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Review Article

Gastric microbiome dysbiosis in chronic atrophic gastritis and gastric cancer: evidence beyond *Helicobacter pylori*

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Abstract: Chronic atrophic gastritis (CAG) is a key precancerous condition in the multistep development of gastric cancer (GC), but the risk of malignant progression varies markedly among patients. Although *Helicobacter pylori* is the best-established trigger of chronic gastritis, glandular atrophy, and intestinal metaplasia, progressive hypochlorhydria, mucosal barrier impairment, and altered local immunity may also reshape the broader gastric microbiota. Apparent *H. pylori*-negative status should therefore be interpreted cautiously, as it may reflect previous infection, eradication, false-negative testing, low bacterial burden in advanced lesions, true never-infected status, or autoimmune AG. Enrichment of non-*H. pylori* taxa alone does not prove microbial replacement or *H. pylori*-independent causation. This review evaluates links between gastric microbiome remodeling and GC risk in CAG, focusing on microbial composition, functional pathways, mucosal immunity, oxidative stress, and epigenetic alterations. Evidence is interpreted according to disease stage, sample source, study design, and causal strength. Cross-sectional studies show stage-associated microbial differences across non-atrophic gastritis (NAG), CAG, intestinal metaplasia, dysplasia, and GC, but cannot establish temporal direction. Mechanistic data from animal, organoid, and cell models remain model-specific, whereas findings from established GC, intratumoral or fecal microbiota, metastasis, prognosis, and immunotherapy mainly reflect tumor-stage biology. Current evidence supports gastric dysbiosis as a plausible marker or context-dependent modifier, rather than an established independent driver. Prospective CAG-stage cohorts, standardized protocols, rigorous *H. pylori* classification, and direct functional validation are needed for clinical translation.

Keywords: Chronic atrophic gastritis, *Helicobacter pylori*, gastric microbiome, dysbiosis, gastric cancer, risk stratification

Introduction

CAG is a premalignant lesion well defined in the multistep cascade of GC development. Histopathologically, progressive loss of gastric epithelial glands, often with associated intestinal metaplasia, pseudopyloric metaplasia and fibrosis also reflects an ongoing process of mucosal injury and remodelling [1]. All these pathological changes are essentially the long-term effect of chronic injury on gastric mucosal tissue and can be regarded as a progressive process from inflammatory damage to structural and functional impairment of the gastric mucosa. Significantly, CAG is not a homogeneous clinical condition and even patients with similar pathological diagnoses may be at different risks for malignant progression based on severity of mucosal injury, related autoimmune responses, or other host factors [2]. Therefore, understanding the biological mechanisms underlying different disease trajectories

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is essential for improving risk assessment and early prevention strategies.

The classic Correa cascade describes a common pathway of intestinal-type gastric carcinogenesis in which *H. pylori*-associated chronic gastritis may progress through CAG, intestinal metaplasia, and dysplasia to GC [3, 4]. This multistep model illustrates how persistent inflammatory stimulation and progressive mucosal remodelling play a crucial role in gastric carcinogenesis. Chronic inflammation has long been held as a central mechanism driving the shift from mucosal injury to premalignant change to malignancy, and CAG can be considered as an important transitional step between inflammatory insult and tumorigenesis [5]. Persistent inflammatory signaling may compromise epithelial integrity, alter immune responses, and disturb metabolic homeostasis, thereby creating a gastric microenvironment associated with neoplastic transformation. Epidemiological studies support an association between *H. pylori* infection and CAG and an increased risk of GC [6]. Nevertheless, the clinical manifestations of *H. pylori* infection differ widely between individuals, indicating that a complex interplay between bacterial virulence factors, host responses and environmental influences both alone and in combination dictates disease outcomes [7]. At the mechanistic level, *H. pylori* may promote gastric carcinogenesis via multiple complementary pathways, including disruption of mucosal barrier integrity, cytotoxin associated gene A (CagA)-mediated cellular reprogramming and activation of oncogenic signaling cascades associated with chronic inflammation, gastric atrophy and intestinal metaplasia [7, 8]. Agents driving these changes are integral to chronic epithelial injury and aberrant repair, two hallmarks of the gastric carcinogenesis process. Of all of the contributory infectious agents, *H. pylori* has the most established pathogenic role due to its high prevalence and significant contribution to GC development, particularly in Asian populations [9, 10]. As a result, the eradication of *H. pylori* has been integrated into both primary and secondary prevention strategies. Variation in cancer risk among individuals with comparable microbial exposures indicates that gastric carcinogenesis is multifactorial and reflects interactions among microbial exposure, host susceptibility, mucosal remodelling, and environmental factors.

Recent advances in gastric microbiome studies have expanded the understanding of CAG-related carcinogenesis beyond a strictly infection-based model. Importantly, microbiome investigations following inflammatory diseases have pointed out that microorganisms may not only be initiators of immune activation but also modulate inflammatory networks via microbial substances (metabolites or structural signals) and immune-pathway interactions [11]. The successive loss of functional acid-secreting glands leading to diminished gastric acid secretion during CAG progression, together with mucosal barrier impairment and distinct local immune responses, likely collectively reshapes the gastric ecological niche [12]. In addition, as the disease progresses, *H. pylori* colonization may decrease or become undetectable and reduced acid secretion caused by gastric atrophy could passively reduce the capacity of gastric acidity to act as a barrier and enable colonization by oral-origin intestinal-derived non-*H. pylori* taxa that would typically be excluded in acidic conditions [13]. These ecological shifts may facilitate gastric microbial dysbiosis and may be associated with the development and progression of GC. *H. pylori* may contribute to gastric ecological remodeling indirectly through persistent inflammation, mucosal injury, and altered acid secretion; however, its effects on the broader gastric microbial community remain incompletely defined. The *H. pylori* virulence factor Tipα activates pro-inflammatory signaling and exacerbates gastric mucosal inflammation, but this observation does not by itself demonstrate that Tipα causes subsequent community-wide gastric dysbiosis [14]. *H. pylori*-negative or post-eradication status should not be regarded as a uniform etiological category, as its detection may be influenced by limitations of diagnostic methods, prior medication exposure, and reduced bacterial burden or spontaneous loss of *H. pylori* associated with advanced gastric mucosal atrophy [15, 16]. Moreover, intestinal metaplasia and hypochlorhydria may also influence *H. pylori* colonization and detection; as a result, an apparently *H. pylori*-negative status could be due to lower detectability after prior infection or successful eradication, but may also represent true never-infection or distinct pathogenic conditions like autoimmune AG [16, 17]. Changes in the gastric microenvironment due to gastric precancerous lesions, especially gastric atrophy and less acid secretion, by reducing

the acidic barrier of the stomach, may promote oral-derived and non-*H. pylori* taxa [18]. Such microorganisms may additionally influence gastric mucosal ecological remodeling by regulating local inflammatory and metabolic responses; however, the available evidence is not robust enough to clarify whether these microbial-level alterations can independently contribute to pathogenesis or whether they represent a distinct *H. pylori*-independent causal pathway leading to disease evolution.

Building on these discoveries, this Review seeks to assess how relevant gastric microbiome remodeling may be to GC risk in patients with CAG. This review will first summarize *H. pylori*-associated inflammatory, epithelial and molecular alterations that are present through the disease course followed by a discussion of stage-related changes in gastric microbial composition and functional potential. Evidence relating to microbial metabolism, mucosal immunity, oxidative stress and epigenetic regulation is then assessed according to disease stage, sample type, study design and declaration of causation strength. Particular emphasis is placed on carefully distinguishing evidence directly related to CAG or other precancerous lesions from contextual evidence derived from studies of established GC, fecal microbiota, intratumoral microbiota, and experimental models.

Review methodology and evidence interpretation

This Review was conducted as a structured narrative review. Relevant studies were initially identified through searches of PubMed, Web of Science, and Scopus from database inception to March 2025, using combinations of terms related to CAG, gastric intestinal metaplasia, gastric dysplasia, GC, *H. pylori*, gastric microbiota, microbiome dysbiosis, microbial metabolites, mucosal immunity, and epigenetic regulation. A supplementary PubMed search using the same concept groups was completed on August 17, 2026, to identify newly indexed studies published after the initial search. Reference lists of relevant reviews and primary studies were additionally screened. Studies were included when they examined gastric microbial composition, microbial function, host-microbe interactions, or microbiome-related interventions in human gastric disease or experimentally relevant models.

To avoid conflating evidence from different disease stages and experimental systems, studies were evaluated according to four dimensions: disease stage, sample source, study design, and strength of causal inference. Prospective human studies enrolling patients at the CAG stage and reporting subsequent histological progression or GC outcomes were considered direct risk evidence. Cross-sectional or case-control studies comparing gastric mucosal or gastric fluid microbiota across different histological stages of gastric disease were considered stage-association evidence [19]. Animal, organoid, and cell studies were considered model-specific mechanistic evidence. Studies based exclusively on established GC tissues, intratumoral microbiota, fecal microbiota, systemic metabolic profiles, tumor stage, metastasis, prognosis, or immunotherapy response were classified as tumor-stage contextual evidence and were not used to infer mechanisms determining malignant progression during CAG.

For studies involving apparently *H. pylori*-negative participants, interpretation additionally considered previous infection or eradication history, diagnostic method, recent antibiotic or proton pump inhibitor exposure, severity of atrophy and intestinal metaplasia, and autoimmune AG whenever these data were available [15, 16, 20]. Causal terminology was reserved for findings supported by direct experimental manipulation within the relevant model. Observational findings were described using association-based terminology, and model-specific findings were not generalized to naturally occurring polymicrobial dysbiosis in human CAG.

H. pylori-associated initiation of gastric carcinogenesis

Infection characteristics and inflammatory signaling

This section focuses on *H. pylori*-associated inflammatory and molecular alterations during early gastric disease. Persistent *H. pylori* colonization activates mucosal innate immune responses through pathogen-associated molecular patterns and inflammation-related signaling pathways, thereby contributing to chronic gastritis and CAG development [21, 22]. In contrast, evidence that non-*H. pylori* dysbiosis has an independent initiating role at this stage remains limited. Accordingly, *H. pylori* should

be regarded as the best-established microbial trigger of CAG, whereas the contribution of the broader gastric microbiota to disease initiation remains uncertain.

During the acute phase of infection, *H. pylori* mainly activates local innate immunity and causes inflammation. Tumor necrosis factor (TNF) signaling through TNFR1 may promote NLRP3 inflammasome assembly, IL-1β maturation and release, and M1 macrophage polarization, thereby amplifying local inflammatory responses [23]. These results suggest that host inflammatory responses to *H. pylori* reflect the combined effects of multiple inflammatory pathways.

The host-pathogen equilibrium is perturbed in chronic infection because acute injury gives way to chronic inflammation. Following severe hyperinflammation, CagA as a major virulence factor of *H. pylori* downregulates overactive NLRP3 pathway by promoting mitophagy to avoid cellular death resulting in sustained low-grade chronic inflammation [24]. By limiting the extent of inflammasome activation needed to stimulate *H. pylori* killing, CagA could prevent acute cellular damage and promote the persistence of *H. pylori*. This transition may favor the persistence of chronic rather than acute inflammation.

Persistent inflammatory signaling may contribute to gastric mucosal barrier damage and tissue remodeling. A JAK1-signal transducer and activator of transcription 1 (STAT1) pathway that remains persistently activated leads to C-C motif chemokine ligand 3 (CCL3) secretion; the p38 mitogen-activated protein kinase (MAPK) cascade promotes epithelial tight junction breakdown, compromising mucosal barrier integrity [25]. Disruption of the barrier could magnify exposure to inflammatory stimuli at mucosal sites and thus potentiate inflammation. Interestingly, simultaneous activation of the extracellular signal-regulated kinase (ERK) signaling pathway stimulated production of matrix metalloproteinase-10 (MMP-10), which drives migration and recruitment of $CD8^+$ T lymphocytes via an MMP-C-X-C motif chemokine ligand 16 (CXCL16) axis to amplify the inflammatory microenvironment locally in a manner facilitating rapid tissue remodeling [26]. These processes are associated with chronic immune-cell recruitment and extracellular matrix remodeling.

Together, these findings suggest that *H. pylori*-associated inflammation represents a sustained mucosal remodeling process rather than a transient host response [27]. Coordinated inflammasome activation, cytokine release, macrophage polarization, epithelial barrier disruption, and chemokine-mediated immune-cell recruitment may amplify repeated cycles of injury and repair [28]. This persistent inflammatory microenvironment can weaken epithelial homeostasis and provide a biological basis for glandular atrophy and precancerous remodeling in CAG.

Virulence factors and signal activation

H. pylori virulence factors provide a direct molecular link between bacterial colonization and epithelial remodeling. Among these factors, CagA is a central effector that can disturb epithelial polarity, junctional organization, cytoskeletal dynamics, and proliferative signaling [29]. These alterations may convert persistent infection into epithelial instability, thereby contributing to early mucosal remodeling during gastric carcinogenesis.

Following T4SS-mediated translocation into gastric epithelial cells, CagA localizes to the cytoplasm and interacts with Src homology 2 domain-containing phosphatase 2 (SHP2), leading to signaling associated with cytoskeletal reorganization, altered cell-cell contacts, and increased epithelial proliferation [30]. Epithelial depolarization and loss of epithelial integrity may contribute to persistent inflammatory signaling and dysregulated proliferation. In parallel, the secreted serine protease HtrA cleaves epithelial junction proteins, including E-cadherin, disrupts junctional integrity, and may facilitate bacterial passage across the epithelium and CagA translocation [31].

In experimental gastric epithelial models, the CagA/T4SS axis has been associated with broad transcriptomic and proteomic alterations affecting pathways related to cell fate, proliferation, and inflammation. In the same experimental context, engagement of the Hippo-Yes-associated protein (YAP) pathway was associated with cytoskeletal remodeling and EMT-like changes [32].

Collectively, CagA/T4SS-mediated epithelial reprogramming and HtrA-mediated junctional disruption represent complementary mechanisms that alter epithelial signaling and barrier integrity [31]. In experimental models, these effects are associated with inflammation-related injury, abnormal repair, and EMT-like remodeling; their contribution to glandular atrophy and precancerous progression in human CAG remains to be defined.

Epigenetic regulation and mechanistic transition

Changes in DNA methylation, histone methylation, and non-coding RNA expression may accompany the progression of *H. pylori*-associated gastric disease toward precancerous lesions [33-35]. Some of these molecular alterations, particularly aberrant DNA methylation, may persist after *H. pylori* eradication [33].

H. pylori infection can modify host gene expression through inflammation-related signaling pathways [36, 37]. In GC cell models, *H. pylori*-associated activation of the STAT3-MYBL2-NF-κB axis has been linked to increased cellular proliferation and migration [37]. These findings provide mechanistic context but do not establish that the same pathway determines progression in human CAG. In another finding, hsa-miR-9-3p/5p were identified as potential common regulators of collagen type IV alpha 1 chain (COL4A1) and catenin beta 1 (CTNNB1). The changes to non-coding RNA expression may occur parallel to changes in β-catenin-related signaling, and the extent of their functional significance remains to be established [38].

H. pylori-associated inflammation has been linked to increased ten-eleven translocation 1 (TET1) expression and to upregulation of DNMT1, DNMT3A, DNMT3B, and EZH2 during gastric carcinogenesis. These findings suggest that locus-specific DNA demethylation may coexist with increased DNMT expression and EZH2-associated histone/chromatin regulation [39, 40]. Some of these DNA methylation alterations may persist after *H. pylori* eradication [33].

Epigenetic dysregulation associated with *H. pylori* infection may constitute an early and potentially persistent molecular alteration in gastric carcinogenesis [33, 40]. Such persistence may help explain why some DNA methylation abnormalities remain detectable after *H. pylori* eradication, although their duration and clinical significance in human CAG remain uncertain [33]. The established and proposed relationships among *H. pylori*-associated inflammation, virulence-factor signaling, and potentially persistent epigenetic alterations are summarized in **Figure 1**.

Stage-associated gastric microbiome remodeling during gastric carcinogenesis

Physiological gastric microbiota and defensive barriers

The stomach is not sterile but contains a microbial community relatively low in abundance associated with the mucosa under physiological conditions. Gastric acidity and proteolytic enzymes serve as very powerful agents of ecological selection, limiting the growth and colonization of many passing microorganisms [41]. Gastric mucus serves as an additional physical and chemical barrier. Mucins compose a gel-like matrix that restricts bacterial adhesion and direct interaction with epithelial cells. MUC5AC is one of the main constituents contributing to the spatial development of the gastric microbiota and homeostasis [42]. It follows that healthy gastric homeostasis reflects a balance between low-biomass microbiota and the physicochemical and immune defenses of the host, rather than a state defined by *H. pylori* dominance.

This defines a physiological state distinct from *H. pylori*-positive NAG. TNF-α, IL-1β, and IFN-γ can induce epithelial defense factors such as lactoferrin, lipocalin 2, complement C3, and CXCL9 during infection. These changes are actually adaptive responses to infection rather than typical properties of the healthy stomach [43]. Concurrently, *H. pylori* may down-regulate certain antimicrobial genes and mucus-associated secretory functions, emphasizing that host defense activation and bacterial immune evasion can occur simultaneously in the same pathological context. Rev-erbα signaling induced by *H. pylori* may also reduce expression of antimicrobial peptides and inhibit innate and adaptive immune clearance, promoting sustained colonization [44]. In CAG, loss of acid-secreting glands and hypochlorhydria may remodel mucus and antimicrobial defenses

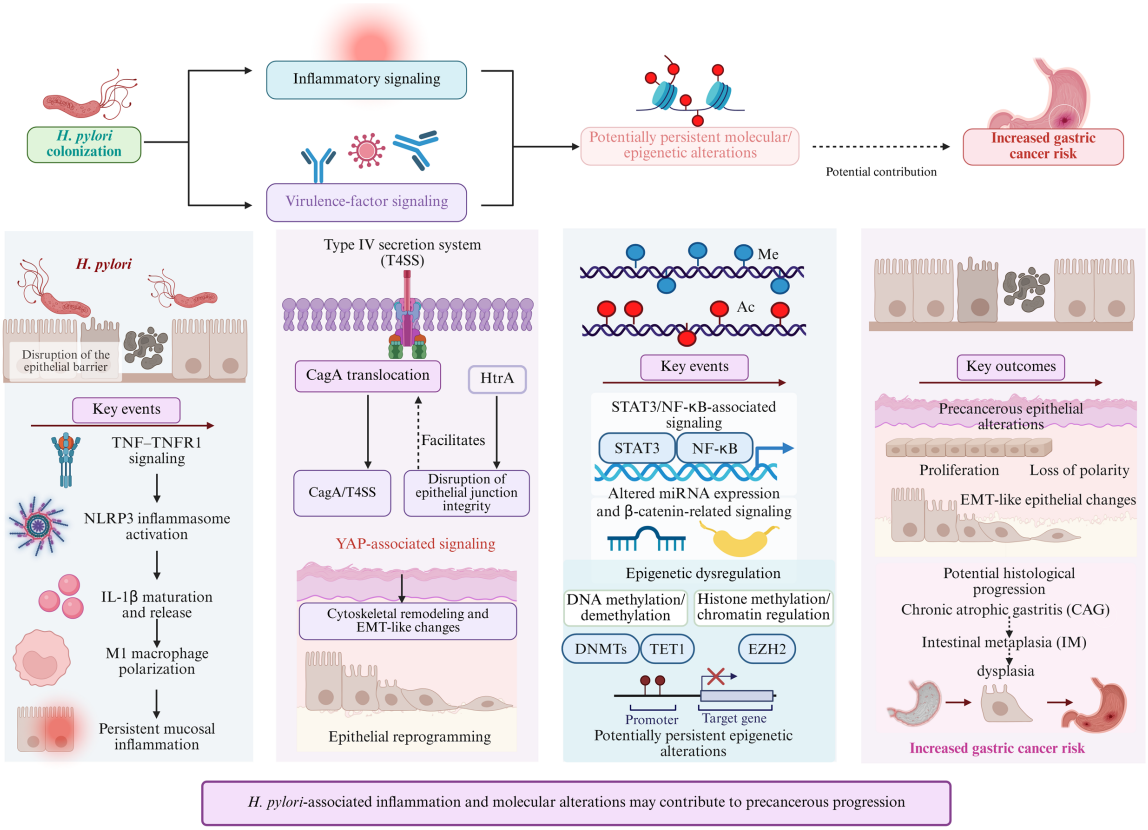


Figure 1. Mechanistic overview of *H. pylori*-associated inflammation, virulence-factor signaling, and potentially persistent epigenetic alterations during gastric preneoplastic remodeling. *H. pylori* infection can impair gastric epithelial barrier function and promote persistent mucosal inflammation through responses involving TNF-TNFR1 signaling, NLRP3 inflammasome activation, IL-1β maturation and release, and M1 macrophage polarization. The T4SS translocates CagA into gastric epithelial cells, where CagA engages SHP2-associated signaling. Separately, the secreted protease HtrA disrupts epithelial junctions and may facilitate CagA translocation. In experimental gastric epithelial models, CagA/T4SS-associated signaling can engage the YAP pathway and is associated with cytoskeletal remodeling, loss of epithelial polarity, dysregulated proliferation, and EMT-like changes. Persistent inflammation and virulence-factor signaling may contribute to STAT3/NF-κB-associated transcriptional changes, altered miRNA expression, and β-catenin-related signaling. DNMT- and TET1-related changes in DNA methylation/demethylation and EZH2-related histone and chromatin regulation may contribute to epigenetic dysregulation. These potentially persistent molecular alterations may accompany CAG, intestinal metaplasia, and dysplasia and may contribute to increased GC risk; the figure does not imply inevitable linear progression.

and thereby weaken gastric ecological filtering. Accordingly, microbial profiles reported in AG differ from those in histologically normal stomachs or NAG, consistent with a disease-stage-dependent model of gastric microbial remodeling [45]. In more advanced atrophy, *H. pylori* abundance or detectability may decline, while oral-derived and opportunistic non-*H. pylori* taxa may expand. But hypochlorhydria alone does not delineate a homogeneous microbial state. The distinct microbial profiles between *H. pylori*-associated AG, autoimmune AG and proton pump inhibitor-associated hypochlorhydria suggest that restructuring of the microbiota is also dependent on disease aetiology, inflammatory context, medication exposure and *H. pylori* status [46].

In established GC, tumor-associated changes in tissue architecture, nutrient availability, redox state, and inflammatory activity may shape local microbial profiles. Differences among non-tumoral, peritumoral, and tumoral gastric microhabitats should therefore be interpreted primarily as features of the established tumor environment rather than as evidence of earlier CAG progression [47]. Thus, rather distinct microbial changes across the healthy stomach, NAG, CAG and established GC need to be reported independently and primarily

interpreted as stage-associated changes unless further substantiated by longitudinal or direct functional evidence.

Dysbiosis signatures and key microbial shifts

Compared with healthy controls and patients with NAG, CAG has been associated with lower gastric mucosal Shannon diversity, altered community structure, and differences in predicted microbial functions. These cross-sectional findings describe stage-associated ecological remodeling but do not establish whether the microbial changes contribute to, or result from, chronic inflammation and glandular atrophy [48, 49].

Cross-sectional studies have also reported stage-specific differences in gastric microbial composition [49, 50]. Genera including *Sphingomonas*, *Ralstonia*, *Brevundimonas*, *Methyloversatilis*, and *Pseudomonas* were among the most abundant genera in patients with CAG, which also showed predicted pathway differences related to xenobiotic biodegradation, metabolism, and cofactor/vitamin metabolism [49]. In contrast, *Peptostreptococcus* and *Bacteroides* were less abundant in CAG than in the corresponding NAG [49, 50]. These differences distinguish CAG from the comparison groups but do not establish an effect on subsequent disease progression.

Indeed, for some microbial taxa, the direction of change is not completely convergent across studies. For example, in a study of patients with corpus AG, *Streptococcaceae* (especially *Streptococcus*) were positively associated with Operative Link on Gastritis Assessment (OLGA)/Operative Link on Gastric Intestinal Metaplasia Assessment (OLGIM) stage and were numerically increased in severe atrophy and intestinal metaplasia, while *Prevotellaceae* showed a stepwise decline [1]. In contrast, when comparing microbiota composition throughout histological stages of *H. pylori*-negative GC, an increase in *Burkholderiaceae* but relative decreases in *Streptococcaceae and Prevotellaceae* were found [51]. Although some studies have reported similar microbial compositions across gastric anatomical sites, increasing evidence indicates that gastric mucosal and gastric juice samples represent distinct microbial ecosystems [51], suggesting that sample type and sampling strategy may influence microbiome findings. The discrepancies observed among studies may stem from differences in sample types, gastric location, disease stage, *H. pylori* status, geographic populations, sequencing platforms, bioinformatic pipelines and taxonomic resolution. Notably, microbial changes detected at family versus genus and species level cannot be regarded as equivalent. While *Streptococcus, Prevotella* and their taxon relatives have been frequently reported, they are more appropriately considered as context-dependent candidate signatures rather than pan-GC risk-markers. To date, no non-*H. pylori* taxon has been prospectively validated as a stable biomarker for progression from CAG to GC. A more consistent but not universal pattern is, at the level of the community, ecological remodeling with reduced *H. pylori* dominance and enrichment in oral-derived or opportunistic taxa during advanced gastric mucosal disease [52].

Oral taxa such as *Slackia*, *Selenomonas*, *Bergeyella* and *Capnocytophaga* have shown higher relative abundance in subjects with more advanced histological lesions and are linked to inflammatory or predicted metabolic pathway alterations. Other than *H. pylori*, the changes in non-*H. pylori* microbiota have been linked to different molecular events in the gastric carcinogenesis continuum, but these associations do not establish a direct causal role in CAG progression [53]. Biological plausibility exists for a bidirectional relationship between gastric mucosal remodeling and microbial dysbiosis, but current evidence does not establish its direction in human CAG. Microorganisms poorly adapted to the normal acidic stomach may expand after glandular atrophy, hypochlorhydria, and barrier impairment [1, 21]. The altered microbial community may in turn modify local inflammatory and metabolic processes and host-bacteria interactions at the mucosal barrier [21]. Cross-sectional studies cannot determine whether these microbial changes precede lesion progression, arise as a consequence of mucosal atrophy, or subsequently modify the disease trajectory.

In summary, CAG is associated with shifts in microbial diversity and composition including enrichment of numerous oral-derived families. Reported enrichment of non-gastric and oral taxa is consistent with ecological niche disruption and may have biomarker relevance,

although causal relationships and prospective predictive value remain unestablished. In addition, these changes offer a descriptive framework for addressing the potential metabolic, immune and epigenetic associations discussed in later sections.

Metabolic and functional associations

Reported differences in microbial functional potential in CAG and other precancerous lesions have been associated with pathways involving amino acid and bile acid metabolism [50, 54]. These predicted functional findings describe stage-associated functional associations rather than measured metabolic activity or causal mechanisms [55]. However, 16S rRNA-based functional predictions, such as those generated using PICRUSt2, depend on reference databases and require confirmation by metagenomic and metabolomic analyses [50, 55]. Such predictions do not measure actual metabolite production and, when derived from cross-sectional studies, cannot establish causality in lesion progression [55]. **Figure 2** summarizes stage-associated ecological remodeling across the physiological gastric niche, *H. pylori*-positive NAG, and CAG, together with potential metabolic associations. It also presents investigational biomarker and risk-stratification applications that require prospective validation.

While evidence from established GC may identify candidate microbial metabolites or pathways, the interpretation should be independent. For instance, stool-based multi-omics analysis in patients with GC demonstrated associations among *Escherichia-Shigella* and systemic inflammation and specific fecal metabolites [56]. These data were obtained after malignant transformation and from fecal rather than gastric mucosal samples, so they do not prove that similar microbiota-metabolite interactions occur in the progression of CAG.

Experimental models can provide mechanistic evidence for specific microorganisms or pathways. In the cited model, *Streptococcus anginosus* promoted tumor-associated phenotypes through a metE-dependent methionine biosynthesis pathway [57]. These findings support a model-specific interaction between a microorganism and a metabolic pathway but do not demonstrate community-level causation in human CAG. Changes in bile acid metabolism and translocation of CagA are associated with *H. pylori*-dependent gastric injury [58], but are not evidence that non-*H. pylori* communities can function independently to replace *H. pylori* as a causal driver.

Overall, precancerous-stage studies support associations between gastric mucosal remodeling and altered microbial metabolic potential. Whether these metabolic changes precede lesion progression, arise as consequences of the altered gastric niche, or subsequently modify disease trajectory remains to be determined in human CAG through longitudinal studies and direct functional validation [50, 54].

Potential metabolic, immune, and epigenetic links between gastric dysbiosis and carcinogenesis

Evidence framework and representative taxa

Existing studies point to possible relationships between gastric microbial community structure, microbial metabolism, mucosal immune responses and alterations in host molecular biology in the course of gastric carcinogenesis. The temporal order and causal relationships among these processes in human CAG remain poorly characterized [21, 50]. Evidence should therefore be interpreted according to disease stage and study design rather than combined into a single continuous causal mechanism.

H. pylori is still an acknowledged cause of chronic gastric inflammation and mucosal injury [21]. Changes in acidity and mucus integrity may favor the enrichment of oral-derived or opportunist microorganisms [1, 21]. Enrichment of *Streptococcus, Neisseria, Prevotella* or related taxa has been reported in some studies of intestinal metaplasia, dysplasia or GC [59]. These patterns have not been uniformly reproduced across populations or disease stages. This variability may be explained by differences in *H. pylori* status, gastric location, sample type and geographic population [1, 51]. The taxa obtained should be considered as recurrent but context-dependent microbial signals rather than stable markers which progressively increase through gastric carcinogenesis. Importantly, current evidence does not support an individual non-*H. pylori* taxon as a prospectively validated biomarker for malignant progression

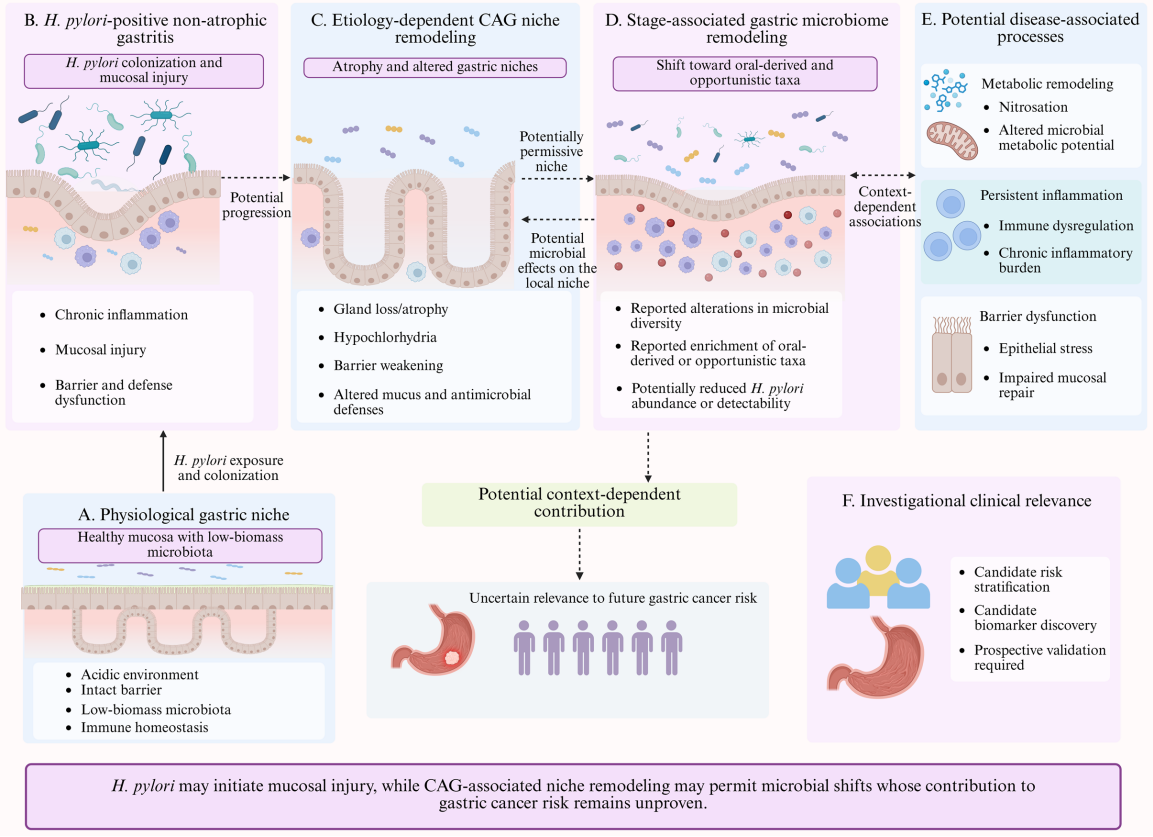


Figure 2. Stage-associated gastric ecological remodeling and potential metabolic associations across the physiological niche, *H. pylori*-positive NAG, and CAG. The physiological stomach is characterized by an acidic environment, intact mucosal defenses, and a low-biomass microbial community. Following *H. pylori* exposure and colonization, persistent infection may contribute to NAG and mucosal injury. In CAG, loss of acid-secreting glands, hypochlorhydria, and impaired mucosal defenses may weaken ecological filtering and create a more permissive niche for the expansion of oral-derived or opportunistic non-*H. pylori* taxa. The etiology and clinical context of hypochlorhydria must be considered because *H. pylori*-associated AG, autoimmune AG, and acid-suppressive medication-associated hypochlorhydria are not microbiologically equivalent. Reduced *H. pylori* abundance or detectability in advanced atrophy does not establish microbial replacement and may reflect previous eradication, sampling limitations, or diminished colonization in the altered mucosa. Cross-sectional studies have associated stage-related microbial differences with predicted functional or reported metabolic changes involving nitrosation and other processes, as well as with persistent inflammation, immune dysregulation, and epithelial barrier dysfunction, but their temporal direction and causal significance remain unresolved. Accordingly, the figure distinguishes established *H. pylori*-associated colonization mechanisms from stage-associated microbiome findings and proposed context-dependent links to GC risk. Candidate biomarker and risk-stratification applications remain investigational and require prospective validation.

in biopsy-based studies of patients with CAG [21, 51].

Further studies on established GC have also demonstrated microbial and metabolic differences in tumor tissues [60]. Tumour-stage evidence reviews have identified gastric mycobiome dysbiosis associated particularly with *Candida albicans*, albeit stating that its causal role in gastric carcinogenesis is far from settled. For instance, tumor-stage microbiota-metabolite interactions have been linked with changes in glycerophospholipid metabolism and phospholipase-related pathways [21, 61]. These results might explain the uncertain microbial ecology post-malignant change, but are not direct evidence of mechanisms determining future GC risk in CAG patients.

Table 1 summarizes representative studies according to disease stage, sample source, study design, and strength of causal inference. Studies are grouped as precancerous-stage association evidence, mixed-stage contextual evidence, model-specific mechanistic evidence, or tumor-stage contextual evidence and

Table 1. Representative studies of gastric microbiome alterations, stratified by disease stage, experimental system, and inferential strength

Disease stage or experimental context	Sample source and study design	Main microbial findings	Functional or mechanistic findings	Evidence category and relevance to CAG	Major limitations	References
AG-intestinal metaplasia stage, modeling precancerous progression toward GC	Human gastric biopsies, cell models, and INS-GAS mice with multi-model validation	DCA-induced microbial dysbiosis with significant enrichment of *Lactobacillus* genus	DCA activated Takeda G protein-coupled receptor 5 (TGR5)-STAT3-KLF5 signaling and was accompanied by alterations in gastric microbiota and bile acid metabolism	Model-specific mechanistic evidence; supports pathway plausibility but not human CAG causation	Predominantly animal-based evidence lacking longitudinal human causal validation	[54]
Bile reflux-associated gastric intestinal metaplasia, a precancerous stage	Rat GIM model integrating 16S sequencing and transcriptomic analysis	Reduced microbial richness with enrichment of *Limosilactobacillus* and related taxa	DCA-driven dysbiosis was associated with the Rikenellaceae RC9-RGD1311575/Fabp1 axis	Model-specific mechanistic evidence; limited direct relevance to human CAG progression	Animal model lacking longitudinal human CAG validation	[119]
Bile reflux gastritis and precancerous gastric lesion stage	Human gastric juice cohort with 16S sequencing and animal validation	Increased LPS-producing bacteria with enrichment of *Prevotella melaninogenica*	TDCA-LPS activation of IL-6/JAK1/STAT3 pro-carcinogenic pathway	Model-specific mechanistic evidence with human association; prospective CAG risk remains unestablished	Limited direct CAG samples and lacking long-term human validation	[72]
Gastric atrophy and intestinal metaplasia precancerous stage	Randomized 1-year follow-up cohort of 587 *H. pylori*-positive patients; 16S rRNA sequencing of 404 gastric biopsy samples comprising 202 paired pre/post-treatment samples after eradication or placebo	Oral bacterial clusters were enriched after eradication and associated with emergence or persistence of gastric atrophy and intestinal metaplasia	Amino acid metabolism and inositol phosphate metabolism were enriched, whereas folate biosynthesis and nucleotide-binding oligomerization domain-like receptor signaling were decreased in atrophy/intestinal metaplasia-associated microbiota	Longitudinal stage-association evidence; relevant to post-eradication precancerous gastric lesions, but direct GC progression risk remains unestablished	Predicted functional analysis based on 16S sequencing; limited direct functional validation and no direct GC outcome validation	[120]
Post-*H. pylori*-eradication chronic gastritis associated with subsequent GC risk	16S sequencing cohort of 288 post-eradication gastric mucosa samples	*Fusobacterium* and *Neisseria* enrichment with gastric dysbiosis	Inflammatory pathway activation and DNA damage induction	Stage-association evidence with mechanistic support; causal CAG progression remains unestablished	Retrospective single-center study lacking causal validation	[21]
H. pylori-positive chronic gastritis cohort including CAG and non-atrophic chronic gastritis	16S sequencing of gastric biopsies from 193 patients, including 124 with CAG and 69 with non-atrophic chronic gastritis	High-virulence *H. pylori* status was associated with reduced microbial diversity and altered community composition	High-virulence *H. pylori* status was associated with altered microbial networks and predicted metabolic functions	Stage-association evidence; no direct causal validation	Single-region cross-sectional study lacking causal validation	[76]
AG, precancerous lesion, and GC stages	Multistage gastric biopsy cohort with 16S sequencing	Oral taxa enrichment with enhanced GC microbial networks	Predicted enrichment of purine and peptidoglycan pathways	Stage-association evidence; temporal and causal relationships remain unestablished	Lacking causal validation and functional experiments	[121]

Note: Evidence categories were defined according to disease stage, study design, and strength of causal inference. Stage-association evidence does not establish temporal or causal relationships, model-specific mechanistic evidence should not be directly generalized to human CAG, and tumor-stage contextual evidence was not used to infer mechanisms determining progression from CAG to GC. Among the studies summarized here, no prospective human study directly demonstrated that a defined gastric polymicrobial signature independently predicts progression from CAG to GC.

should not be interpreted as equivalent; no eligible prospective human study identified in this review provided direct evidence that a defined gastric polymicrobial signature predicts progression from CAG to GC [21, 62].

Context-dependent metabolic and signaling effects

At the metabolic level, urease activity derived from *H. pylori* should be separated from general metabolic changes related to non-*H. pylori* dysbiosis [50, 63]. Urease hydrolyzes urea to ammonia, which alters its surrounding acid-base microenvironment and allows for long-term colonization; urease-associated inflammatory responses can also contribute to epithelial damage [63]. In parallel, expansion of non-*H. pylori* communities may modify a wider range of metabolites, including secondary bile acids and metabolites related to nitrate reduction and nitrosation [50, 54, 64]. Among these metabolites, deoxycholic acid (DCA) has been linked to STAT3 activation, bile-acid metabolism disturbances and gastric intestinal metaplasia [54]. Therefore, these metabolite classes should be regarded and classified individually instead of being generalized as uniformly pro-inflammatory or barrier-disruptive. More broadly, tumor-centric evidence suggests that microbiota-derived metabolites, including short-chain fatty acids (SCFAs), secondary bile acids, one-carbon metabolites, and tryptophan-derived ligands, may influence DNA methylation, histone acetylation, and chromatin remodeling through several potential pathways [65, 66]. These findings should therefore be regarded as mechanistic context rather than direct evidence of CAG progression.

SCFAs such as acetate, propionate, and butyrate are essential microbial metabolites that modulate gut barrier integrity and immune homeostasis. SCFAs exert pleiotropic and context-dependent effects through multiple mechanisms. Physiological levels of butyrate improve barrier function in intestinal epithelial monolayers, whereas excessive exposure to butyrate has been reported to decrease transepithelial electrical resistance (TER) and make the epithelium more leaky. Mechanistically, butyrate increases the activity of AMPK and promotes tight junction assembly as indicated by redistribution of mRNA and proteins for occludin and claudins, which started to reassemble tight junctions after an initial disturbance [67]. Furthermore, butyrate can directly inhibit NF-κB-dependent transcription of pro-inflammatory cytokines. Under conditions of mucosal injury, by contrast, excessive exposure of epithelial stem or progenitor cells to butyrate may suppress proliferation and delay healing. In addition to their direct regulatory effects on epithelial barrier function, SCFAs signal through free fatty acid receptors such as FFAR2/GPR43 and FFAR3/GPR41. Receptor expression and downstream effects vary by experimental context and tissue environment, and the same signaling pathways may support protective immune responses or, under other conditions, acute epithelial inflammation [68]. Consequently, the biological impacts of SCFAs depend on factors such as anatomical site, receptor expression, local concentration and molecular species as well as tissue context and epithelial metabolic state. As most mechanistic evidence is from intestinal or experimental models, these results should not be directly translated to human gastric epithelium or CAG. Consequently, alterations in gastric SCFA profiles should be cautiously regarded as potentially influencing the host under certain experimental conditions rather than as established pathogenic mediators [69].

Metabolic, inflammatory, epithelial, and microbial alterations have been reported across gastric disease stages, but their temporal order, directionality, and causal relationships remain unclear. **Figure 3** presents a hypothesis-generating framework for interpreting context-dependent associations among prior or persistent *H. pylori* exposure, host susceptibility, gastric mucosal remodeling, microbial community changes, candidate metabolic signals, mucosal immune responses, and host molecular alterations. The framework does not establish a causal feedback network or demonstrate that the wider gastric microbiota independently contributes to progression in patients with CAG, including those who are classified as *H. pylori*-negative [21, 50, 51].

Evidence from human studies and experimental models

Gastric microbiome studies have shown that gastric microbial composition differs across stages, including gastritis, CAG, intestinal metaplasia, dysplasia, and established GC [1, 70].

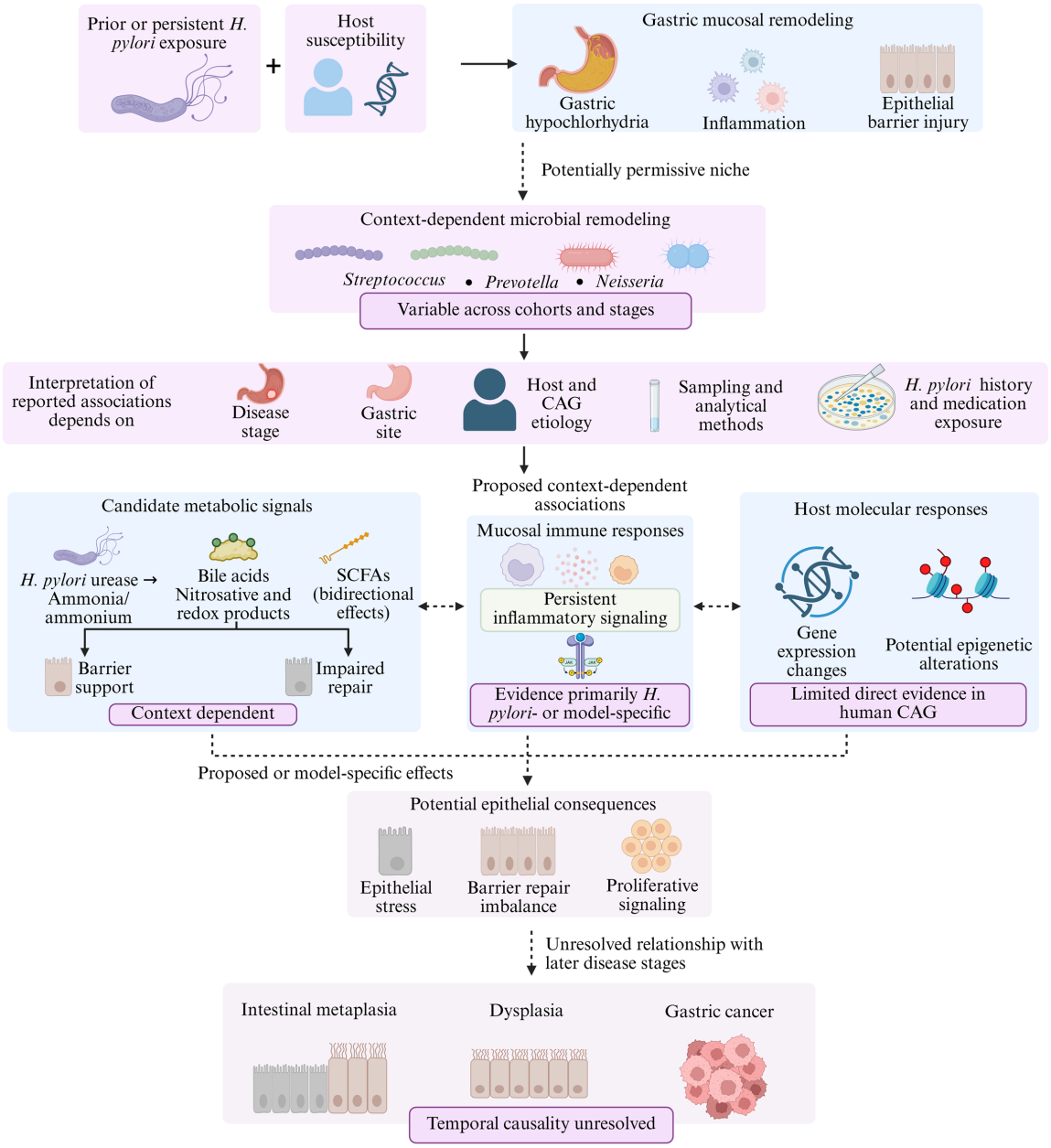


Figure 3. Proposed context-dependent associations among gastric microbial remodeling, candidate metabolic signals, mucosal immune responses, and host molecular alterations in CAG. The figure presents a hypothesis-generating framework in which prior or persistent *H. pylori* exposure and host susceptibility are associated with gastric mucosal remodeling and context-dependent changes in the gastric microbiota. Interpretation of reported microbial patterns depends on disease stage, gastric site, CAG etiology, *H. pylori* history, medication exposure, sampling strategy, and analytical methods. Three evidence domains are distinguished: candidate metabolic signals, mucosal immune responses, and host molecular alterations. *H. pylori*-specific urease-mediated ammonia/ammonium production is separated from context-dependent observations involving bile acids, nitrosative and redox products, and SCFAs. Proposed links among these domains are supported mainly by cross-sectional human associations or model-specific experiments and should not be interpreted as a validated causal feedback network in human CAG. Their relationships with epithelial remodeling and later disease stages, including intestinal metaplasia, dysplasia, and GC, remain temporally and causally unresolved. Whether these microbial features independently modify future GC risk remains unproven.

Enrichment of *Streptococcus*, *Prevotella*, *Neisseria*, and other oral-derived taxa has been reported across several cohorts, although the direction and magnitude of these changes have

not been consistent across studies [1, 13, 70]. These cross-sectional stage-association studies do not establish which taxa precede lesion progression versus those that are detected alongside changes in gastric acidity, tissue architecture and inflammation [1, 13].

Fusobacterium nucleatum has been reported to be enriched in established or advanced GC and associated with tumor stage or clinical outcome [71]. These observations support a tumor-stage or prognostic association. They do not establish that *F. nucleatum* was present before malignant transformation or participated in the initiation of GC during CAG.

Mechanistic evidence is provided for specific models from selected experimental studies. Taurodeoxycholic acid (TDCA)- and lipopolysaccharide (LPS)-induced IL-6/JAK1/STAT3 signaling was shown to generate proliferative or premalignant phenotypes in the tested cellular and animal systems [72]. Among the potential cofactors examined, co-colonization with *Streptococcus salivarius* provided significant enhancement of more severe gastric pathology in insulin-gastrin transgenic (INS-GAS) mice compared to *H. pylori* infection alone under the tested conditions [73]. This study shows that defined interspecies interaction can alter *H. pylori*-mediated pathogenesis in a model system. It does not prove that naturally occurring polymicrobial dysbiosis causes progression from human CAG to GC by itself.

Taken together, current evidence supports stage-associated gastric microbial remodeling and model-specific functional effects of selected microorganisms [21, 51]. Critically, no prospective human study identified in this review has directly demonstrated that a defined gastric polymicrobial signature independently predicts or causes progression from CAG to GC [21, 50]. Current human evidence therefore supports an association and potential biomarker value rather than an established causal role.

Host-microbe interactions across precancerous and cancer stages

Mucosal immunity and inflammatory responses

Metabolic, immune and epigenetic changes can accompany host-microbe interactions through the various stages of gastric disease [21, 50, 74]. These relationships may contribute to further microenvironmental remodeling, but it is still unclear whether they comprise self-sustaining feedback loops in CAG progression. Mucosal immune alterations have been associated with gastric dysbiosis in gastric disease, although the temporal direction of this relationship remains uncertain [21, 50].

Persistent or previous *H. pylori* infection may coexist with chronic inflammation, gastric atrophy, hypochlorhydria, and epithelial damage [1, 75]. These mucosal alterations may create conditions associated with changes in the gastric microbiota, including reduced diversity and altered relationships between *Helicobacter* and non-*Helicobacter taxa* in some studies [1, 76]. Declining *H. pylori* detection in advanced atrophy may reflect reduced detectability or absence of active infection rather than replacement by other microorganisms. Accordingly, the observed microbial differences may reflect, at least in part, mucosal remodeling and should not be interpreted as evidence of an irreversible transition from a healthy microbiota or an independent causal pathway [1, 75]. Moreover, *H. pylori* induces inflammation, whereas IL-17A produced by Th17 cells is associated with enhanced gastric inflammation and may perpetuate damage to the mucosa [77].

Lower levels of gastric acid may allow for increased colonization with non-*H. pylori* taxa during advanced atrophy [1, 78]. Whether such microorganisms subsequently help maintain inflammation during CAG remains to be determined. In established GC, the activation of NF-κB signaling by *F. nucleatum* has been associated with mast-cell infiltration and enhanced CXCL8 production via tumor cell-mast cell crosstalk [79]. These findings provide a potential mechanism of microbial immune modulation in established GC. They should not be interpreted as evidence that the same axis mediates *H. pylori*-independent inflammation or contributes to malignant progression during CAG.

Furthermore, these findings highlight that adaptive immune responses may also shape the inflammatory mucosal environment. Mucosal-associated invariant T cells can release multiple pro-inflammatory cytokines, and OX40 co-stimulation may further promote IL-9 secretion

and disrupt local immune homeostasis [80]. Whether these immune responses predict malignant progression in patients with CAG remains unknown. Carriage of the ATG16L1 rs2241880 G allele has been correlated with the increase in inflammatory response to *H. pylori*, endoplasmic reticulum stress and precancerous gastric lesions [81]. Such an association suggests that the host genetic background might affect mucosal responses to infection and dysbiosis.

H. pylori also modulates innate antimicrobial immunity. It suppresses interferon regulatory factor 3 (IRF3) activation and negatively modulates stimulator of interferon genes (STING) and retinoic acid-inducible gene I (RIG-I) pathways, thereby dampening the innate antibacterial response. STING deficiency leads to enhanced Th17-mediated inflammation, whereas *H. pylori* infection upregulates tripartite motif-containing 30a (Trim30a) in a partially STING-dependent manner [82]. NLRP3 inflammasome activation has been identified in *H. pylori*-positive gastritis and experimental deletion of NLRP3 reduces M1 macrophage polarization and inflammatory injury [23]. These results point to a potential involvement of innate immune dysregulation in chronic gastritis and precancerous mucosal remodeling. Chronic retention of IL-17 signalling might offer a biological link between persistent inflammation and neoplastic development. IL-17A promotes oxidative stress in an NF-κB-NOX1 signaling pathway and may orchestrate a microenvironment by regulating inflammatory-cell infiltration and cytokine production. On the mechanistic basis, genetic ablation of IL-17A dramatically suppressed development of gastric tumors in experimental models [83], supporting its involvement in inflammation-associated gastric tumorigenesis. Nevertheless, these experimental findings do not demonstrate that IL-17A independently predicts malignancy progression in CAG patients.

Mucosal immune responses may represent an interface between gastric microbial alterations and persistent inflammation. Current evidence does not establish a uniform transition from an *H. pylori*-dominant inflammatory state to a non-*H. pylori* polymicrobial inflammatory state before malignant transformation [75, 78].

Oxidative stress and epigenetic alterations

Oxidative stress may be associated with chronic gastric inflammation and epigenetic changes in epithelial cells [84]. Direct evidence that non-*H. pylori* community dysbiosis induces epigenetic remodeling during human CAG remains very limited [74]. Mechanistic assessment is mostly limited to *H. pylori*-mediated inflammation, oxidative stress or established GC models [39, 84]. Thus, these results need to be seen as supporting evidence for infection- or model-dependent pathways rather than as proof for a polymicrobial epigenetic mechanism in general.

Active DNA demethylation modifies cancer-associated gene expression in the presence of chronic oxidative stress by TET1 [85]. In these gastric epithelial models, the findings support an inflammation-TET1 rather than a general microbiota-reactive oxygen species (ROS)-TET axis. In addition, *H. pylori*-induced inflammation can activate NF-κB signaling to enhance TET1 expression and further cause guanine nucleotide-binding protein subunit beta-4 (GNB4) promoter demethylation, connecting the inflammatory signal with epigenetic modification [39]. The reported elevation of DNMTs and EZH2 together with GNB4 promoter demethylation suggests the presence of locus-specific demethylation along with aberrant hypermethylation in gastric carcinogenesis [39, 40].

In *H. pylori*-infected gastric epithelial cells, oxidative stress has been associated with both cellular damage and adaptive survival responses. Reduced intracellular GRP78 expression and increased ROS production were accompanied by enhanced aggresome formation and proliferative and survival phenotypes in the experimental model [86]. In addition to its known roles in cellular stress responses, oxidative stress may occur alongside histone modifications and other epigenetic and post-translational regulatory processes [34, 84]. ROS produced during chronic gastric inflammation may alter regulatory protein activity and cellular processes related to stress responses and proliferation [84, 86]. p300-mediated SIAH2 acetylation in *H. pylori*-infected gastric epithelial cells may result in SIAH2 stabilization, while SIAH2 regulation can influence ROS accumulation [86, 87]. Hence, oxidative stress may both

contribute to direct molecular damage and interact with epigenetic and post-translational networks associated with epithelial cell fate and malignant transformation [86].

In addition to histone acetylation changes, alterations of DNA methylation associated with *H. pylori* infection may represent another epigenetic mechanism associated with gastric carcinogenesis [84, 88]. *H. pylori* infection has been reported to cause demethylation of glucosylceramidase beta 1 (GBA1), as well as reduce sensitivity to ferroptosis, contributing to enhanced survival in GC cell models. These epigenetic changes also have the potential to enhance cancer cell survival by reducing sensitivity to ferroptosis [88]. Nevertheless, these findings were primarily based on experimental models of *H. pylori*-induced GC and whether this mechanism occurs during the CAG-GC transition is not yet known.

Oxidative stress may also affect protein regulation through altered small ubiquitin-like modifier (SUMO) conjugation. In *H. pylori*-infected experimental models, ROS exposure was associated with upregulation of SAE1 and SUMO1/2/3 and increased SUMOylation-related protein expression. These changes were reversed after ROS inhibition, indicating their dependence on oxidative stress [89]. These findings extend the potential regulatory effects of *H. pylori*-associated ROS beyond DNA methylation and histone modification to post-translational regulation.

Experimental studies support links among *H. pylori*-associated inflammation, oxidative stress, and selected epigenetic alterations [84]. Whether wider gastric microbial communities independently induce or maintain comparable epigenetic changes during human CAG has not been established [74]. Longitudinal studies integrating gastric mucosal microbiome profiling with genome-wide DNA methylation measurements are required to determine the temporal and causal relationships among these processes [74, 75].

Host genetic susceptibility and microbiota interactions

The transition from CAG to GC is multifactorial and may reflect interactions between host genetic susceptibility and *H. pylori* virulence factors that influence inflammatory responses and disease susceptibility [90, 91]. Host genetic background may affect inflammatory thresholds, mucosal epithelial responses, immune recognition, responses to microbial colonization, and the biological consequences of chronic infection [91, 92]. The host should therefore be considered an active modifier of disease susceptibility rather than a passive recipient of microbial signals.

Polymorphisms of inflammation-related genes have been linked to susceptibility to precancerous gastric lesions and may modulate the risk for progression of these lesions. Associations among high-virulence *H. pylori* strains (e.g., VacA m1- and cagE-positive strains), the IL1B-511T and IL8-251T polymorphisms, and intestinal metaplasia have varied by sex in some populations [93]. In total, these observations suggest that the genetic background of a host can influence susceptibility to both post-infectious inflammation and persistent signals evoked by virulent strains of colonization and their subsequent pathobiologic effects. Besides interacting with host genetic predisposition, *H. pylori* may favor oncogenic signaling via epigenetic and genomic changes. In particular, *H. pylori* exposure has been associated with promoter demethylation and copy-number gains affecting genes involved in epithelial-mesenchymal transition, cell-cycle regulation, and immune responses. In vitro exposure to *H. pylori* increased COL4A1 expression and β-catenin signaling, changes associated with a proliferative and migratory epithelial phenotype [38]. Together, these observations suggest that host susceptibility may modify inflammatory responses, epithelial signaling, and the biological consequences of microbial exposure and may thereby contribute to inter-individual variation in GC risk.

The interaction between the metabolic and immune pathways may shape an immunosuppressive tumor microenvironment in GC. Squalene epoxidase (SQLE) upregulation induced by *H. pylori* via CagA promotes palmitoyl-CoA accumulation, enhancing PD-L1 stability and inhibiting T cell-mediated anti-tumor immunity [94]. Additional mechanisms mediating this microbial immune modulation have been identified in tumor-stage studies. *F. nucleatum* has been implicated in IL-17/NF-κB/RelB signaling,

tumor-associated neutrophil recruitment, up-regulation of PD-L1 expression in tumor-associated neutrophils and local immune suppression in established GC [95]. Importantly, these observations offer a glimpse of microbial immune regulation at the tumor stage yet do not reflect causal proof of mechanisms that underlie cancer risk in CAG.

Thus, host genetic susceptibility may modify the magnitude and biological consequences of *H. pylori*-associated inflammation, mucosal epithelial responses, responses to microbial colonization, and susceptibility to gastric mucosal atrophy [91, 96]. This host-microbe perspective may help interpret part of the inter-individual heterogeneity in CAG progression.

Advances in clinical and experimental research

Multi-omics dissection and mechanistic networks

Multi-omics approaches have provided an increasingly detailed view of the coordinated microbial and molecular alterations associated with CAG and other gastric precancerous lesions. Integrated analyses across metagenomic, transcriptomic, proteomic, and metabolomic datasets have identified stage-associated differences in *H. pylori* abundance, the relative abundance of non-*H. pylori* taxa, microbial functional potential, and local immune features [50, 97, 98]. Collectively, these findings indicate that gastric precancerous lesions are associated with microbial dysbiosis, altered host molecular pathways, and local immune alterations. In this context, studies on the gastric microecosystem in CAG have increasingly incorporated multi-omics integration and explored potential clinical applications. **Table 2** summarizes representative methodological approaches, principal findings, candidate applications, and major validation limitations in gastric microbiome research.

Associations between microbial dysbiosis, inflammatory protein expression and aberrant DNA methylation have been identified from integrative multi-omics studies at the precancerous stage. As well as these coordinated changes, inflammatory signaling factors including CCL20 and TNFR superfamily member 9 (TNFRSF9) were also linked to the changes, with statistical mediation effects identified, although this did not establish causal mediation [99]. At the same time, CAG patients exhibit lower 16S rRNA-based microbial richness and diversity along with concurrent changes in multiple metabolic and carcinogenesis-related pathways [50]. Together, these data indicate that coordinated microecological and host molecular remodeling occurs during CAG; yet their largely cross-sectional design does not inform whether any of these alterations are temporally ordered or causally related to subsequent malignant transformation. Crucially, none of these cross-sectional associations should be interpreted as evidence that the microbial or molecular cohorts identified here prospectively predict malignant transformation in CAG patients. Findings from multi-omics in established GC should not be conflated with evidence generated at the CAG or precancerous stage. Alterations in microbial composition and immune-related networks in tumor-stage studies have been detected from GC tissues. Changes in chromatin regulation and glycerophospholipid metabolism were observed in other multi-omics analyses [61]. These findings, while elucidating aspects of microbiota-host signaling following malignant transformation, do not demonstrate the same changes occurring in pre-cancerous stages nor their relationship to future GC risk amongst CAG patients. Thus, they should be interpreted as tumor-stage contextual evidence and not direct evidence for CAG to GC progression mechanisms.

Although multi-omics studies are increasingly common, many remain cross-sectional; methodological differences further limit causal inference and comparability [100, 101]. Future microbiome studies should also avoid treating *H. pylori*-negative patients as a homogeneous group [16, 102]. Whenever possible, previous infection and eradication history, diagnostic methods, recent antibiotic or acid-suppressive therapy, the severity of atrophy and intestinal metaplasia, and autoimmune gastritis should be documented. Without such stratification, associations attributed to non-*H. pylori* dysbiosis may reflect infection-status misclassification, medication effects, or ecological consequences of mucosal atrophy rather than necessarily indicating an independent causal mechanism [16, 102, 103]. At the mechanistic level,

Table 2. Representative methodological advances and candidate translational applications in gastric microbiome research

Study context and design	Sample source and key methods	Principal findings	Key taxa or metabolites	Candidate applications	Major limitations and validation needs	References
Multi-omics intervention study integrating gut microbiota and gastric tissue profiling in a CAG rat model	Cecal-content 16S rRNA sequencing integrated with gastric-tissue transcriptomics and liquid chromatography-mass spectrometry (LC-MS) metabolomics	BBR alleviates atrophic inflammation and suppresses MAPK signaling	Firmicutes/Bacteroidota, *Muribaculaceae*, *Lactobacillus johnsonii*	Evaluation of therapeutic efficacy and multi-omics biomarker discovery in CAG	Limited to animal models; lacks validation in clinical cohorts	[115]
Cross-sectional multistage integrative multi-omics study	Faecal 16S sequencing with untargeted LC-MS of faeces/tissue	The atrophic stage emerged as a prominent microbial and metabolic transition point with stage-discriminative signatures	Actinobacteria, *Bifidobacterium*, MG, arachidonic acid derivatives	Candidate non-invasive disease discrimination and risk stratification in high-risk populations	Small, cross-sectional cohort; some signals fail FDR correction	[122]
Gastric mucosal microbiome stratification in a high-risk Mongolian population	Biopsy-based V3-V4 16S sequencing with immunohistochemistry and network analysis	Non-*H. pylori* enrichment is associated with IM and GC and supports stage-associated microbial remodeling.	*Lactobacillus*, *Enterococcus*, *Parvimonas*, *Fusobacterium*	Candidate risk stratification and microbiome characterization in endemic populations and patients with IM	Cross-sectional design; predictive inference (16S/PICRUSt) limits causality	[48]
Prospective multi-omics study of eradication-driven microbiome remodelling	Targeted metabolomics of gastric biopsy with 16S-based integrative networks	Eradication reshapes metabolic profiles and microbe-metabolite interactions	*Helicobacter*, *Fusobacterium*; ceramides/glycosylceramides	Candidate post-eradication response assessment in IM/low-grade intraepithelial neoplasia	Limited sample size and follow-up; no GC progression observed	[106]
ABCD stratification-based gastric microbiome network and risk modelling	16S sequencing with WGCNA co-occurrence networks and eigengene analysis	Pink/brown modules correlate with high-risk ABCD groups	Nitrate-reducing taxa and T4SS-associated modules	Potential adjunctive risk stratification for future endoscopic surveillance studies	Limited intestinal metaplasia samples; single-centre and lacking functional validation	[123]
Case-control oral-gastric shotgun metagenomic study in intestinal metaplasia	Oral/gastric shotgun metagenomics with conditional regression	Coordinated dysbiosis of oral-gastric microbiota and functional pathways	*N. elongata*, *P. stomatis*, *F. alocis*, LPS pathway	Candidate oral-gastric microbial signatures for disease discrimination and risk stratification	Small cohort and single time-point sampling limit causal inference	[13]
Spatial microbiome dynamics in gastric precancerous lesions	Whole-slide imaging with in situ hybridization and immunohistochemistry	Non-*H. pylori* bacteria infiltrate the lamina propria in CG/GIM lesions	*H. pylori* and eubacterial 16S rRNA signals	Candidate biomarker discovery and spatial characterization of precancerous lesions	Single-centre, small cohort with limited taxonomic resolution	[124]
Meta-analytic integration of multi-cohort 16S data with dietary translation	Re-analysis using linear discriminant analysis effect size (LEfSe), random forest, PICRUSt2 and reverse ecology	Reproducible AG-associated microbial signatures were identified, with exploratory inference of potentially relevant dietary factors	*Bacteroides*, *Weissella*, *Actinomyces*, *Streptococcus*	Candidate subtype classification and hypothesis generation for microbiome-informed dietary studies	Heterogeneity and incomplete staging; limited species-level resolution	[125]
Mucosal biopsy-based microbiome markers for disease staging	16S V3-V4 sequencing with QIIME and LEfSe	Stage-specific restructuring of the gastric microbiota was observed across SG, AG, GIN, and GC, with the highest richness in AG	Gastric intraepithelial neoplasia (GIN) enriched in *Romboutsia* and associated with butyrate SCFAs	Endoscopic microbiome markers for precancerous stratification	Small single-centre cohort; limited high-grade GIN and low resolution	[53]
Cross-sectional microbiome study assessing post-eradication recovery and risk	Gastric biopsy 16S sequencing with QIIME2, LEfSe and PICRUSt2	*H. pylori* reduces diversity; partial recovery after eradication	*Helicobacter* dominant; enrichment of *Curvibacter*/*Acinetobacter*	Assessment of post-eradication microbial recovery and candidate risk-associated signatures	Small cohort; cross-sectional design limits causal inference	[102]
Stage-specific microbiome biomarkers in *H. pylori*-negative cohorts	Paired mucosal and gastric fluid 16S sequencing with QIIME	Diversity declines and community restructuring occurs from SG to GC	*Ralstonia* increased; GC enriched in *Streptococcus spp.*	Candidate microbial markers for discrimination of IM/dysplasia stages	Limited AG samples; lack of GC gastric fluid validation and dietary control	[51]

Note: Evidence should be interpreted according to disease stage, sample source, and study design. Studies based on established GC or fecal microbiota provide contextual rather than direct evidence for CAG progression, whereas animal intervention studies provide model-specific evidence. Unless otherwise stated, these candidate applications have not been prospectively validated for predicting progression from CAG to GC.

model-specific causal relationships have been demonstrated for selected taxa and pathways under experimentally controlled conditions; for example, *Streptococcus anginosus* enhances tumor progression through a methionine metabolism pathway mediated by metE [57].

Multi-omics approaches have improved the characterization of associations among microbial community structure, metabolism, inflammatory regulation, and epigenetic alterations across gastric disease stages [50, 99]. Nevertheless, differences in disease stage, sample type, study population, analytical platform, and the cross-sectional design of many available studies limit comparability, temporal and causal inference, and clinical translation, particularly regarding the validated prediction of future GC risk in patients with CAG [21, 50].

Beyond integrating additional omics layers, the validity of future gastric microbiome studies will depend on addressing features specific to low-biomass gastric samples [104]. Relative-abundance data alone cannot distinguish a true expansion of a taxon from depletion of other organisms, and small amounts of reagent or environmental contamination can disproportionately influence apparent community structure. Accordingly, studies should combine sequencing with absolute microbial-load measurements, include extraction blanks and other negative controls, and assess taxa detected consistently across paired or replicate biopsies [104, 105]. Strain-resolved metagenomics or culture-based confirmation could help distinguish persistent mucosa-associated colonizers from transient oral or food-derived organisms, whereas transcript-based assays could help identify metabolically active populations. Spatially paired sampling from the antrum and corpus, together with lesion and adjacent non-lesional mucosa where applicable, would further clarify whether a signal reflects diffuse CAG or a local tissue microenvironment [78]. Reporting DNA extraction methods, biopsy processing time, sequencing batch, and read-depth thresholds would also improve reproducibility across centers.

A candidate microbial driver should satisfy a sequential evidence chain: it should be detectable before histological worsening, show an association with progression, correspond to a measured metabolite or host response, and produce a relevant phenotype after controlled manipulation in an appropriate experimental model [21, 100]. Reversal or attenuation of that phenotype after removing the organism or disrupting the implicated pathway would provide stronger evidence than taxonomic enrichment alone. Applying these criteria would help prevent signatures detected only in feces or established tumors from being misclassified as mechanisms of CAG progression and would distinguish potential causal contributors from ecological passengers.

Biomarkers and early detection potential

Composite microbial models that incorporate both taxonomic and metabolic features may show stronger discrimination of gastric lesion progression than simpler models [106]. Nonetheless, their predictive accuracy specifically for progression from CAG to GC has not yet been validated in a prospective setting [100, 106]. These models are therefore best considered as potentially useful discrimination or stratification tools, but not yet validated prognostic biomarkers.

At the precancerous stage, *Gemella, Streptococcus,* and *Actinomyces* have been reported to occupy more central positions within microbial interaction networks [107]. Although these network features may indicate ecological disruption, they do not establish a causal role in lesion progression. In separate cohorts, random forest models based on differential microbial profiles distinguished NAG from AG [108]. Such models characterize existing disease states but have not been shown to prospectively predict progression from CAG to GC.

At the taxon level, stage-dependent remodeling patterns across the disease spectrum have been observed in genera such as *Veillonella*, *Dialister*, *Granulicatella*, and *Helicobacter*. The area under the curve for microbial models separating established GC from superficial gastritis (SG) was also approximately 0.85 in this population [109]. Discriminating among patients who already have different disease states is not equivalent to prospectively predicting which patients with CAG will develop GC. Thus, these results can be interpreted only as cross-sectional diagnostic data and not validated predictions of CAG cancer risk. These

findings support the potential use of microbial profiles and microbiota-derived extracellular vesicles for the non-invasive discrimination of existing gastric disease states [110]. Further studies are required to determine whether these markers are specific to gastric mucosal pathology and can prospectively predict malignant progression in patients with CAG.

Current evidence is largely derived from single-center or regional cohorts with limited external validation [100, 106]. Differences in disease stage, analytical methods, *H. pylori* status, medication exposure, and geographic population may affect the comparability of microbial signatures [100, 101]. Thus, individual taxa should be considered context-dependent rather than stable risk markers. Composite biomarkers integrating multiple taxa, metabolic features, and clinical variables may be more robust [106]. Future studies require multicenter prospective cohorts, standardized protocols, and independent validation.

Microbiome-related intervention strategies

Gastric microbiome alterations have been proposed as potential targets for intervention, but they have not been established as independent causal drivers of progression from CAG to GC in patients with CAG [111, 112]. The clinical significance of microbiome-mediated effects on *H. pylori* colonization, inflammatory responses, mucosal barrier function or microbial community composition remains unclear. Evidence from animal models or in vitro gastritis studies does not demonstrate that these interventions prevent histological progression or GC in patients with CAG [113].

Probiotics are one of the most researched microecological interventions. In *H. pylori*-infected INS-GAS mice, supplementation with a probiotic combination containing *Lactobacillus salivarius* and *Lactobacillus rhamnosus* reduced gastric inflammation and premalignant lesions, which was associated with downregulation of NF-κB-, IL-17-, and TNF-associated inflammatory pathways and remodeling of the gastric and intestinal microbiota [113]. These results suggest that probiotics can impact host inflammatory responses and gut microbiome composition, but probably in a strain- and context-dependent manner. In the tested experimental model, *Lactobacillus plantarum* ZJ316 reduced *H. pylori*-induced gastritis, accompanied by attenuation of inflammatory signaling and changes in gastric microbiota composition [114].

Plant-derived compounds have also been investigated as microbiome-modulating interventions, primarily in experimental models. In experimental CAG models, berberine (BBR) was associated with changes in the abundance of Muribaculaceae and *Lactobacillus johnsonii* and reduced pro-inflammatory M1 macrophage polarization [115, 116]. Complementary cell experiments suggested that activation of IL-4-STAT6 signaling contributed to M2 macrophage polarization under *H. pylori*- or LPS-stimulated conditions [116]. These model-specific findings support potential anti-inflammatory and microbiome-modulating effects of BBR but do not demonstrate that it delays histological progression or prevents GC in patients with CAG.

Microbiome-related interventions have biological plausibility as potential adjunctive approaches, particularly in *H. pylori*-associated inflammation [113]. Before clinical implementation, strain-specific evidence and larger prospective trials with longer follow-up and histological outcomes are required [117]. At present, these interventions should be regarded as investigational rather than established strategies for cancer prevention in CAG.

Conclusions and perspectives

CAG is an important precancerous condition in the multistep development of GC. *H. pylori* is a well-established cause of chronic gastric inflammation and precancerous mucosal injury. Progression from chronic gastritis through atrophy, intestinal metaplasia, and dysplasia to GC is accompanied by alterations in epithelial signaling, acid secretion, mucosal barrier integrity, immune responses, metabolism, and gastric microbial composition. Current evidence is insufficient to conclude that non-*H. pylori* dysbiosis independently drives progression from CAG to GC in patients with CAG [111]. An apparently *H. pylori*-negative result in CAG or GC does not necessarily indicate a never-infected state; it may reflect previous infection followed by loss of detectable colonization, successful eradication, medication-related or sampling-related false-negative testing, or reduced bacterial abundance in advanced atrophy,

intestinal metaplasia, or hypochlorhydria [118]. Persistent mucosal or microbial abnormalities after *H. pylori* is no longer detectable may therefore represent residual effects of previous infection, consequences of the altered gastric niche, or additional host and environmental modifiers.

As gastric acid secretion decreases and mucosal defenses become impaired, non-*H. pylori* taxa may expand and interact with local inflammatory, metabolic, and epithelial processes. Model-specific functional effects have been reported for selected microorganisms. For example, *Streptococcus anginosus* promoted gastric inflammation, atrophy, and tumor-associated changes in a murine model [112]. Evidence from a single microorganism and experimental system cannot be generalized to naturally occurring dysbiotic communities or used to establish an independent causal mechanism in human CAG. CAG-associated dysbiosis should therefore be considered a potential biomarker or disease modifier rather than an established driver of malignant progression. Longitudinal studies are needed to determine whether microbial changes precede lesion progression, arise as consequences of atrophy and hypochlorhydria, or subsequently modify local mucosal processes [100]. Integrating microbial community features with host and environmental factors may help explain inter-individual heterogeneity in precancerous progression.

Current data linking CAG-associated microbiota to cancer risk derive mainly from cross-sectional association studies and limited functional experiments conducted in vitro or in vivo [100, 111]. Disease stage, sample source, *H. pylori* status, geographic population, sequencing and analytical platforms and bioinformatic workflows are highly heterogeneous in published studies of the human microbiome to date. Collectively, these findings establish an association between gastric microbial dysbiosis and disease stage, whereas any independent or context-dependent contribution to progression remains unproven [100]. Resolving these uncertainties will require prospective cohorts beginning at the CAG stage, standardized gastric tissue sampling and analytical methods, spatially resolved analyses, multi-omics integration, and direct functional validation.

Future studies should determine whether microbial signatures add predictive value to established histopathological and clinical risk factors, including *H. pylori* exposure history and host susceptibility. Current microbial models primarily distinguish existing disease states and have not been sufficiently validated for prospective prediction of progression from CAG to GC [100]. Microbiome-modifying interventions likewise remain investigational [117]. Accordingly, microbiome-informed surveillance or intervention should not enter clinical practice until validated in multicenter prospective studies with histological progression or GC incidence as predefined outcomes.

Disclosure of conflict of interest

None.

Abbreviations

AG, atrophic gastritis; BBR, berberine; CAG, chronic atrophic gastritis; CagA, cytotoxin associated gene A; CCL3, C-C motif chemokine ligand 3; COL4A1, collagen type IV alpha 1 chain; CTNNB1, catenin beta 1; CXCL16, C-X-C motif chemokine ligand 16; DCA, deoxycholic acid; ERK, extracellular signal-regulated kinase; EZH2, enhancer of zeste homolog 2; GBA1, glucosylceramidase beta 1; GC, gastric cancer; GIN, gastric intraepithelial neoplasia; GNB4, guanine nucleotide-binding protein subunit beta-4; INS-GAS, insulin-gastrin transgenic; IRF3, interferon regulatory factor 3; LC-MS, liquid chromatography-mass spectrometry; LEfSe, linear discriminant analysis effect size; LPS, lipopolysaccharide; MAIT, mucosal-associated invariant T cells; MAPK, mitogen-activated protein kinase; MMP-10, matrix metalloproteinase-10; NAG, non-atrophic gastritis; NOD, nucleotide-binding oligomerization domain; OLGA, Operative Link on Gastritis Assessment; OLGIM, Operative Link on Gastric Intestinal Metaplasia Assessment; RIG-I, retinoic acid-inducible gene I; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SG, superficial gastritis; SHP2, Src homology 2 domain-containing phosphatase 2; SQLE, squalene epoxidase; STAT1, signal transducer and activator of transcription 1; STING, stimulator of interferon genes; SUMO, small ubiquitin-like modifier; T4SS, type IV secretion system; TDCA, taurodeoxycholic acid; TER, transepithelial

electrical resistance; TET1, ten-eleven translocation 1; TGR5, takeda G protein-coupled receptor 5; TNF, tumor necrosis factor; TNFRSF9, TNFR superfamily member 9; Trim30A, tripartite motif-containing 30A; YAP, Yes-associated protein.

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