant.”

RESULTS
TCR-β−/− mice fail to control H. felis infection, but are protected against gastric preneoplasia
We and others have reported previously that C57BL/6 mice lacking αβ T cells due to a targeted mutation of the gene encoding the β-chain of the TCR are protected against the early infection-associated gastritis that is a hallmark of T cell proficient animals (Roth et al., 1998; Smythies et al., 2000; Sayi et al., 2009). To assess whether the relative resistance to the earliest detectable histopathological symptoms of Helicobacter infection translates into long-term protection from disease, we infected WT C57BL/6 and TCR-β−/− mice with H. felis for 3 months; we chose H. felis due to its documented virulence in mice (Fox et al., 2002, 2003; Sayi et al., 2009). WT mice infected with H. felis were colonized persistently, albeit at rather low levels (Figure 1A) as reported previously (Sayi et al., 2009), and the majority developed gastritis, atrophy, epithelial hyperplasia, and/or intestinal metaplasia (Figures 1B,C). In contrast, TCR-β−/− mice were colonized at higher levels (Figure 1A), and were completely protected from infection-associated gastric preneoplastic lesions (Figures 1B,C). The results indicate that αβ T cells contribute critically to Helicobacter control and to gastric Helicobacter-associated immunopathology and confirm previous results that have used SCID mice (Smythies et al., 2000) and Rag-1−/− and TCR-β−/− mice (Roth et al., 1998; Sayi et al., 2009, 2011) for H. pylori or H. felis infections.

NEITHER IL-12-DEPENDENT TH1 NOR IL-23-DEPENDENT TH17 CELLS ARE ABSOLUTELY REQUIRED FOR THE CONTROL OF EXPERIMENTAL H. FELIS INFECTION
To assess the contribution of Th1 and Th17 cells to H. felis infection control, we infected WT, IL-12p35−/−, and IL-23p19−/− mice with H. felis for 3 months and compared their colonization levels. All three groups were colonized at comparable levels (Figure 2A), and exhibited the wide intragroup variation in H. felis colonization densities that is a hallmark of this infection (see Figure 1A). To assess whether the defect in generating functional Th1 and Th17 subsets is a well-documented feature of IL-12p35−/− and IL-23p19−/− mice, respectively (Cua et al., 2003; McGeachy and Cua, 2008), would manifest in decreased levels of the respective signature cytokines IFN-γ and IL-17, we isolated RNA from the gastric mucosa of all animals included in the study. To our surprise, neither the gastric mucosal expression of IFN-γ (Figure 2B), nor of IL-17 (Figure 2C), was linked to the genotype of the mice, suggesting either that the bulk of both cytokines is produced by sources other than Th1 and Th17 cells, or that factors other than IL-23 and IL-12 influence Th17 and Th1 polarization in the context of Helicobacter infection. In conclusion, H. felis infection is controlled by T cells, but independently of IL-12-dependent Th1 and IL-23-dependent Th17 cell subsets.

IL-12 AND IL-23 ARE NOT ABSOLUTELY REQUIRED FOR THE INDUCTION OF GASTRIC PRENEOPLASTIC PATHOLOGY
To determine a possible contribution of IL-12-dependent Th1 and IL-23-dependent Th17 cell subsets to gastritis and gastric preneoplastic pathology, the gastric histopathology of all H. felis-infected mice of the three genotypes was examined and scored with respect to the severity of gastritis, atrophy, epithelial hyperplasia, and intestinal metaplasia (Figures 3A,B). All WT, IL-12p35−/−, and IL-23p19−/− mice had developed mild to severe gastritis in the course of the infection, and no significant differences were observed between groups in terms of the average severity grade (Figures 3A,B). Virtually all WT, and a majority of IL-12p35−/− and IL-23p19−/− mice had further developed atrophy, hyperplasia, and metaplasia; again, considerable variation was observed within groups (as reported previously, Sayi et al., 2009) and no significant differences were obtained between groups. The combined results suggest that gastric cancer precursor lesions develop readily in H. felis-infected mice, even under conditions where the generation of Th1 or Th17 cells is impaired due to the lack of the respective Th-polarizing cytokines IL-12 and IL-23.

NEITHER TH1 NOR TH17 CELLS ARE ABSOLUTELY REQUIRED FOR THE CONTROL OF EXPERIMENTAL INFECTION WITH AN H. PYLORI PATIENT ISOLATE
To confirm our findings in an alternative model of Helicobacter-induced disease, we infected animals of the three genotypes with a recently described H. pylori patient isolate, strain PMSS1 (Arnold et al., 2011). This strain is highly virulent in mice due to its Cag pathogenicity island-encoded type IV secretion system; the pathology induced by PMSS1 is qualitatively similar to H. felis-induced lesions, both in terms of the kinetics and severity of disease (Arnold et al., 2011). As observed with H. felis, there were no significant differences in colonization levels between the three host strains (Figure 4A). The evaluation of gastric histopathology revealed relatively minor differences between the strains, which reached statistical significance for some parameters (Figure 4B). Th17-deficient IL-23p19−/− mice appeared to be somewhat protected against advanced preneoplasia, as atrophy, hyperplasia, and metaplasia were less common and less severe in this group. A similar finding was recently reported by another lab utilizing the PMSS1 derivative SS1 in 3-month infection experiments conducted in the same IL-23p19−/− strain (Horvath et al., 2012), supporting the notion that IL-23-dependent Th17 cells contribute to H. pylori-induced gastric immunopathology. In conclusion, the two infection models combined imply that neither Th1 nor Th17 cells are critical for Helicobacter control, but suggest that IL-23 (and Th17 cells) may contribute to the gastric T cell-driven immunopathology associated with this infection.

DISCUSSION
Several previous studies have addressed the contribution of Th1 and Th17 cells to infection control and gastric preneoplastic...
pathology. We and others found that IFN-γ production by T cells, and the expression of the Th1 lineage-committing transcription factor T-bet, respectively, are required for *H. pylori*-induced gastric preneoplasia in mice (Sayi et al., 2009; Stoicov et al., 2009). Similarly, Sheh et al. (2010) noted an increased mutation frequency in the *H. pylori*-infected murine gastric mucosa that they attributed to *H. pylori*-specific Th1 responses and prolonged exposure to oxidative stress. The available data on a causal role of Th17 cells in gastric pathology is somewhat conflicting. Whereas Shi et al. (2010) reported that both IL-17 neutralization and IL-17 gene targeting reduced gastric inflammation, the groups of Otani et al. (2009) and Algood et al. (2009) each detected more, rather than less, gastric inflammation upon IL-17 neutralization (Otani et al., 2009) and in IL-17A receptor gene-targeted mice (Algood et al., 2009). All studies available thus far on a possible Th17 contribution to gastric

![Diagram](image-url)
T cell subsets in Helicobacter infection

pathology share the caveat of examining one specific Th17 cytokine (IL-17), which, to complicate things further, is also expressed by other cell types such as innate lymphoid tissue inducer cells (Takatori et al., 2009), γ/δ T cells and various non-lymphocyte sources. However, Th17 cells produce two forms of IL-17 – IL-17A and IL-17F – in addition to IL-22 and IL-21, lymphocyte sources). However, Th17 cells produce two forms of IL-17 – IL-17A and IL-17F – in addition to IL-22 and IL-21, of both cytokine transcripts directly precedes the effector phase of Th cell subset (Becher and Segal, 2011). We therefore believe that IL-23p19−/− mice with their complete defect in generating IL-23-dependent Th17 responses (and IL-12p35−/− mice defective for Th1 responses; Cua et al., 2003; McGeeachy and Cua, 2008) represent the best currently available models to dissect the contribution of both subsets to immunity and to gastric disease.

To our surprise, we found that neither subset was alone required for the control of H. felis or H. pylori infection, as colonization levels – known to be tightly controlled by T cells – did not differ across the three mouse strains analyzed. The results suggest that fundamentally different mechanisms govern the spontaneous (rather ineffective) control of Helicobacter infections, and the effective clearance of H. pylori in vaccinated mice. Whereas the development of vaccine-induced protective immunity and the clearance of H. pylori challenge infections by vaccinated mice depends crucially on both Th subsets (Hitzler et al., 2011), this is not the case for spontaneous infection control. The Th17 dependence of vaccine-induced protection could be attributed directly to the signature cytokine IL-17, as administration of an IL-17-neutralizing antibody during the challenge phase reduced bacterial clearance (Velin et al., 2009). Indeed, the appearance of IL-17+ and IFN-γ+ CD4+ T cells in the gastric mucosa of vaccinated, challenged mice and the production of large amounts of both cytokine transcripts directly precedes H. pylori clearance in all studies that have investigated this association (DeLariva et al., 2009; Velin et al., 2009; Hitzler et al., 2011). The recruitment of neutrophils and mast cells, both of which contribute critically to the effector phase of H. pylori clearance (Velin et al., 2005; Sayi et al., 2009; Hitzler et al., 2011), depends directly on Th1 and Th17 cells and their signature cytokines (Hitzler et al., 2011). The fact that we find levels of both IFN-γ and IL-17 to be high irrespective of p19 and p35 expression argues that, at least in the context of Helicobacter infections, other cell types may serve as more important sources of these cytokines, or factors other than IL-12 and IL-23 are more relevant for governing Th subset polarization. In fact, Wong et al. (2009) have shown previously that macrophage migration inhibitory factor (MIF) is essential for Th1 differentiation in the Helicobacter-infected host, as MIF-deficient mice fail to generate Th1 responses to the infection and thus are protected against Th1-mediated immunopathology.

Our findings on the contribution of Th1 and Th17 cells to gastric infection-associated pathology were less clear. Whereas gastritis and gastric preneoplastic pathology developed in all three strains upon H. felis infection irrespective of IL-23 and IL-12 expression, a clear reduction in most pathology scores was seen in IL-23p19−/− mice in the H. pylori infection model. The results obtained in this model corroborate the findings of a recent study that also reported reduced gastritis upon H. pylori infection of IL-23p19−/− mice (Horvath et al., 2012). The differences obtained by Horvath et al. (2012) were particularly pronounced for chronic inflammation, and less strong with respect to overall inflammation. Preneclastic pathology characterized by atrophic gastritis, hyperplasia, and metaplasia was not observed upon infection with the SS1 strain used by Horvath et al. (2012) and could therefore not be assessed. While the difference in susceptibility of IL-23p19−/− mice toward H. pylori and H. felis infection is intriguing, the findings need to be reproduced with additional isolates of both species suitable for murine infection before definitive conclusions can be drawn.

In humans, Th responses to H. pylori have been known for a long time to be strongly biased toward Th1. This notion was recently verified once again in a longitudinal study by Perez-Perez et al. (2010), which examined IgG subclass responses in paired serum samples obtained in 1973 and in 1994 from H. pylori-infected, healthy donors. Most (89%) donors exhibited IgG1/IgG4 ratios that were consistent with a predominant
Th1 response and were remarkably stable over the 21-year period (Perez-Perez et al., 2010). Although the Th1-predominant response to H. pylori is largely ineffective at clearing the infection (Perez-Perez et al., 2010), it may have positive side effects in the prevention or suppression of co-infections. Perry et al. (2010) recently presented evidence from H. pylori-infected humans and cynomolgus macaques showing that the Th1 response to H. pylori may have beneficial bystander effects on a co-existing Mycobacterium tuberculosis (Mtbc) infection. The initial hint of an inverse correlation between active tuberculosis and H. pylori came from the observation that IFN-γ responses to Mtbc antigen were 1.5-fold stronger in H. pylori-infected individuals with positive tuberculin skin tests (i.e., latent tuberculosis infection) than in their H. pylori-negative counterparts (Perry et al., 2010). Follow-up studies comparing the H. pylori infection status of active tuberculosis cases and non-progressing household contacts revealed a significantly higher H. pylori seroprevalence in the latter group. This finding was corroborated by a significant inverse relationship between natural H. pylori infection and active tuberculosis in cynomolgus macaques challenged with Mtbc (Perry et al., 2010).

In humans, observational studies suggest a contribution of H. pylori-specific Th1 (and Th2) responses to gastric disease; as mentioned above, patients with peptic ulcer disease showed
Hitzler et al. T cell subsets in Helicobacter infection

FIGURE 4 | IL-23p19−/− and IL-12p35−/− mice do not differ significantly from wild type animals with respect to H. pylori infection control; infection-associated immunopathology is reduced in IL-23p19−/− mice. (A) Colony forming units (CFU) as determined by plating and colony counting of wild type (WT; n = 9), IL-23p19−/− (n = 13), and IL-12p35−/− (n = 15) mice infected with H. pylori strain PMSS1 for 3 months. Note that of the 13 infected IL-23p19−/− animals, only 9 were available for colony counting. (B) Histopathology scores assigned to every mouse shown in (A) for all indicated parameters on a scale of 0–6. Medians are indicated by horizontal lines; each symbol represents one mouse. Data are from two pooled experiments.

stronger gastric Th1 and Th2 responses to H. pylori than asymptomatic carriers, whose responses had a strong regulatory component (Robinson et al., 2008). On the other hand, polymorphisms in the IL-1 gene cluster suspected of enhancing production of IL-1-beta (IL-1β) are associated with an increased risk of both H. pylori-induced hypochlorhydria and gastric cancer (El-Omar et al., 2000). IL-1 signaling in T cells critically regulates early Th17 differentiation (Chung et al., 2009). IL-1 gene cluster polymorphisms may thus potentially contribute to gastric hypochlorhydria and gastric cancer through the induction of Th17 cells; the observation that the stomach-specific expression of human IL-1β is in itself sufficient to induce gastric inflammation and gastric cancer in transgenic mice supports this notion (To et al., 2008). In line with this observation, we have recently reported that IL-1 receptor-deficient mice are completely protected against gastritis and preneoplasia in our H. felis-induced disease model, which we attributed to the complete lack of Th1- and Th17-polarized T cell responses to the infection (Hitzler et al., 2012).

In summary, the results presented here suggest that neither Th1 nor Th17 cells are by themselves absolutely essential for the spontaneous control of Helicobacter infections or for the induction of gastric preneoplastic pathology under all circumstances. Whether both Th subsets synergize to fulfill these functions, or other Th subsets are implicated as well, remains an open question for future investigations.

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