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REVIEW

New perspectives on gastric disorders: the relationship between innate lymphoid cells and microbes in the stomach

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Abstract

A growing number of studies in recent years have revealed the changes in the gastric microbiota during the development of gastric diseases, breaking the stereotype that the stomach is hostile to microorganisms beyond *H. pylori*. After a decade of intensive research, the discovery of innate lymphoid cells (ILCs) has provided a new perspective on the immune response in many diseases. In the context of defense against infectious pathogens, the pre-existing innate defense mechanism of tissue-resident ILCs can rapidly recognize and respond to microbes to eliminate infection at the earliest stages. Here, we outline the basic function of ILCs in the gastric mucosa and in shaping the gastric microbiome. We discuss the interactions between the gastric microbiota and ILCs, explaining how the ILCs actively drive the immune response against bacterial pathogens that can lead to the development of the gastric disease.

Keywords Stomach · Innate lymphoid cells · Microbiome · Mucosal immunology · Gastric disease

Introduction

The human body, including its skin, lungs, gastrointestinal tract, and other mucosal tissues, is home to various types of microbes that play a crucial role in maintaining health [1]. The microbiota colonizing in the intestinal tract has been the most extensively studied due to its high diversity and abundance of microbial species compared to other parts of the body. However, research into the gastric microbiome has been limited for many years. This was largely due to the specific environment of the stomach as a sophisticated endocrine organ for digestion and storage, which was thought to be inhospitable to bacteria, leading to the perception of the stomach as a 'sterile organ' [2]. In addition, previous understanding of the composition and function in gastric microbiome has trailed behind that of the gut microbiome, so the gastric microbiome has often been confused with its gut in counterpart some studies [3]. In fact, the microbiome in the stomach was not studied in detail prior to the discovery of *H. pylori*. Recently, with the development of advanced techniques for analyzing the microbial content of the stomach, the scope of human microbial research has gradually expanded beyond the study of *H. pylori* [4].

The gastric mucosa is a dynamic environment where the host continuously interacts with a diverse community of commensal microorganisms. Although the information on the gastric microbiome has been available for about a decade, the immunological role of the stomach as affected by the microbiota has long been overlooked. However, recent emerging research suggests that the gastric mucosa plays an integral role in immune function, engaging in both innate and adaptive immune responses to maintain microbial balance and immune homeostasis [5, 6]. As such, when the gastric mucosa is exposed to pathogenic or commensal bacteria, both epithelial cells and innate immune cells are mobilized in a complex process to defend the host. Despite this important role of the gastric microbiota, information on the impact of bacteria on immune responses is still limited.

In this review, we will describe the basic features of the gastric microbiota and gastric mucosal immunity and summarize the interactions between them as it related to the pathogenesis of gastric diseases.

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Microbiota composition in the stomach

The traditional view of the stomach as a 'sterile organ' was fundamentally challenged by the discovery of *Campylobacter pyloridis* (now known as *Helicobacter pylori*) in 1982 [7]. This finding demonstrated that bacteria could not only survive but also thrive in the acidic environment of the stomach, fundamentally changing our understanding of the microbial landscape in the stomach. The scientific literature showed that the biomass of the gastric microbiota is relatively low, 10^2 to 10^3 per gram of gastric content, so the study of the gastric microbiota was limited in previous research [8]. Recent advances in high-throughput sequencing technology have led to a paradigm shift in gastric research, describing the composition of the gastric microbiome and breaking the stereotype that the stomach is hostile to microorganisms other than *H. pylori*. Comprehensive microbiome analysis using bacteria-specific 16 S rRNA sequencing has revealed that the major phyla comprising the gastric microbiota are *Proteobacteria* and *Firmicutes*, along with *Bacteroidetes*, *Actinobacteria*, and *Fusobacteria* (Table 1) [9, 10]. Notably, the dominant genera associated with the gastric mucosa are *Neisseria*, *Prevotella*, *Haemophilus*, *Fusobacterium*, *Streptococcus*, and *Veillonella*, which differ significantly from those found in the intestine, namely *Ruminococcus*, *Faecalibacterium* and *Bacteroides* [11]. Therefore, the gastric microbiota is unique compared to the lower intestinal tract and fecal microbiota [4].

Although the gastric microbiota contains relatively low bacterial diversity, the species richness is markedly higher in the corpus than in the antral mucosa [12]. The gastric microbiome also includes the community of non-adherent, transient bacteria, in addition to the persistent bacteria that adhere to the gastric mucosa [13]. Bacterial sequencing provides a picture of the configuration for the gastric microbiota at a specific point in time during the digestive process.

However, whether chronic colonization or transient passage of bacteria from upstream sites (e.g., mouth, nose, esophagus) remains to be inconclusive. The ability of the transient bacteria to interact with the host and penetrate the mucosal layer is attracting increasing attention in the field.

Gastric immunity and homeostasis

The mucosal immunity in the stomach is a crucial part of mucosal defense in human, but its immunological functions are relatively understudied compared to intestinal mucosal immunity. Gastric mucosal cellular immunity is critical for maintaining gastric immune homeostasis, and acts through the synergistic interaction of both innate and adaptive immune responses. The adaptive immune system includes T and B cells; $CD4^+$ T cells have been found to be essential for the cellular immunity of the gastric mucosa, particularly in Th1 and Th17 cells [14]. B cells exert humoral immune functions by internalizing foreign antigens and presenting them to $CD4^+$ T cells in the form of peptides bound to major histocompatibility complex class II (MHC class II) molecules. However, less is known about the innate lymphocyte populations, including natural killer (NK) cells and innate lymphoid cells (ILCs).

The gastric mucosal immune cells interact with gastric epithelial cells and signaling molecules to maintain mucosal health [15]. The gastric mucosal barrier is comprised of three main layers: the epithelial layer, the lamina propria, and the mucosal muscle layer [16]. The epithelial surface of the stomach forms a physical barrier to the 'outside', thereby providing a first layer of defense against infection. In additional to secreting mucus, which forms a physical barrier, the gastric epithelial cells express MHC class II molecules as antigen-presenting cells, thereby contributing to immune defense [17]. Unlike the intestinal tract, the lamina propria of the stomach lacks diffuse lymphoid tissue, and it has been

Table 1 Composition of the microbiome in healthy human stomach

ID	Country of Origin	Sample Type	Bacteria Composition in Stomach	Sequencing Methods	Reference
1	Human (Venezuela, US)	Corpus biopsy samples	*Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Bacteroidetes.*	G2 PhyloChip	Contreras et al. [12]
2	Human (US)	Corpus biopsy samples	*Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria and Fusobacteria.*	16 S rRNA	Bik et al. [10].
3	Human (China)	Mucosal/gastric juice	*Firmicutes, Proteobacteria.*	16 S rRNA	She et al. [3].
4	Human (US)	Gastric aspirate	*Actinobacteria, Proteobacteria, Fusobacteria, Fimicutes*	16 S rRNA	Bassis et al. [13].
5	Human-infants (US)	Gastric aspirate	*Firmicute, Proteobacteria, Tenericute, Actinovacteria*	16 S rRNA	Milisavljevic et al. [14].
6	Human (Brazil)	Gastric aspirate	*Veillonella sp, Lactobacillus sp, and Clostridium sp*	16 S rRNA	Zilberstein et al. [15].
7	Human (US)	Gastric aspirate	*Bacteroidetes species, Proteobacteria, Actinobacteria*	16 S rRNA	Seekatz et al. [16].

thought that there are no immune cells directly involved in immune responses under normal conditions. However, our recent study clearly indicates that innate immunity is a key regulator of gastric mucosal protection, inducing B cells activation via IgA response [6]. In addition, it is also known that other immune cells, such as macrophages, dendritic cells (DCs), and NK cells, are recruited to the lamina propria from the periphery through the blood and initiate an immune response, when gastric mucosa infected by pathogenic microorganisms [16].

ILCs are classified into five major groups based on cytokine profiles and developmental transcription factors: as three groups, group 1 innate lymphoid cells (ILC1s), group 2 innate lymphoid cells (ILC2s), group 3 innate lymphoid cells (ILC3s), and two additional subsets, NK cells and lymphoid tissue inducer (LTi) cells [18]. ILC1s and ILC3s are important for mucosal protection, whereas ILC2s are associated with allergy and chronic inflammation [19]. In contrast to T and B cells, ILCs do not express specific antigen receptors [20, 21]. Studies in both mouse and human gastric mucosa show that ILCs are predominantly ILC2s, with fewer ILC1s and limited ILC3s [22]. It is known that these subsets are plastic, as ILC2 and ILC3 cells can be converted to ILC1 by the upregulation of T-bet and the downregulation of GATA-3 and RORγt, respectively, in both cases coupled with the acquisition of producing IFN-γ [23]. Therefore, strategic modulation of ILCs could be a profound focus for further research.

ILC1s have no or limited direct cytotoxicity against virus-infected cells or cancer cells, but have substantial potential for cytokine and chemokine production capabilities, which is their primary different from NK cells [24, 25]. The population of NK cells can be divided into two compartments, one that circulates in the blood and primary lymphoid organs and the other that resides in tissues such as the gastrointestinal intraepithelial layer and lamina propria layer [26, 27]. In particular, in the context of gastric cancer, several studies have demonstrated that ILC1s play a role in the anti-tumor immune response [28].

ILC2s have a dual role in the gastric mucosa. On the one hand, the regular roles of ILC2s in mucosal immunity are their contributions to maintaining mucosal integrity and tissue remodeling, as well as the anti-parasite effect. On the other hand, some studies have shown that the majority of ILC2s contribute to tumorigenicity. In addition, targeting ILC2s may have therapeutic potential in preventing gastric inflammation and cancer development, and even reversing the pathological changes associated with metaplasia after disease onset [29]. Another study found that there is substantial accumulation of ILC2s in the stomach after injury, which is blocked in mice lacking IL-33, attenuating the development of mucin-secreting metaplasia, expansion of foveolar and tuft cell lineages, and the infiltration and activation of macrophages and eosinophils. These results indicate that ILC2s perform a central role in coordinating gastric epithelial repair after severe tissue damage [30].

The role of ILC3s in gastric disease remains unclear, as they are predominately found in the intestine. In both physiological and inflamed gastric mucosa, ILC3s are present in low frequencies and may have limited impact on local immune response. However, studies have shown that the levels of ILC3s and IL-22 in patients with gastritis, precancerous lesions, and gastric cancer are significantly higher than those in healthy populations, suggesting that ILC3s may play a role in gastric disease and have important immune functions [31]. Further studies are needed to elucidate the relationship of molecular mechanisms between ILC3s and gastric disease pathology.

Overall, mucosal ILCs are crucial for maintaining mucosal homeostasis, pathogen defense, and tumor surveillance. Their interactions with local bacteria, both commensal and pathogenic, significantly influence their function and the immune response to inflammation and cancer. In the following sections, we will explore the implications of interactions between innate immunity and gastric bacteria in gastric disease.

ILC regulating gastric microbiome and mucosal defense

The gastrointestinal mucosa is exposed to a wide variety of microorganisms, which is an important factor in shaping the host immune system. The mucosal immune system, in turn, directly or indirectly controls the microbial community. ILCs play a critical role in maintaining the integrity of the mucosal barrier by acting as the first line of defense against pathogenic bacteria. Therefore, the ILCs are in close interaction with the gastric microbiota. However, studies on ILCs and their relationship with gastric microbiota are relatively limited.

According to recent studies, the gastric microbiome plays an important role in the activation and development of ILCs. ILC2s, the predominant subset in the gastric mucosa, are interdependent with the microbiome. ILC2s were previously believed that their development is dispensable on the gastric microbiota. However, the study showed a significant reduction of ILC2s in germ free (GF) mice, suggesting that ILC2s present in the stomach are dependent on microbiota in an IL-7R-dependent manner [6, 22]. A significantly higher expression of IL-7R on ILC2s in the stomach compared to other tissues indicates that they rely on the IL-7 signaling, which is induced in the stomach by commensal bacteria for activation [19]. In addition, commensal bacteria can induce

the secretion of IL-7 and IL-33 in the gastric mucosa and, in turn, trigger the proliferation and activation of ILC2s, thereby enhancing their defense against pathogens such as *H. pylori* [32]. Another study reported that members of the S24-7 family within the order *Bacteroidales* are also suggested as candidate bacteria for ILC2 induction [6].

In turn, ILCs can also affect the gastric microbiome to protect mucosal integrity. For example, the secretion of cytokines such as IFN-γ by ILC1s and NCR-ILC3 could contribute to the clearance of intracellular bacteria by promoting the activation and phagocytosis of macrophages and dendritic cells [33]. Meanwhile, the IL-22 production by ILC3s could further induce the production of several antimicrobial peptides such as defensins and cathelicidins by epithelial cells [34]. Overall, ILC3s may regulate the overgrowth of pathogenic bacteria by producing cytokines and antimicrobial peptides, enhancing mucosal integrity, and activating the downstream adaptive immune system [35]. While much of the research on ILCs and their interactions with microorganisms has focused on the intestinal tract, there is a growing interest in understanding these immune cells within the gastric mucosa. The interplay between local immune responses and the gastric microbiome is increasingly recognized as critical in the context of gastric diseases.

Potential role of ILCs induced by *H. pylori* and gastric disease

H. pylori is one of the most studied bacteria in the upper GI tract and is known as only bacterium classified as a Class I carcinogen [36, 37]. It is highly adapted to the human gastric mucosa and thrives in the stomach, having co-evolved with humans over tens of thousands of years. The gastric mucosa is damaged by innate and adaptive immune responses after *H. pylori* infection, but gastric diseases does not occur in the early stage of infection [38]. In general, ILCs are a source of cytokines very early in the course of infection and therefore play a crucial role in the immune response and activation of the downstream adaptive immune response [39]. A study showed that ILC2s may be a novel candidate actor and promoter of preferred type 2 immunity in *H. pylori* infection [6, 40]. Our study also showed that stomach ILC2s can be activated by IL-7 and IL-33, and secrete IL-5, which subsequently activates B cells to become IgA-producing plasma cells, contributing vigorously to the protective ability of gastric mucosa [6]. This plays a critical role in the control of *H. pylori* infection in the stomach [22, 41]. In addition, the expression of IL-33 as a stomach alarmin, which potently activates ILC2s, is chronically increased when the environmental bacterial load is increased during the *H. pylori* infection [6]. In contrast, Buzzelli et al. showed that ILC2 could initiate an effective Th2 immune response, and increased STAT3 activation with chronic infection, causing marked gastropathy, particularly in the gastric cardia [42]. The difference of these two studies is most likely due to different duration of infection, and further studies are needed to clarify the exact role of ILC2s at the early stage of gastric disease. Of note, a recent clinical study showed that ILC2s are virtually absent in the human gastric mucosa compared to mouse, where stomach ILC3s are the dominant population. Specifically, NKp44-expressing ILC3s were highly increased in the gastric mucosa of asymptomatic *H. pylori* infected individuals [43]. Despite the small sample size of the study, we inferred that ILC3-like cells, rather than ILC2s, are required for mucosal protection under certain conditions, such as making *H. pylori* coccoid form. Studies are needed to determine whether this discrepancy exists in human and mice. Another study demonstrated a gradual predominance of ILC2s in the progression of *H. pylori*-induced pathologies using clinical samples at different disease stages [40]. The discrepancy between two clinical studies was attributed to several factors, including different stage of gastric disease, severity of the infection, and dietary differences.

H. pylori induced gastritis preferentially colonizes the antrum during the early stages of infection [44, 45]. Innate immune mechanisms are activated after *H. pylori* infection. Recent studies have shown that ILC2s are the critical intrinsic regulators of the early response to severe injury in the stomach and that the development of spasmolytic polypeptide-expressing metaplasia (SPEM) is driven by ILC2s and recruited macrophages [46]. However, it remains unclear whether IL-13 or other ILC2-derived peptides promote the maintenance or progression of metaplastic lineages, particularly during chronic injury and inflammation [47]. In the *H. pylori*- associated gastric carcinoma, a study found that the transcription factor GATA-3 is acquired by *H. pylori* in the gastric mucosa, and GATA3 levels are positively correlated with *H. pylori* -associated gastric neoplasia [48]. GATA 3 is a critical transcription factor for ILC2 development at multiple stages, and it is also reported that the GATA 3 enhancer region contributes to ILC2 development [49]. Another study also showed that ILC2s are increased during gastric tumor development, and the pharmacological inhibition of IL-13 produced by ILC2 could reduce gastric tumor growth [50]. Thus, ILCs represent significant potential targets for the treatment of *H. pylori*-associated disease and play an important role at several key stages, from gastritis to gastric cancer (Fig. 1).

In summary, current knowledge suggests that the activation of ILCs and their cytokine production is dependent on the exposure to bacteria such as *H. pylori*. In addition, the specific species that contribute to disease remain to

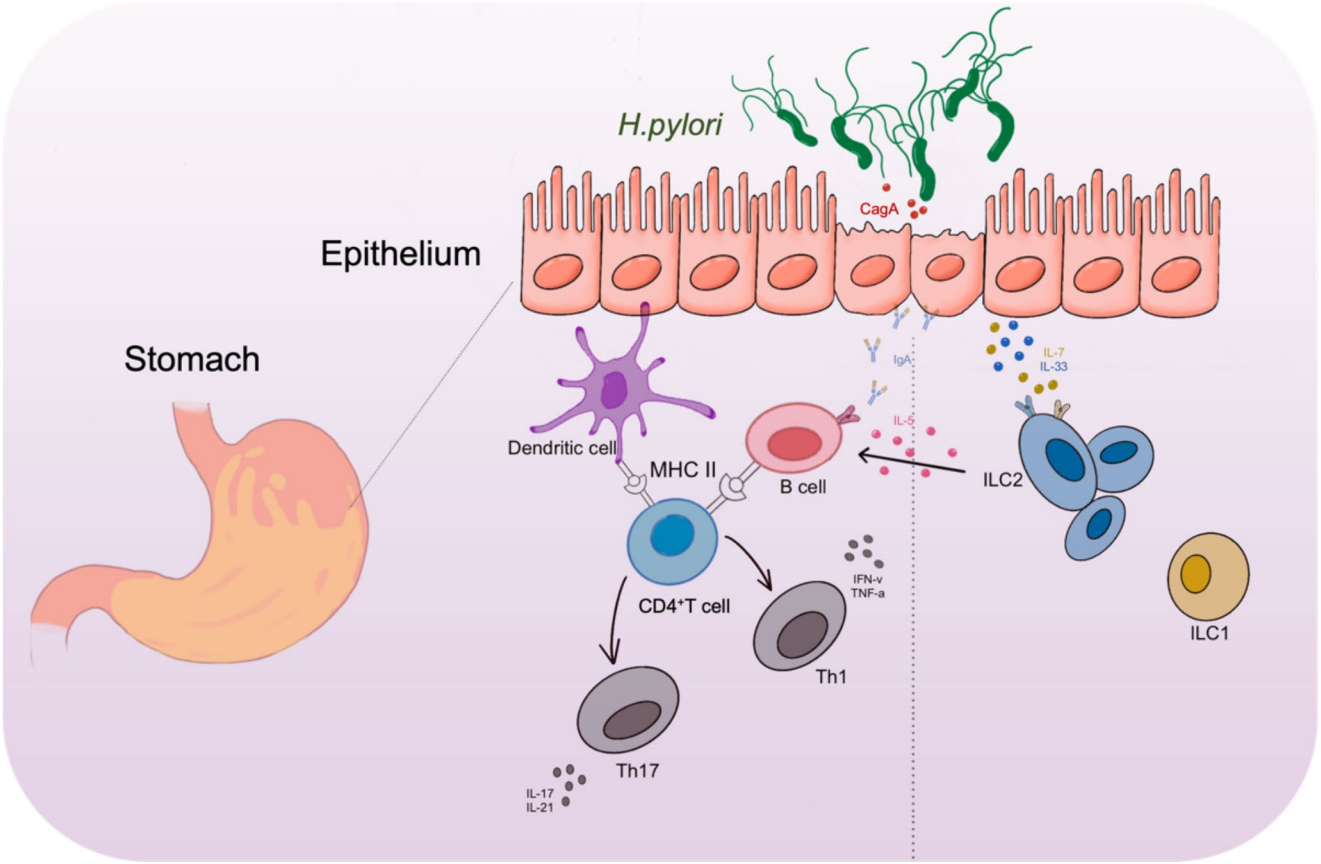

Fig. 1 Shaping innate immune and adaptive immune responses to *H. pylori*

be clarified, and the immune responses involving ILC1s, ILC2s, ILC3s and NK cells in the gastric disease could be the next question to be answered.

H. pylori damages the gastric mucosa via virulence factors, such as CagA. These factors can disrupt the tight junctions of the gastric epithelium, leading to mucosal damage and triggering both innate and adaptive immune responses. Upon infection, IL-33 are activated by epithelial stress signals, which triggers a significant accumulation of ILC2s in the mucosa. Subsequently, accumulation of IL-5 produced by ILC2 promotes IgA production by B cells to exert its mucosal barrier protective function. T cells play a role later in the infection. B cells and dendritic cells present antigens to $CD4^+$ T cells via MHC-II them. In addition, $CD4^+$ T cells differentiate into Th1 and Th17 subsets to maintain immune balance.

H. pylori infection in gastric disease progression

Recent research highlights the intricate relationship between the gastric microbiota and the development of gastric diseases, with the immune system playing a crucial role in shaping the microbiota. With microbial infection, the immune homeostasis of the gastric mucosa could be disrupted, leading to an imbalance in gastric mucosal homeostasis, resulting in a variety of gastric mucosal diseases. Currently, the studies on the gastric system-associated crosstalk between the chronic infection and gastric disease have been focused on the effect of *H. pylori* and other related microbiome. Meanwhile, considerable research suggests that ILCs are associated with the key nodes of the disease development described above by producing cytokines or engaging in communication with specific cells [16, 51].

As expected, compositional and functional alterations of the microbiome accompany the progressive dysbiosis through the gastric disease stages. An increasing number of studies have explored the microbial changes that occur during the gastric disease process [8]. There are some studies suggesting that the bacterial richness and diversity gradually decrease from healthy states, superficial gastritis, gastric ulcer, and gastric cancer [52–54]. However, there is still no consensus on the alteration patterns of the gastric microbiome.

H. pylori is a major factor in the development of gastritis, gastric ulcers, and gastric cancer. The functional and structural features of *H. pylori* allow it to achieve primary

infection and to colonize the deep gastric mucus layer and gastric pits, with a small proportion colonizing the deeper parts and attaching to gastric cells. Meanwhile, *H. pylori* can modulate the acidity of stomach to alter the gastric microbiome profile, leading to the onset and development of gastric diseases. In the process of chronic *H. pylori* infection, due to the presence of *H. pylori* virulence factors, such as cytotoxin-associated gene A (Cag A) etc., which cause damage to host cell DNA and reduce the ability of the infected cells to repair DNA damage [55, 56]. In addition, the motility of *H. pylroi* provide through its flagella and helical shape allow it to migrate between regions of the stomach. The stomach has several functionally and histologically distinct regions, such as corpus and antrum [57].

However, it is important to note that eradication of *H. pylori* neither ascertains the restoration of the gastric microbiota nor complete elimination of gastric carcinogenesis [8]. Furthermore, patients with persistent inflammation after *H. pylori* eradication still have a high abundance of pathogenic microbes [58]. This means that *H. pylori* eradication therapy alone may not prevent the development of gastric disease.

The involvement of non-*H. Pylori* in gastric disease

Although *H. pylori* is generally considered to be the main cause of gastric disease, there are other diverse members besides *H. pylori*. Recently, several studies have shown that other microbiota can also potentially exert their impact throughout the pathogenesis of gastric disease through various mechanisms. *Streptococcus anginosus* (*S. anginosus*) is a Gram-positive bacterium commonly found in the oral cavity and gastrointestinal tract [59, 60]. One study showed that the *S. anginosus* rapidly induces acute gastritis and subsequently chronic gastritis, gastric mucinous metaplasia, and dysplasia in conventional mice and germ-free mice after long-term infection. Mechanistically, *S. anginosus* produces proinflammatory cytokines, including CCL20 and CCL8, to induce acute gastric inflammation [61]. The surface protein TMPC on *S. anginosus* mediates its attachment and colonization of gastric tissues, hence serving as a virulence factor to induce gastric carcinogenesis during long-term infection [62]. In mice, *Provotella melaninogenica* (*P. melaninogenica*) promotes gastric inflammation by activating the signal transducer and activator of STAT3 pathway [63], and it can also trigger anti-inflammatory M2 polarization of macrophages through the TLR4/PI3K/AKT pathway, which subsequently promotes the growth of gastric cancer cells. The role of non-*H. pylori* in the stomach remains to be clarified and further mechanisms are needed for a deeper understanding of this issue. Meanwhile, the currently available information on non-*H. pylori* and ILCs is still unclear or unknown. Our understanding of the non-*H. pylori* gastric microbiome is just beginning to be unraveled.

Overall, current studies still focus heavily on microbial alterations and function, how microbial metabolism and its metabolic products affect gastric disease. Furthermore, compared to non-*H. pylori* infection, gastric pathobionts may work together with *H. pylori* to promote the development of gastric disease. Thus, it is necessary to clarify these microbial interactions and their specific mechanisms involving ILCs in the future.

Conclusion

In *H. pylori* or other non-*H. pylori* microbial infection-associated gastric disease, the gastric mucosal immunity plays an important role in the onset and development of the disease. ILCs have emerged as critical players in regulating immune responses and maintaining tissue homeostasis in various organs, including the intestinal tract and stomach. Their innate immunity nature enables a rapid and robust innate immune response and strong immunosurveillance potential against infection and gastric disease. ILCs seems to be ideal targets for therapy but the effective modulation of ILCs and be achieved to treat gastric diseases remains to be seen. Despite an immune response capable of eliminating most pathogens, *H. pylori* has evolved a number of mechanisms to circumvent both innate and adaptive immune responses, enabling the bacterium to persistently infect and colonize the host [64]. Currently, the role of non-*H.pylori* in gastric disease is expanding, but only limited studies have been conducted.

Taken together, further research is needed to better understand the role of the gastric immune system not only in the infectious state, but also in the induction of inflammation or tumor induction, which is crucial for the research and development of more effective methods for diagnosis, prevention, and treatment of gastric diseases.

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Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no conflict of interest in this study.

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