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REVIEW

Streptococcus anginosus: the potential role in the progression of gastric cancer

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Abstract

Gastric cancer (GC) is among the most common and aggressive malignancies worldwide, characterized by a poor prognosis. Research on its pathogenesis and progression continues to evolve. *Streptococcus anginosus* (*S. anginosus*, SA) is a Gram-positive coccus commonly found in the oral cavity and upper respiratory tract, serving as a commensal bacterium in the oral, gastrointestinal, and genitourinary tracts. It is frequently associated with abscess formation in various organs and tissues, as well as other purulent infections. In recent years, *S. anginosus* has gained increasing attention for its role in GC progression, potentially leading to chronic gastric inflammation and precancerous lesions, and ultimately promoting the development of GC. Emerging evidence indicates a strong association between *S. anginosus* and the malignant progression and unfavorable prognosis of GC. This review summarizes the role and underlying mechanisms of *S. anginosus* in GC and proposes that *S. anginosus* plays a pivotal role in its initiation and progression, underscoring its potential therapeutic significance.

Keywords *Streptococcus anginosus* · Gastric cancer · Infection · Progression

Introduction

Gastric cancer (GC) ranks among the five most common malignancies worldwide and is associated with high incidence and mortality (Sung et al. 2021). Numerous studies have identified host-related factors, including ABO blood type, genetic susceptibility, and environmental influences, such as microbial infections, as critical contributors to GC initiation and progression (Rawla and Barsouk 2019; Malfertheiner et al. 2023). Chronic *Helicobacter pylori* (*H. pylori*, HP) infection is the most well-established risk factor for GC, promoting chronic inflammation and a multistage progression of gastric lesions that can lead to carcinogenesis over a prolonged latency period. Consequently, the World Health Organization (WHO) has classified *H. pylori* as a Group I carcinogen (Liu et al. 2024). *H. pylori* infection is closely linked to various gastric diseases. Although most carriers remain asymptomatic, persistent infection increases the risk of chronic gastritis, gastric ulcers, and GC (Burclaff et al. 2020). *H. pylori* survives in highly acidic environments by secreting urease. It can induce chronic inflammation of the gastric mucosa through mechanisms such as oxidative stress, DNA damage, inflammatory responses, and conditional apoptosis, ultimately leading to the development of GC (Duan et al. 2025).

The human body harbors a diverse array of microorganisms, including bacteria, eukaryotes, and viruses, with bacteria being the most abundant and extensively studied. The gut microbiome is a complex ecosystem shaped by various factors, such as diet, environmental conditions, and host genetics, all of which influence its composition. Microbial metabolites play a critical role in human health and disease pathogenesis (Campana et al. 2022). Beyond *H. pylori*, the gastric microbiota comprises numerous other microbial species. Although the acidic gastric environment and protective mucin layer naturally limit bacterial colonization, emerging evidence suggests that the entire gastric microbiome—not just *H. pylori*—contributes to GC development (Ye et al. 2025). Advances in molecular biology techniques have enabled the identification of a diverse range of bacterial species in the human stomach, many of which have

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been implicated in GC initiation and progression (Wen et al. 2021). Several studies have demonstrated that a substantial proportion of gastric microbiota associated with GC originate from the oral cavity.

The human oral microbiome is a highly complex ecosystem, predominantly composed of bacteria, with a richness and diversity second only to that of the gut (Deo and Deshmukh 2019). The *Streptococcus anginosus* group (SAG) is a commensal colonizer of the oral cavity and upper respiratory tract. However, under conditions of immune compromise or mucosal damage in the lower respiratory tract, it can lead to pulmonary infections, including lung abscesses and pleural infections (Mukae et al. 2016). *Streptococcus anginosus (S. anginosus*, SA*)* was previously underrecognized, but accumulating evidence has demonstrated its association with gastrointestinal malignancies (Narikiyo et al. 2004; Kono et al. 2022; Shukla et al. 2024). A recent article published in *Cell* reported that the presence of *S. anginosus* is significantly associated with gastritis, atrophic gastritis, intestinal metaplasia, and GC, suggesting it may serve as an important driving factor in gastric carcinogenesis (Fu et al. 2024). As research on *S. anginosus* advances, its role in GC pathogenesis is being increasingly explored. This review summarizes the mechanisms by which *S. anginosus* contributes to GC development and progression, while also discussing its potential applications in the prevention and treatment of GC.

S. anginosus

The SAG is a subset of the *Streptococcus milleri* group (SMG) and a commensal bacterium residing in the oral cavity, gastrointestinal tract, and genitourinary system. It comprises three species: *S. anginosus*, *Streptococcus intermedius* (*S. intermedius*), and *Streptococcus constellatus* (*S. constellatus*) (Claridge et al. 2001). SAG was first identified and described by Andrewes and Horder in 1906 (Fujiyoshi et al. 2002), and in 1956, Guthof successfully isolated it from dental abscesses. Due to its poor growth under aerobic conditions, SAG is often overlooked in routine microbiological laboratories, contributing to limited clinical recognition (Jiang et al. 2020). It was not until 1980 that SAG gained renewed attention as a significant pathogen responsible for pyogenic infections (Asam and Spellerberg 2014).

On blood agar plates, SAG colonies typically measure less than 0.5 mm in diameter and emit a characteristic butterscotch-like odor (Asam and Spellerberg 2014). SAG is generally sensitive to penicillin. *S. anginosus* can be isolated from patients' blood, urogenital, and gastrointestinal specimens. and the recovery of its from clinical samples suggests that the gastrointestinal tract is the primary reservoir of infection (Claridge et al. 2001). *S. anginosus* is a Gram-positive coccus, typically appearing in pairs or short chains, with a diameter ranging from 0.6 to 1.0 μm. It stains purple, is non-motile, and lacks spore-forming ability (Hamada and Slade 1980). The formation of biofilms provides a protective environment, allowing the bacterium to evade host immune responses and resist antibiotic treatment (Petersen et al. 2006). As a catalase-negative member of the *Streptococcus* genus, *S. anginosus* exhibits remarkable adaptability, capable of growing under both aerobic and anaerobic conditions. It demonstrates variable hemolytic patterns, including alpha, beta, and gamma hemolysis (Ruoff 1988). At the molecular level, *S. anginosus* possesses multiple virulence factors, such as hemolysins, prothrombin activators, and adhesion molecules, which facilitate colonization, invasion, and immune evasion within the host (Kuryłek et al. 2022). The bacterium secretes enzymes, including hyaluronidase, to degrade the host extracellular matrix, promoting tissue invasion and infection (Kuryłek et al. 2022).

S. anginosus is highly sensitive to penicillin, with a minimum inhibitory concentration (MIC) ranging from 0.03 to 0.06 μg/mL. β-lactam antibiotics (e.g., penicillins, cephalosporins), glycopeptides (e.g., vancomycin), daptomycin, and linezolid demonstrate excellent efficacy against *S. anginosus*. In certain cases, penicillin-resistant *S. anginosus* remains susceptible to vancomycin (Qian et al. 2024). Historically, *S. anginosus* was largely overlooked, as it was considered a component of the normal human microbiota. Its symbiotic role within the human microbiome has contributed to frequent misdiagnosis, particularly in microbiological infection samples. However, increasing evidence in recent years has implicated *S. anginosus* in various diseases (Pilarczyk-Zurek et al. 2022), including cancer, leading to heightened research interest in this bacterium.

S. anginosus and infectious diseases

S. anginosus is a common pathogen implicated in various infections, exhibiting diverse clinical manifestations, distinct treatment approaches, and variable prognoses. The most frequently reported infections include respiratory tract infections, pyogenic infections, and bloodstream infections. *S. anginosus* commonly colonizes the skin and soft tissues, oral cavity, upper respiratory tract, gastrointestinal tract, and urogenital system. In individuals with compromised immune function or lower respiratory tract mucosal damage, the bacterium can cause pulmonary infections, which, in severe cases, may progress to lung abscesses or pleural infections. It is particularly associated with infections of the gastrointestinal tract, skin and soft tissues, and oral cavity (Mukae et al. 2016). Risk factors for *S. anginosus* infections include dental procedures, periodontal disease, smoking,

myocardial infarction, excessive alcohol consumption, malignancies, type 2 diabetes, central nervous system disorders, chronic kidney disease, chronic respiratory diseases, heart failure, and liver disease (Jiang et al. 2020; Pilarczyk-Zurek et al. 2022). Among these, malignancies and type 2 diabetes are the most frequently reported (Fazili et al. 2017).

A study analyzing saliva from different age groups have found that *S. anginosus* shows an increasing trend with age. This may be related to the greater opportunity for various infectious diseases to occur with age, such as endocarditis and upper gastrointestinal cancers (Morita et al. 2004; Narikiyo et al. 2004). Similarly, another study examining saliva samples from individuals with alcohol dependence found *S. anginosus* levels to be approximately five times higher in this group compared to non-alcoholics. This finding suggests a specific association between *S. anginosus* and alcohol-induced periodontal disease as well as upper gastrointestinal cancer (Morita et al. 2005). Alcohol use disorder is often linked to poor oral hygiene, leading to deteriorated oral health and an increased prevalence of periodontal disease. Research has demonstrated that patients with severe periodontitis exhibit significantly elevated *S. anginosus* levels in their saliva, which decline following systematic periodontal treatment. This suggests a potential role for *S. anginosus* in mediating periodontal inflammation (Kumagai et al. 2003). Moreover, *S. anginosus* has been isolated not only from dental abscesses but also from cases of infectious endocarditis and abscesses in the brain, liver, spleen, and corpus cavernosum, indicating a possible role in hematogenous dissemination (Kuryłek et al. 2022). However, some researchers propose that the hepatobiliary system or urinary tract may represent more likely sources of *S. anginosus* bacteremia (Suzuki et al. 2016). *S. anginosus* bacteremia is associated with more severe infections and leads to higher mortality rates (Kim et al. 2024). Additionally, *S. anginosus* has been detected in the gastric mucosa of patients with GC and has been shown to induce acute and chronic gastritis, gastric parietal cell atrophy, metaplasia, and dysplasia in mouse models (Isakov 2024).

Researchers have reported a case in which a pericardial-esophageal fistula was the initial manifestation of advanced esophageal cancer (EC), with pericardial abscess cultures testing positive for *S. anginosus* (Ferreira et al. 2024). Additionally, a patient diagnosed with Lemierre syndrome (LS) was found to have concomitant esophageal squamous cell carcinoma. *S. anginosus* was identified in both the drainage culture of the cervical abscess and blood cultures, leading researchers to suggest that *S. anginosus* may serve as a causative pathogen of LS and that its associated bacteremia could be linked to EC (Osman et al. 2017). Another case involved a patient with multiple liver abscesses and *S. anginosus* bacteremia, who was later diagnosed with rectal adenocarcinoma, suggesting a potential association between *S. anginosus* bacteremia and colorectal cancer (CRC) (Masood et al. 2016). Similarly, Dadeboyina et al. reported a case in which a patient with *S. anginosus* bacteremia was subsequently diagnosed with metastatic colonic adenocarcinoma and concurrent aortic and mitral valve endocarditis, further supporting a possible relationship between *S. anginosus* bacteremia and CRC (Dadeboyina et al. 2020). These findings raise the possibility that *S. anginosus* infection may play a synergistic role in cancer pathogenesis. However, further research is required to clarify and confirm this association.

S. anginosus and other cancers

Before reviewing the role of *S. anginosus* in GC, it is essential to summarize its involvement in other malignancies. Researchers performed 16 S rRNA gene sequencing on saliva samples from patients with oral squamous cell carcinoma (OSCC) and healthy individuals to compare oral microbiome composition and cytokine levels. Their findings suggest that *S. anginosus* may contribute to OSCC progression by upregulating inflammatory cytokines, including IL-6, IL-8, TNF-α, IFN-γ, and GM-CSF (Rai et al. 2021). Similarly, Mäkinen et al. reported an increased abundance of *S. anginosus* in the salivary microbiome of OSCC patients (Mäkinen et al. 2023), though this association may also be influenced by long-term betel nut chewing (Hernandez et al. 2017).

A study found that patients with advanced OSCC exhibited an increased frequency of *S. anginosus*-specific granzyme B-expressing $CD8^+$ T cells in peripheral blood. In patients with tumor recurrence, the interval between initial tumor resection and recurrence was positively correlated with the frequency of *S. anginosus*-reactive $CD8^+$ T cells, suggesting that *Streptococcus*-reactive $CD8^+$ T cell responses may contribute to antitumor immunity in OSCC (Wang et al. 2018). Additionally, some studies have reported a higher prevalence of *S. anginosus* co-infection with human papillomavirus (HPV), particularly HPV-16, in OSCC patients, suggesting a potential synergistic association between *S. anginosus* and HPV (Robayo et al. 2019). Xu et al. demonstrated that exposure of the OSCC cell line SCC15 to varying concentrations of *S. anginosus* supernatant enhanced autophagy activity, significantly inhibiting cell proliferation, migration, and invasion (Xu et al. 2021).

Similarly, 16 S rRNA gene sequencing of saliva samples from patients with oropharyngeal cancer (OPC) and healthy individuals revealed a significant increase in *S. anginosus* abundance among cancer patients. This finding led to the hypothesis that *S. anginosus* could serve as a non-invasive diagnostic biomarker for OPC (Panda et al.

2020).Furthermore, *S. anginosus* infection may contribute to EC development through inflammation, and its eradication could potentially reduce EC risk (Narikiyo et al. 2004). Southern blot and PCR analyses have detected *S. anginosus* DNA sequences in EC and GC tissues, further suggesting a potential association (Sasaki et al. 1998).

In CRC, studies have reported elevated *S. anginosus* levels in both saliva and the gastrointestinal tract of patients (Uchino et al. 2021). Furthermore, the abundance of *S. anginosus* in fecal samples was significantly higher in advanced CRC cases (Alhhazmi et al. 2023), suggesting its potential role in CRC progression by fostering an inflammatory environment (Camañes-Gonzalvo et al. 2024). Kono et al. observed increased *S. anginosus* levels in the mucosal tissue surrounding CRC, with the bacteria infiltrating adjacent normal tissues and altering the local microenvironment to facilitate tumor progression (Kono et al. 2022). A significant increase in *S. anginosus* abundance has also been observed in gallbladder cancer (GBC), suggesting its potential involvement in GBC pathogenesis (Shukla et al. 2024). Furthermore, researchers have reported an increased abundance of *S. anginosus* in the urine of female bladder cancer (BC) patients (Chorbińska et al. 2023), indicating a possible sex-specific association that warrants further investigation. Compared to other cancers, the role of *S. anginosus* in the development of GC should not be underestimated. Although research on *H. pylori* has been dominant, it cannot account for all GC cases. *S. anginosus* may represent a novel microbial factor that fills this explanatory gap.

Microbiome and GC

GC is a multifactorial disease, with its initiation, progression, and metastasis dependent on alterations in the tumor microenvironment. As a key component of this microenvironment, the microbiome plays a crucial role in human health, and its compositional changes have been increasingly associated with various diseases (Rajilic-Stojanovic et al. 2020). The diversity and richness of the human gastrointestinal microbiome vary by anatomical region, with the highest microbial abundance in the oral cavity and intestines, while the esophagus and stomach harbor comparatively fewer microorganisms (Petkevicius et al. 2024). Due to its highly acidic environment and other antimicrobial factors, the stomach was historically considered an exclusive habitat for *H. pylori*, with limited capacity to support other microbial species. However, beyond *H. pylori*, microbial phyla such as Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria have also been identified in the gastric mucosa (Huang et al. 2023). In individuals infected with *H. pylori*, this bacterium constitutes approximately 90% of the gastric microbiota, significantly reducing overall microbial diversity (Heidary et al. 2024). *H. pylori* infection plays a pivotal role in the early stages of gastric carcinogenesis, initiating a cascade of pathological changes—from gastritis to intestinal metaplasia, dysplasia, and ultimately GC. This sequential process is known as the Correa cascade (He et al. 2022).

H.pylori infection is the most well-established risk factor for GC; however, other microbial communities may also contribute to disease progression. Due to variations in study cohorts and confounding factors, findings on the dominant bacterial taxa within the GC-associated microbiome remain inconsistent. In an analysis of gastric mucosa-associated bacterial communities in patients with non-atrophic gastritis and intestinal metaplasia, Francisco et al. reported that increased levels of *Neisseria*, a specific *Lactobacillus* species, and *Clostridiales* Family XI correlated with greater gastric mucosal damage, while *Porphyromonas*, TM7, and *S. anginosus* were significantly reduced (Aviles-Jimenez et al. 2014). A subsequent study identified an enrichment of *Lactobacillus*, *Escherichia-Shigella*, *Nitrospirae*, *Burkholderia fungorum*, and *Lachnospiraceae* in GC tissues (Wang et al. 2016). Additionally, specific bacterial species such as *Pasteurella stomatis* (*P. stomatis*), *Dialister pneumosintes* (*D. pneumosintes*), *Slackia exigua* (*S. exigua*), and *S. anginosus* were implicated in GC development (Coker et al. 2018). Furthermore, Ferreira et al. observed an increased abundance of *Actinobacteria* and *Firmicutes* in the GC microbiome, whereas *Bacteroidetes* and *Fusobacteria* were significantly reduced. By integrating these microbial taxa with the microbial dysbiosis index, their study demonstrated that microbial dysbiosis effectively distinguishes gastritis from GC (Ferreira et al. 2018).

With advances in microbiome research, the enrichment of oral microorganisms in the gastric mucosa has garnered significant attention, particularly due to their markedly increased abundance in GC tissues compared to precancerous stages (Wen et al. 2021). Patients with GC exhibit reduced oral microbial α-diversity relative to those with gastritis. In GC patients, *anginosus* is significantly more abundant in both saliva and gastric tissue, whereas *Fusobacterium*, *Haemophilus*, *Neisseria*, *Parvimonas*, and *Peptostreptococcus* are present at lower levels (Huang et al. 2021). Additionally, a study identified *Neisseria*, *Prevotella*, and *Aggregatibacter* as the most representative bacterial groups in GC tissues, all of which are symbiotic or opportunistic pathogens commonly found in the oral cavity (Hu et al. 2018). Moreover, *H. pylori*, a key indicator of gastric precancerous lesions and an early warning marker, is not only present in the stomach of GC patients but can also be detected in their oral cavity. *H. pylori* is widely recognized as a major risk factor for GC. Sung et al. demonstrated that following *H. pylori* eradication, distinct oral microbial

communities in the gastric mucosa are associated with the onset and persistence of mucosal atrophy and intestinal metaplasia. These bacteria include *Peptostreptococcus*, *Streptococcus*, *Slackia*, *Prevotella*, *Rothia*, and *Granulicatella* (Sung et al. 2020). Microbial dysbiosis plays a crucial role in GC initiation and progression, particularly in the context of non-*H. pylori* microbial community shifts. These findings offer new research directions and potential strategies for GC prevention and treatment.

S. anginosus and GC

GC remains a leading cause of cancer-related mortality worldwide, with over one million new cases diagnosed annually. While *H. pylori* infection is a well-established primary risk factor, its eradication does not entirely prevent GC, indicating that additional factors, such as the gastric microbiota, play a crucial role in its pathogenesis (Xia et al. 2025). Early studies utilizing 16 S rRNA gene sequencing in GC samples have identified *S. anginosus* DNA (Sasaki et al. 1998), drawing increasing attention to its potential role in gastric carcinogenesis. Similarly, microbial profiling of the gastric tumoral microhabitat via MiSeq sequencing has demonstrated a significant enrichment of *S. anginosus* within GC tissues (Liu et al. 2019). A meta-analysis further revealed distinct microbial shifts across disease progression, from healthy individuals to gastritis, intestinal metaplasia, and GC. Among these, *S. anginosus* was one of the most significantly enriched bacteria in GC patients, displaying strong discriminatory potential between GC and gastritis samples (Li et al. 2023). Additionally, 16 S rRNA sequencing studies have identified notable alterations in the tongue coating microbiota of GC patients compared to healthy individuals, characterized by reduced microbial diversity and significant changes in the relative abundance of specific bacterial taxa. *S. anginosus* is considered a potential oncogenic factor in GC, as it can metabolize ethanol into acetaldehyde, a Group I carcinogen (Wu et al. 2018).

In recent years, increasing attention has been directed toward the pathogenic mechanisms of *S. anginosus* in GC. A study classified GC patients into six subtypes based on intratumoral microbiota composition, revealing that patients with a high abundance of *S. anginosus* had significantly poorer prognoses. The abundance of *S. anginosus* was markedly higher in tumor tissues than in adjacent normal tissues and was closely associated with unfavorable survival outcomes (Yuan et al. 2024). *S. anginosus* was successfully isolated, cultured, and validated through whole-genome sequencing. In clinical samples and independent patient cohorts, *S. anginosus* was significantly enriched in GC tissues compared to normal tissues. Notably, this enrichment was not observed in EC or CRC tissues, suggesting that *S. anginosus* may serve as a GC-specific microbial biomarker. Cox regression analysis further confirmed *S. anginosus* as an independent risk factor for poor prognosis in GC (Yuan et al. 2024). In a mouse model of N-methyl-N-nitrosourea (MNU)-induced GC, *S. anginosus* significantly increased tumor incidence and progression. Similarly, in the MFC cell xenograft model, both low and high doses of *S. anginosus* promoted tumor growth, whereas antibiotic treatment reversed this effect (Yuan et al. 2024). Immunohistochemical analysis revealed that *S. anginosus*-treated tumors exhibited reduced $CD8^+$ T-cell infiltration and increased expression of proliferation (Ki-67), invasion, and metastasis markers (N-cadherin and vimentin) (Yuan et al. 2024). Co-culture experiments with GC cell lines (AGS and MKN1) demonstrated that *S. anginosus* and its metabolic products significantly enhanced cell proliferation, migration, and invasion. Moreover, *S. anginosus* inhibited $CD8^+$ T-cell differentiation in peripheral blood mononuclear cells (PBMCs), further highlighting its role in immune evasion and tumor progression (Yuan et al. 2024). Metabolomic analysis revealed that *S. anginosus* reshapes the tumor immune microenvironment by regulating arginine metabolism. In *S. anginosus*-enriched tumor tissues, metabolites related to arginine and proline metabolism, such as ornithine, were significantly upregulated, while arginine levels were reduced. This metabolic shift was attributed to the arginine deiminase (ADI) pathway of *S. anginosus*, which converts arginine into ornithine, thereby promoting tumor growth and suppressing immune responses (Yuan et al. 2024). Collectively, these findings indicate that *S. anginosus* plays a critical role in GC initiation and progression. By altering arginine metabolism, promoting ornithine accumulation, and inhibiting $CD8^+$ T-cell differentiation, *S. anginosus* contributes to an immunosuppressive tumor microenvironment. These results suggest that *S. anginosus* is not only a potential biomarker for GC but also a promising therapeutic target for future interventions.

Fu et al. reported that *Streptococcus S. anginosus* was significantly enriched in the gastric mucosa of patients with GC, with its abundance progressively increasing as the disease advanced, reaching its highest levels in GC tissues. Moreover, *S. anginosus* was strongly associated with gastritis, atrophic gastritis, intestinal metaplasia, and GC, suggesting its potential role as a key driver of gastric carcinogenesis (Fu et al. 2024). In subsequent mouse experiments, two weeks after conventional mice were infected with *S. anginosus*, the bacterium was detected in the gastric mucosa, accompanied by acute gastritis characterized by neutrophil infiltration and a significant upregulation of pro-inflammatory cytokines, including *Ccl20* and *Ccl8*. After three months of persistent infection, chronic inflammation developed, with lymphocyte infiltration and inflammatory lesion formation. By nine months, parietal cell atrophy

emerged, progressing to moderate-to-severe atrophy at twelve months, along with mucinous intestinal metaplasia and low-grade dysplasia. The severity of *S. anginosus*-induced inflammation was comparable to that caused by *H. pylori*, and co-infection with both pathogens significantly exacerbated gastric inflammation and disease progression (Fu et al. 2024). In germ-free mice, *S. anginosus* infection for nine months resulted in mucinous intestinal metaplasia, accompanied by increased Ki-67-positive proliferating cells and downregulation of tight junction proteins (CLDN18, OCLN, and ZO-1), indicating that *S. anginosus* can induce gastric precancerous lesions even in the absence of other microbial influences. Additionally, in the YTN16 tumor xenograft model, *S. anginosus* significantly promoted tumor growth, as evidenced by increased tumor volume and weight, elevated expression of the proliferation marker Ki-67, and reduced TUNEL-positive apoptotic cells (Fu et al. 2024). Further investigations revealed that *S. anginosus* mediates colonization and signal transduction in gastric epithelial cells through the interaction between its surface protein TMPC and the host receptor Annexin A2 (ANXA2). TMPC-ANXA2 binding activates the mitogen-activated protein kinase (MAPK) signaling pathway, leading to the phosphorylation of ERK1/2 and JNK, which in turn activates downstream targets, including p-AKT, Cyclin D1, c-Myc, and c-Jun, thereby promoting cell proliferation and inhibiting apoptosis. In ANXA2-knockout mice, MAPK signaling was effectively blocked, highlighting the critical role of the TMPC-ANXA2 axis in the tumorigenic effects of *S. anginosus* (Fu et al. 2024). Transcriptome analysis further demonstrated that *S. anginosus* infection significantly activated the Ras/MAPK/PI3K-AKT signaling cascade in host cells, whereas ANXA2 silencing or TMPC deletion substantially suppressed this pathway. These findings indicate that *S. anginosus* serves as a crucial driver of GC by inducing chronic gastric inflammation and precancerous lesions via the TMPC-ANXA2-MAPK axis, ultimately facilitating tumor development (Wong and Tan 2024). However, as this study primarily utilized murine models, further research is required to determine whether these pathogenic mechanisms are applicable to humans.

Bibliometric analysis of the relationship between autoimmune gastritis (AIG) and GC has shown that AIG-induced hypochlorhydria alters the gastric microbiota, fostering the growth of specific bacterial species, particularly *S. anginosus*. *S. anginosus* is now recognized as the second key bacterial factor in gastric carcinogenesis after *H. pylori* (Isakov 2024; Senthil Kumar et al. 2024). Mouse models have demonstrated that *S. anginosus* promotes gastric mucosal cell proliferation, disrupts gastric barrier function, and drives gastric tumorigenesis via pro-inflammatory mechanisms. Specifically, *S. anginosus* activates macrophages, leading to elevated production of pro-inflammatory cytokines (TNF, IL-6, IL-1β) and mediators (NOS2, COX2), while simultaneously activating the NF-κB signaling pathway. These processes facilitate the transition from hyperplastic metaplasia to dysplasia (Isakov 2024; Senthil Kumar et al. 2024). AIG-associated hypochlorhydria-induced alterations in the gastric microbiome, particularly the overgrowth of *S. anginosus*, may contribute to GC development in young patients without *H. pylori* infection. This microbial shift, especially the proliferation of *S. anginosus*, could represent a novel oncogenic driver in AIG, particularly among *H. pylori*-negative young individuals (Isakov 2024; Senthil Kumar et al. 2024).

Wang et al. recently conducted in vitro experiments in which GC cell lines were co-cultured with *S. anginosus*. The results demonstrated that *S. anginosus* significantly enhanced cell proliferation, invasion, migration, and resistance to apoptosis. In a subsequent MNU-induced mouse model, oral gavage with *S. anginosus* led to notable thickening of the gastric mucosa, characterized by epithelial hyperplasia and increased cell infiltration. Moreover, the relative abundance of *S. anginosus* in fecal samples was significantly elevated, confirming successful colonization. *S. anginosus*-treated mice exhibited decreased survival, suggesting that *S. anginosus* accelerates disease progression and contributes to increased mortality (Wang et al. 2025). Immunohistochemical analysis of gastric tissues revealed significantly elevated expression of IL-1β, IL-18, and GSDME in the *S. anginosus*-treated group compared to controls. The pronounced upregulation of these inflammatory cytokines and the pyroptosis-related marker GSDME indicates the induction of pyroptosis and highlights the role of *S. anginosus* in modulating the inflammatory milieu of the gastric microenvironment. Additionally, Western blot analysis of *S. anginosus*-infected cells showed increased expression of GSDME, cleaved caspase-3, and NLRP3, further confirming the activation of pyroptosis. These findings suggest that *S. anginosus* not only induces inflammatory responses but also promotes a pro-tumorigenic microenvironment through the pyroptosis signaling pathway. Although pyroptosis is generally regarded as an anti-tumor immunity, its chronic activation in the tumor microenvironment may promote immune evasion and tumor cell proliferation, ultimately contributing to inflammation-driven gastric carcinogenesis (Wang et al. 2025) (Fig. 1) (Table 1).

Other potential mechanisms of *S. anginosus* in GC

Microorganisms previously believed to be exclusive to the oral cavity have been identified in the gastric mucosa, with multiple cohort studies highlighting similarities between the oral and gastric microbiomes (Coker et al. 2018; Huang

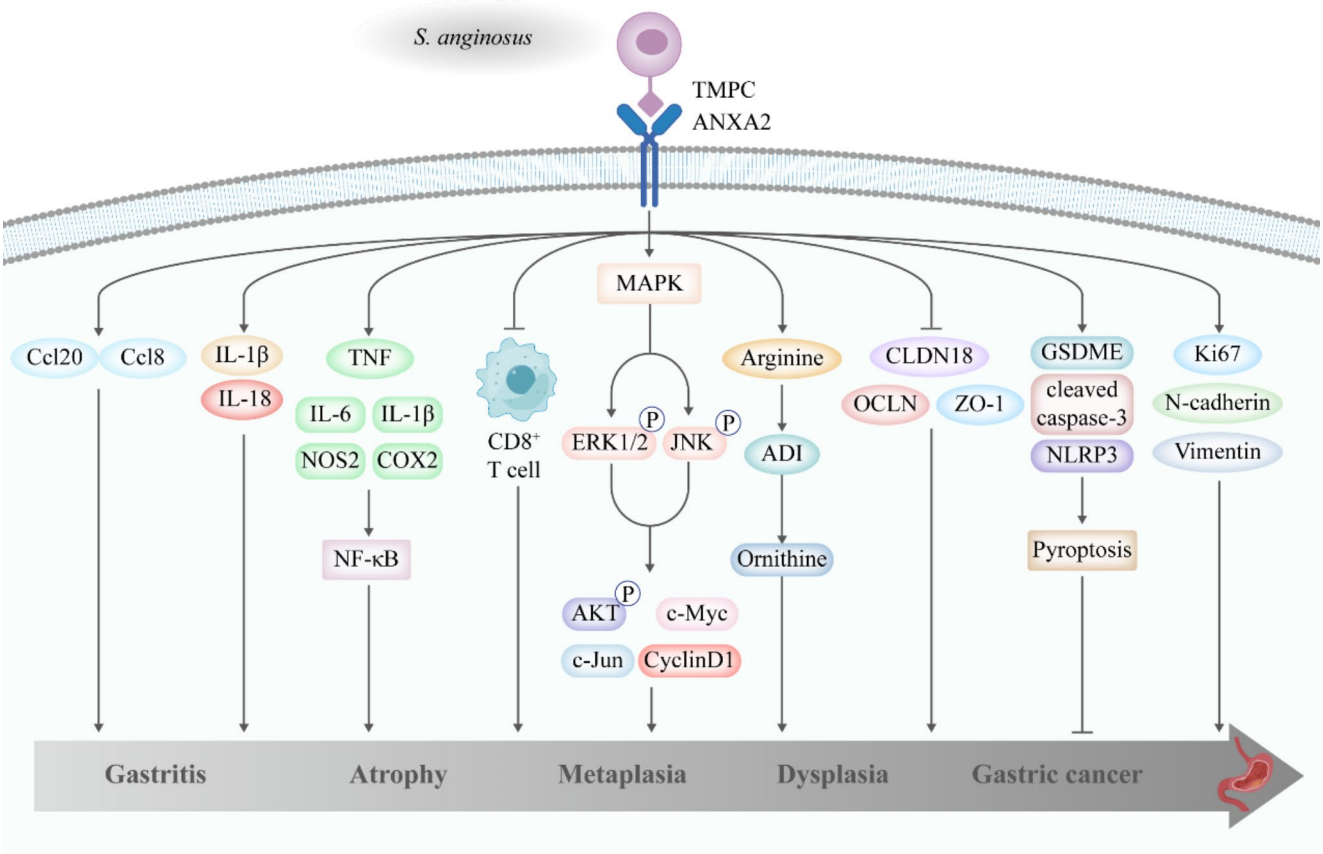

Fig. 1 The pathogenic mechanisms of *S. anginosus* in the development of GC

Table 1 Summary of the studies with focus on *S. anginosus* in GC

Study type	Methods	Sample type	Major findings	References
Clinical observational study	16 S rRNA sequencing	Tumor tissues and adjacent normal tissues from GC patients	S. anginosus was significantly enriched in GC tissues, suggesting a potential association with GC development.	Sasaki et al. 1998
Clinical observational study	16 S rRNA sequencing	Tumor tissues and adjacent normal tissues from GC patients	S. anginosus was upregulated in the GC tumor microenvironment, indicating its potential involvement in GC development.	Liu et al. 2019
Secondary Research	Meta-analysis	Literature data	*S. anginosus* was significantly enriched in GC tissues and could distinguish between GC and gastritis samples.	Li et al. 2023
Clinical observational study	16 S rRNA sequencing	Tongue mucosal tissue of GC patients	S. anginosus is considered a potential oncogenic factor in GC	Wu et al. 2018
In vitro and animal study	Bacterial co-culture, cell-based assays, MFC cell xenograft model	GC cell lines and mouse models	S. anginosus exhibits immune evasion and tumor progression effects in gastric cancer.	Yuan et al. 2024
Animal study	Bacterial infection, histological analysis of mouse tissues	Mouse models	*S. anginosus* accumulates in the gastric mucosa of mice, inducing gastritis, atrophy, and tumor formation, thereby promoting the development of gastric cancer.	Fu et al. 2024
Secondary Research	Bibliometric analysis	Literature data	Reduced gastric acid secretion in AIG leads to alterations in the gastric microbiota and overgrowth of S. anginosus.	Isakov 2024
Animal study	Histological analysis of mouse tissues	Mouse models	S. anginosus drives gastric carcinogenesis through pro-inflammatory responses.	Senthil Kumar et al. 2024
In vitro and animal study	Bacterial co-culture, cell-based assays, histological analysis of mouse tissues	GC cell lines and mouse models	*S. anginosus* promotes GC progression through pyroptosis and induction of inflammatory responses.	Wang et al. 2025

et al. 2021). Oral microbes can enter the digestive tract through saliva and food intake, ultimately reaching the stomach. Under normal conditions, the stomach's highly acidic environment suppresses the growth of most microorganisms. However, reduced gastric acid secretion or impairment of the gastric mucosal barrier allows oral microbes to colonize and proliferate in the gastric mucosa, disrupting gastric microbial homeostasis (Huang et al. 2021).

Adhesion is essential for bacterial colonization and represents a critical initial step in infection. *S. anginosus* commonly adheres to extracellular matrix components such as fibronectin, fibrinogen, and laminin, while its affinity for collagen is limited (Allen and Höök 2002). Additionally, the bacterial capsule is a key virulence factor in streptococci. Whole-genome analysis has identified capsule polysaccharide synthesis locus in all three species of the *S. anginosus* group (Kilian et al. 2014). Beyond the capsule, β-hemolysin serves as another major virulence factor of *S. anginosus* group. Study has shown that *S. anginosus* β-hemolysin is homologous to streptolysin S (SLS) of *Streptococcus pyogenes*, encoded by a similar gene cluster (Tabata et al. 2013). SLS is a highly cytotoxic hemolysin that facilitates bacterial invasion by breaching epithelial barriers, inducing tissue damage, and evading host immune defenses, leading to cytotoxic effects on various cell types (Asam et al. 2015).

Sasaki et al. identified a novel bioactive antigen, *S. anginosus* antigen (SAA), from the supernatant of *S. anginosus*. Their study demonstrated that the SAA protein directly stimulates macrophages to produce nitric oxide (NO) and inducible nitric oxide synthase (iNOS) independently of γ-interferon (Sasaki et al. 2001). Elevated NO concentrations in tissues induce oxidative and nitrosative DNA damage, disrupt sugar chains between adjacent bases, and promote genetic mutations, thereby contributing to tumorigenesis (Sasaki et al. 2001). Chronic inflammation has been shown to induce overexpression of NF-κB in local tissues, a process strongly associated with tumor angiogenesis. NF-κB promotes the formation of vasculature within tumor tissues by activating dual signaling pathways involving vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2) (Rhodus et al. 2005). Moreover, emerging evidence suggests that *S. anginosus* can activate the NF-κB signaling pathway, thereby contributing to the progression from hyperplastic metaplasia to dysplasia (Senthil Kumar et al. 2024).

Furthermore, *S. anginosus* colonization can induce chronic inflammation, impairing the repair mechanisms of damaged local tissues. This dysregulation disrupts DNA replication and elongation processes, leading to uncontrolled cell proliferation and differentiation, ultimately increasing the risk of malignant transformation (Korde et al. 2011). The presence and translocation of *S. anginosus* are associated with GC development, potentially driving tumorigenesis through chronic inflammation and genetic mutations.

S. anginosus and GC diagnosis

A multicenter observational study revealed that *S. anginosus* was significantly more abundant in the gastric tissue and feces of GC patients than in those with chronic gastritis. The abundance of *S. anginosus* in GC tissue was 1.9 times that of healthy gastric mucosa, while its fecal abundance was 22.2 times higher (Zhou et al. 2022). Furthermore, in early-stage GC patients, *S. anginosus* abundance was 2.6 times higher than in late-stage patients and significantly elevated compared to the chronic gastritis group, indicating its early enrichment in gastric carcinogenesis (Zhou et al. 2022). Additional analysis showed no significant enrichment of *S. anginosus* in the feces of patients with colorectal adenoma, CRC, EC, or inflammatory bowel disease, whereas its enrichment was markedly elevated in GC patients, suggesting a GC-specific fecal signature (Zhou et al. 2022; Alhhazmi et al. 2023). Moreover, *S. anginosus* exhibited a positive correlation with *H. pylori* in GC tissues, a relationship not observed in chronic gastritis, suggesting a potential synergistic role in gastric carcinogenesis (Zhou et al. 2022). These findings indicate that *S. anginosus* is significantly enriched in the early stages of GC and underscore its potential as a fecal biomarker for noninvasive GC screening.

Conclusion and future perspective

GC is one of the most aggressive malignancies globally, with a poor prognosis. Despite significant advancements in diagnostic techniques across many countries, the majority of patients are diagnosed at an advanced stage, leading to unfavorable outcomes. This review provides a comprehensive analysis of gastric microbiota dysbiosis, with a particular emphasis on the association between *S. anginosus* and GC. Gastric microbial imbalance plays a crucial role in gastric carcinogenesis, particularly through the involvement of non-*H. pylori* microbial communities. These microorganisms may contribute to tumorigenesis through multiple mechanisms, including the induction of chronic inflammation, disruption of host immune responses, and production of carcinogenic metabolites. The dysbiosis and translocation of oral microbiota are key factors in GC development. However, the specific mechanisms by which ectopic oral bacteria promote gastric carcinogenesis and the identification of oral bacterial species uniquely linked to GC remain inadequately understood.

Growing experimental evidence has established a strong association between *S. anginosus* and GC, with the bacterium successfully identified or isolated from most tumor tissues, where its abundance is significantly elevated. Meta-analysis indicates that *S. anginosus* can distinguish between GC and gastritis samples (Li et al. 2023). However, the causal relationship between *S. anginosus* infection and tumor development remains uncertain, merely detecting *S. anginosus* in tumor tissues is insufficient to establish its carcinogenic role, particularly given the lack of significant differences between precancerous samples and controls. Fu et al. suggested that *S. anginosus* accumulates in the gastric mucosa of mice, inducing gastritis, atrophy, and tumor formation, revealing that it may promote GC through the TMPC-ANXA2-MAPK axis (Fu et al. 2024). Another study found that *S. anginosus* promotes GC progression through pyroptosis and the induction of inflammatory responses. *S. anginosus* not only induces inflammatory responses but also drives a pro-tumor microenvironment through the pyroptosis signaling pathway (Wang et al. 2025). Additionally, it is worth noting that physiological differences between mice and humans may limit the generalizability of the findings.

Future investigations should consider potential confounding factors related to *S. anginosus*, implement standardized protocols, and utilize high-resolution microbiome sequencing technologies to minimize inter-study heterogeneity. These approaches will facilitate the precise identification of GC-associated microbes and provide deeper insights into the dynamics of the gastric microbiome and bacterial interactions. Given that *S. anginosus* promotes GC progression through the GSDME-mediated pyroptosis pathway, future research may explore ways to inhibit this pyroptotic response. Such targeted therapies could help reduce inflammation and slow GC progression. Furthermore, *S. anginosus* may become a target for combination immunotherapy. By modulating immune responses triggered by bacterial infections, the effectiveness of immune therapies, such as immune checkpoint inhibitors, could be enhanced. Large-scale, multicenter prospective studies are essential to further investigate the causal relationship between *S. anginosus* and GC, ultimately establishing its role as a potential biomarker for GC prevention, diagnosis, treatment, and prognostic evaluation.

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Declarations

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