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REVIEW

Animal models and pathogenesis of gastric cancer: from premalignant conditions-to-metastasis

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ABSTRACT Gastric cancer (GC) remains one of the most prevalent malignancies of the gastrointestinal tract worldwide, ranking fifth in incidence and continuing to be a leading cause of cancer-related mortality. Elucidating the mechanisms underlying GC development and progression, as well as exploring effective preventive and therapeutic strategies, is therefore of paramount importance. Animal models are indispensable tools in this endeavor, providing platforms to investigate carcinogenic processes, recapitulate disease features, and evaluate therapeutic interventions, thereby bridging the gap between laboratory discoveries and clinical application. However, the establishment of reliable GC models remains challenging due to variations in tumor induction techniques, experimental conditions, and the profound heterogeneity and aggressive metastatic potential of GC. In this review we systematically summarize animal models used for studying gastric premalignant conditions and GC organized by disease stage. We analyze recent advances and limitations of each model, considering methodologic approaches, underlying mechanisms, and translational potential. Particular emphasis is placed on aligning model characteristics with contemporary clinical challenges. Ultimately, we highlight the pivotal role of animal models in advancing precision medicine for GC, offering novel perspectives to inform both mechanistic research and therapeutic development.

KEYWORDS Gastric cancer; animal model; gastric premalignant conditions; carcinogenesis

Introduction

Gastric cancer (GC) is a major global health concern, ranking fifth in incidence and fourth in cancer-related mortality worldwide. Approximately 1.09 million new cases were reported in 2020 and this number is projected to increase by 62% to 1.77 million by 2040[1]. The epidemiologic distribution of GC exhibits striking geographic variation with the highest incidence reported in Eastern Asia and substantially lower rates reported in North America and Northern Europe. The disease burden is particularly pronounced among males and in regions with a high Human Development Index, such as East Asia. An increasing trend in younger populations has also been observed, highlighting the growing global impact of GC[2].

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Animal models are widely used in cancer research, providing essential platforms for mechanistic studies, drug discovery, and therapeutic validation. Commonly used models in GC research include chemical or biological induction models, xenograft models, and genetically engineered models. Despite the utility, these models have important limitations, including interspecies anatomic differences, the absence of systems that can faithfully recapitulate the entire cascade of GC progression, and challenges in fully reproducing the complex heterogeneity of the human tumor microenvironment (TME).

In this review we summarize strategies for constructing GC animal models, covering the selection of experimental animals and commonly used methodologies (**Figure 1**), while outlining the advantages, limitations, and applicability. We further integrate model construction and application across different stages of GC pathogenesis, thereby clarifying the relationship between models and disease progression and enhancing the relevance to clinical questions. Finally, we provide perspectives on future research directions, offering guidance for refining models to address key scientific challenges and support personalized cancer therapy, ultimately reinforcing the role of models as translational bridges between basic research and clinical practice.

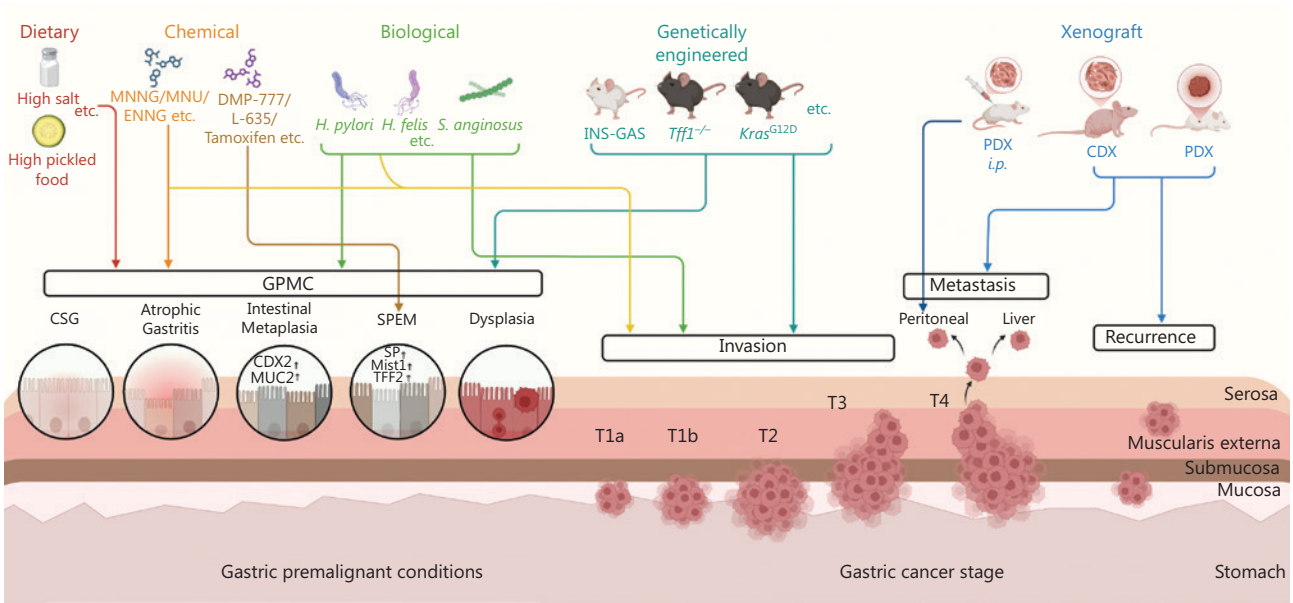


Figure 1 Modeling approaches for mice GC and the alignment with disease progression. The upper part summarizes the induction strategies; lower part depicts the corresponding pathological stages from GPMC to invasion, metastasis, and recurrence, with arrows mapping each modeling approach to the stage it most commonly recapitulates. From left to right: Dietary → GPMC. Chemical → GPMC and SPEM. Biological → GPMC and Invasion; combined with Chemical → Invasion. Genetically Engineered → GPMC and Invasion. Xenograft → Peritoneal metastasis; CDX and PDX → Metastasis and Recurrence. The lower panel illustrates sequential disease states: GPMC, including CSG, Atrophic Gastritis, Intestinal Metaplasia, SPEM and Dysplasia, followed by Invasion (T1a, T1b, T2, T3), Metastasis at T4 (Peritoneal, Liver), and Recurrence. Brackets denote stage groupings; arrows indicate directionality of modeling relevance with different colours. The stomach wall layers (Mucosa, Submucosa, Muscularis externa, Serosa) are shown to orient depth of invasion. Abbreviations: CDX, cell line–derived xenograft; CSG, chronic superficial gastritis; ENNG, N-ethyl-N′-nitro-N-nitrosoguanidine; GC, gastric cancer; GPMC, gastric premalignant conditions; i.p., intraperitoneal; IM, intestinal metaplasia; INS-GAS, insulin-gastrin transgenic mouse; MNNG, N-methyl-N′-nitro-N-nitrosoguanidine; MNU, N-methyl-N-nitrosourea; PDX, patient-derived xenograft; SPEM, spasmolytic polypeptide–expressing metaplasia; T1a/T1b/T2/T3/T4, primary tumor depth (TNM). The figures were created with BioRender.

Classification of GC

GC is divided into intestinal-, diffuse-, and mixed/indeterminate-types based on histologic characteristics, according to Lauren's classification[3]. Familial clusters caused by genetic factors account for approximately 10% of GC cases, whereas most GC cases are sporadic with the intestinal-type GC (IGC) the most common subtype[4]. Unlike the multifactorial, multi-step cascade that occurs in IGC, diffuse-type GC lacks clearly defined precursor lesions[5]. Specifically, diffuse-type GC typically exhibits a poorly differentiated phenotype with complete loss of glandular structures, carries a high risk of peritoneal dissemination, is associated with poorer prognosis, and represents a relatively rare but clinically more aggressive subtype[6].

Correa et al.[7] described a stepwise cascade of oncogenic progression following chronic *Helicobacter pylori* infection, as follows: normal gastric mucosa → chronic superficial gastritis (CSG) → chronic atrophic gastritis (CAG) → gastric intestinal metaplasia (GIM) → dysplasia → eventually progressing to IGC. The key pathologic states within this cascade are collectively referred to as gastric premalignant conditions (GPMC). GPMC include atrophic gastritis (AG), GIM, dysplasia (now more often termed intraepithelial neoplasia[8]), and some gastric epithelial polyps according to the inaugural 2025 American College of Gastroenterology guidelines[9]. The global prevalence estimates for AG, IM, and dysplasia are approximately 25.4%, 16.2%, and 2.0%, respectively[10].

Although terms, such as gastric precancerous lesions (GPLs) or precancerous lesions of GC[10,11] are often used interchangeably in the literature, the terms share the core concept of denoting pathologic states with an increased risk of progression to GC. Early prevention, interruption, or reversal of the Correa cascade can effectively halt this malignant progression and reduce disease incidence[9]. Therefore, elucidating the molecular mechanisms that drive the evolution of GPMC and identifying stage-specific biomarkers are critical research priorities with animal models playing an indispensable role in mechanistic validation and exploration.

CAG is a chronic condition characterized by the loss of gastric glands, mucosal thinning, and thickening of the muscularis mucosae caused by persistent inflammation or injury. CAG may occur with or without spasmolytic polypeptide-expressing metaplasia (SPEM), intestinal metaplasia (IM), or dysplasia, and generally follows a protracted course[12]. As a major risk factor for GC, AG increases disease incidence by approximately 3.5-fold and may progress to IM and dysplasia[13].

GIM refers to the pathologic replacement of damaged gastric mucosal epithelium with intestinal-type epithelial cells. Moreover, the global prevalence of GIM is increasing[14]. GIM is categorized into three subtypes based on morphology and mucin secretion patterns: type 1, or complete intestinal metaplasia (CIM); and types 2 and 3, collectively known as incomplete intestinal metaplasia (IIM)[15]. GIM markedly increases the risk of GC, with an estimated annual progression rate of about 0.1%[16]. The risk escalates progressively from Type 1 to Type 3, with IIM carrying a higher likelihood of progressing to dysplasia and cancer compared with CIM[17]. As such, IIM serves as an important marker for identifying individuals at elevated risk of GC[18].

Metaplasia describes the presence of a normal cell lineage in a location where a normal cell lineage is not typically found. Both acute and chronic injury to the gastrointestinal mucosa can trigger the development of metaplastic lineages, including pyloric metaplasia, pseudopyloric metaplasia (PPM), ulcer-associated cell lineage (UACL), and SPEM[19]. Among these metaplastic lineages, IM and SPEM are most closely linked to the pathologic progression of IGC[20].

SPEM, also referred to as pseudopyloric or mucinous metaplasia, is a gastric metaplastic response first identified in animal models and later confirmed in humans. SPEM is strongly associated with chronic Helicobacter pylori *(H. pylori)* infection and gastric adenocarcinoma[21]. SPEM shares morphologic features with PPM but can be distinguished by specific molecular markers, such as TFF2 and MUC6[22]. SPEM often represents the earliest metaplastic response to gastric injury. Under persistent inflammatory conditions, SPEM may act as a precursor to IM, dysplasia, and ultimately IGC. Although IM and SPEM have been reported in humans, most murine models of gastric metaplasia only exhibit SPEM[23]. The cumulative evidence indicates that SPEM serves as an initial response to chronic injury, and under sustained inflammatory stimuli, may represent a potential cellular origin for IM, dysplasia, and subsequent malignant transformation[24].

Individuals with precursor lesions remain at elevated risk for GC, even after *H. pylori* eradication. Of note, eradication efficacy diminishes as progression along the Correa cascade advances[18,25]. In parallel, the activation of gastric stem cells and accumulation of genetic alterations drive the transition from metaplasia-to-dysplasia-to-GC[26]. Consequently, GIM represents a pivotal juncture in carcinogenesis[27], although emerging evidence suggests that partial reversal may be possible[28]. These insights highlight the importance of additional risk factors to *H. pylori*. Therefore, future research should prioritize early eradication strategies and the development of novel interventions aimed at reversing mucosal injury.

Selection of experimental animals

Rodents

Rats

Rats provide several advantages as experimental models due to a larger body size, which facilitates surgical manipulation and sample collection. Wistar rats have a low incidence of spontaneous tumors and possess gastric mucosal structures that closely resemble humans, making rats well-suited for studying the progression from chronic inflammation to GC. Male Wistar rats are frequently selected to improve the success rate and histologic fidelity of N-methyl-N′-nitro-N-nitrosoguanidine (MNNG)-induced GC[29]. Sprague–Dawley (SD) rats, derived from the Wistar strain, offer additional benefits, including superior adaptability, strong disease resistance, well-characterized genetic backgrounds, and metabolic stability, making SD rats highly suitable for long-term toxicologic and pharmacologic studies. However, SD rats are typically more costly than Wistar rats. At present, 4–5-week-old male Wistar rats remain the most widely used strain in GC research[30]. Despite the advantages, rat models also have notable limitations, such as higher acquisition and maintenance costs and greater housing space requirements compared to mouse models.

Mice

The commonly used immunocompetent mouse strains include C57BL/6 and BALB/c. C57BL/6 mice exhibit a Th1-biased cellular immune response and are widely used in genetic engineering studies owing to the availability of well-established gene-editing tools. In contrast, BALB/c mice mount balanced Th1/Th2/Th17 responses that more closely resemble human immunity and are therefore preferred for *H. pylori* vaccine research[31]. Several less commonly used strains have also been applied in GC research. For example, 615 mice were the first reported strain in which GC was induced through methylbenzylnitrosamine (MBNA) exposure[32], while FVB mice, especially INS-GAS FVB mice, have been used to study GC pathogenesis[33]. Immunodeficient mice provide an important platform for xenograft studies but require strict rearing conditions. Although mice offer distinct advantages, including short reproductive cycles, efficient breeding, and advanced genetic modification systems, mice rarely develop spontaneous gastric tumors. As a result, most murine models of GC rely on induction with chemical

carcinogens or infection with mouse-adapted *Helicobacter* strains, such as *H. pylori* SS1 or *H. felis*. Because these strains differ in pathogenicity from human *H. pylori* isolates, *Helicobacter* strains may introduce mechanistic discrepancies compared to human gastric carcinogenesis[34].

Mongolian gerbils (MG)

The MG model, first established by Watanabe et al. in 1998[35], successfully recapitulates key stages of human gastric disease progression, including severe chronic gastritis, ulcers, IM, and ultimately adenocarcinoma. Yoshizawa et al.[36] demonstrated *H. pylori* infection–induced SPEM in the fundic glands of MG in 2007. Prolonged infection resulted in SPEM glandular expansion, progression to gastritis cystica profunda, and subsequent IM with SPEM and IM frequently co-existing in later stages to form a continuous pathologic spectrum. The MG model closely mirrors human gastric carcinogenesis and provides a valuable system for investigating *H. pylori*–induced pathophysiologic processes[37]. Nevertheless, a broader utility of the MG model is limited by differences in IM incidence compared to humans, less common husbandry practices, and a restricted capacity to replicate the genetic mutations observed in human GC, often requiring validation through complementary models.

Other species

Dogs

Spontaneous canine GC exhibits notable molecular and therapeutic similarities to human disease[38]. Shimosato et al.[39] established a canine GC model in 1971 *via* MNNG induction. Xiao et al.[40] subsequently demonstrated the chemopreventive effect of high-dose folic acid in N-ethyl-N′-nitro-N-nitrosoguanidine (ENNG)-induced GC using 16 male Beagle dogs. Unlike in humans, The association between canine GC and *H. pylori* is weak. Instead, a variety of novel non-*H. pylori* species have been identified in dogs, raising concerns about potential zoonotic transmission[41,42]. Although GC is rare in the general canine population, Belgian Shepherd dogs display a strong breed predisposition, often presenting with complex histologic features, such as signet ring cell carcinoma, that do not strictly follow the human Correa cascade[43,44]. This unique heterogeneity provides a valuable perspective for investigating non-classical pathways of gastric tumorigenesis.

Pigs

Pigs possess anatomic and physiologic features that closely resemble humans. Eaton et al.[45] established the first gnotobiotic piglet model of *H. pylori* infection in 1989, which reproduced gastritis pathology similar to that observed in humans. This model demonstrated that highly motile strains (e.g., strain 26,695) achieved superior colonization and induced more severe gastritis than low-motility or non-motile strains (e.g., strain Tx30a), making the gnotobiotic piglet model particularly valuable for studying bacterial virulence factors and antimicrobial efficacy. Koga et al.[46] subsequently confirmed the suitability of the model for chronic infection studies by showing *H. pylori* persistence for > 22 months accompanied by a robust antibody response. These features highlight the utility of the gnotobiotic piglet model for evaluating antibiotics and vaccines. More recently, advances in CRISPR/Cas9 technology have enabled the efficient generation of genetically engineered pigs, opening new avenues for developing GC models that better recapitulate human disease.

Rhesus monkeys

Mätz-Rensing et al.[47] established an *H. pylori*–infected rhesus monkey model in 2001, documenting progressive gastric mucosal atrophy over 18 months and confirming stable colonization of *H. pylori* strains in the gastric mucosa. As non-human primates, rhesus monkeys closely replicate *H. pylori* infection patterns that occur in humans, including the development of chronic gastritis and the potential progression to atrophic gastritis. The immune response of rhesus monkeys, dominated by Th1-mediated chronic inflammation, also parallels that of humans, making rhesus monkeys a reliable model for long-term studies of chronic *H. pylori* infection. However, the high natural prevalence of *H. pylori* among captive rhesus monkeys complicates experimental infection studies[48]. Moreover, experimental infection with human-derived *H. pylori* strains is frequently unsuccessful or only leads to transient colonization[49], often necessitating the use of specific strains, such as human-derived *H. pylori* J166[50]. In addition, the substantial cost of rhesus monkeys considerably limits the widespread use as an experimental model.

Ferrets

Fox et al. first isolated and identified a gastric *Helicobacter* species from ferrets in 1989 [*H. mustelae* (*Hm*)], providing the earliest evidence of gastric *Helicobacter* pathogenicity in an animal and laying the foundation for model development in other species. Shortly thereafter, Fox et al.[51] demonstrated the susceptibility of ferrets to chemical carcinogenesis, showing that MNNG administration combined with *Hm* infection significantly increased the incidence of GC, thereby modeling the potential role of *H. pylori* as a co-carcinogen in humans. The high natural prevalence of *Hm* infection in ferrets produces gastric pathology closely resembling human *H. pylori* infection, while the availability of specific pathogen-free ferrets further enhances utility for mechanistic studies[52,53]. Nonetheless, ferret, pig, and rhesus monkey models often lack adequate characterization of the active inflammatory component severity, which differs from the chronic active gastritis typically observed in human *H. pylori* infection[53].

Zebrafish

Zebrafish represent a powerful tool for dissecting oncogenic mechanisms and enabling high-throughput screening. Neal et al.[54] developed transgenic zebrafish models, providing

the first direct *in vivo* evidence of the carcinogenic synergy between *CagA* and *p53* mutations in GC development, while also inspiring exploration of multiple pathogenic factors at different stages of the disease course. A major advantage of zebrafish is the high engraftment rate in patient-derived xenograft (zPDX) models, which exceeds the engraftment rate in mice and permits real-time visualization of angiogenesis and metastasis[55]. However, zebrafish lack gastric gland cells and the genes required for gastric-specific functions, relying instead on the intestinal bulb to mimic gastric epithelium. This limitation compromises the fidelity of GC TME modeling[56,57]. Future optimization strategies include refining zPDX models or applying CRISPR/Cas9 to introduce gastric-specific gene expression systems or generate immune-reconstituted zebrafish, thereby improving the accuracy of GC simulation and enhancing translational relevance.

Although rodents remain the predominant models for GC research due to the low cost, ease of handling, and high tumor induction rates, differences in gastric anatomy and *H. pylori* colonization compared to humans limit the translational precision. Therefore, non-rodent species increasingly serve as important complementary models, offering unique advantages that extend the scope of GC research and provide valuable insights for refining rodent-based systems (**Figure 2**). The applications, advantages, and limitations of these five non-rodent models are summarized in **Table 1** to assist researchers in selecting the most appropriate experimental system.

Strategies for constructing gastric premalignant conditions and GC animal models

Environmental and inducible models

Chemical carcinogens and pathogen-induced models

Chemical carcinogens (e.g., MNNG and MNU) and pathogens (e.g., *H. pylori*) are well-recognized inducers of gastric carcinogenesis and are widely utilized in experimental models. However, multiple carcinogenic factors, including lifestyle and dietary habits, pathogen infections, and chemical carcinogens, often act synergistically during GC development.

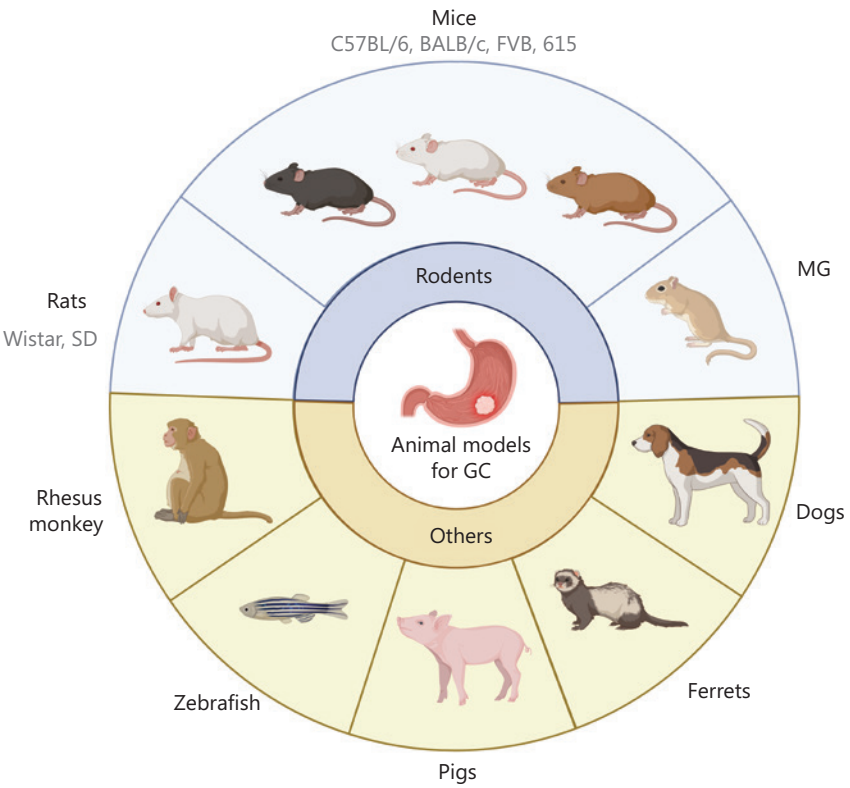


Figure 2 Spectrum of experimental animals used in GC research. The schematic organizes commonly used species into two categories. Rodents (upper half) include rats (e.g., Wistar and Sprague–Dawley), mice (e.g., C57BL/6, BALB/c, FVB, and 615), and mongolian gerbils. Others (lower half) depict rhesus monkeys, zebrafish, pigs, ferrets, and dogs. The central node ("Animal models for GC") denotes the shared application to GC studies. Species names and subgroup examples correspond to labels shown in the diagram; the icons are illustrative. GC, gastric cancer; MG, Mongolian gerbils; SD, Sprague–Dawley. The figures were created with BioRender.

Table 1 Comparison of non-rodent animal applications in GC models

Model species	Advantages	Limitations	Applications
Dogs	• Gastric capacity like humans • High genetic homology • High susceptibility in specific breeds (e.g., Belgian shepherd) • Shared environmental exposures	• Low spontaneous GC incidence (<1%) • Pathology differs from human Correa cascade • Weak Hp association	GC genetics, environmental carcinogen, and chemoprevention studies
Pigs	• Anatomy and physiology closely resemble humans • Potential for genetic engineering	• High cost and complex procedures. • Rare progression to IM or dysplasia • Lack of detailed gastritis severity description	Hp virulence, vaccine, and therapy evaluation
Rhesus monkeys	• Immune response and chronic inflammation pathology highly mimic humans • Stable gastric Hp colonization.	• High cost and strict ethical restrictions • Experimental Hp infection is challenging • Lacks description of active gastritis severity	Long-term Hp infection and host immune response studies
Ferrets	• High natural *H. mustelae* infection rate. • Pathologic features like human Hp infection • Low cost, easy breeding, suitable for longitudinal study	• Lack of specific pathogen-free ferrets may limit mechanistic studies • Lacks description of active gastritis severity	Mechanisms of combined MNNG and Hp carcinogenesis
Zebrafish	• High genetic homology and reproductive capacity • Transparent embryos support real-time imaging • Small sample size requirements • Ease of genetic manipulation	• Lacks gastric gland structure • Limited TME fidelity • Requires model optimization	High-throughput drug screening; zPDX models for proliferation/metastasis observation

GC, gastric cancer; Hp, *Helicobacter pylori*; *H. mustelae*, *Helicobacter mustelae*; IM, intestinal metaplasia; MNNG, N-methyl-N′-nitro-N-nitrosoguanidine; TME, tumor microenvironment; zPDX, zebrafish patient-derived xenograft.

Consequently, constructing animal models based on combined factors can more accurately replicate the etiologic complexity of human GC and significantly increase tumor incidence and progression rates. The distinct mechanisms, pathologic characteristics, and inherent limitations of these environmental and inducible models are comprehensively evaluated in **Table 2**.

Microbiome host interaction models

H. pylori or felis

Warren et al.[75] successfully isolated a spiral-shaped gram-negative bacterium from the gastric mucosa of a patient with chronic active gastritis in 1982. This bacterium was later identified as *H. pylori* and subsequently classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC)[76]. Lee et al.[77] were the first to culture *H. felis* from cat gastric mucosa in 1990, thereby establishing the first bacterial gastritis animal model. This model demonstrated disease progression from acute-to-chronic active inflammation in the stomachs of *H. felis*–infected mice that closely resembled long-term *H. pylori* infection in humans. Notably, the pathologic changes induced by *H. felis* vary significantly across mouse strains and genders. Specifically, C57BL/6 mice develop higher rates of gastric atrophy than BALB/c mice, which is likely due to the Th1-prone immune response[68], while infected females are more susceptible to GC-related changes than males[78]. Lee et al.[37] isolated the *H. pylori* Sydney strain (SS1) in 1997, which is cagA- and vacA-positive. This strain robustly colonizes in C57BL/6 mice and consistently induces chronic active gastritis, mucosal atrophy, and SPEM, making SS1 a standard model for studying pathogenesis and vaccine development.

The non-H. pylori gastric microbiome

While *H. pylori* has historically been regarded as the predominant inhabitant of the stomach, advances in isolation techniques, 16S rRNA sequencing, and metagenomics have revealed a diverse microbial community. These microorganisms interact with one another and the host, contributing to the development and progression of GPMC and GC.

Streptococcus anginosus is a newly identified initiator of gastric disease. Coker et al. first applied 16S rRNA analysis to gastric mucosal samples from 81 patients and identified a microbial panel (including *Peptostreptococcus stomatis* and

Table 2 Comparison of common environmental and inducible GC models

	Carcinogenic mechanisms	Induced pathology	Advantages	Limitations	Applications	References
Chemical carcinogens						
MNNG	Alkylating agent; causes DNA damage leading to atrophy, IM, and carcinogenesis	Adenocarcinoma (histology like human); penetrates pyloric and fundic mucosa	• High tumor induction rate • Histology closely mimics human GC • Simple operation	• Mice are generally resistant • Lack of organ specificity • Long induction period	Constructing GPMC and GC models	39,58-62
MNU	Alkylating agent; induces somatic mutations in epithelial cells promoting GPMC and GC	Mice gastric adenocarcinoma (retains gastric phenotype but histology differs from human)	• More potent than MNNG in mice • Simple operation	• Frequent forestomach squamous cell carcinoma increases mortality • Lack of organ specificity • Long induction period	Establishing murine GC models and cell lines	63,64
ENNG	Ethylated derivative of MNNG; higher specificity for canine gastric mucosa	Adenocarcinoma (histology like human); diffuse-type GC and signet-ring cell carcinoma	• High specificity for canine gastric mucosa • Strong invasion and metastasis capabilities	• High maintenance costs and ethical considerations for canine research • Long induction period	Evaluating anti-metastatic drugs and treatment strategies for advanced GC	65,66
Pathogen infections						
Hp-infected mice	CagA/VacA disrupts signaling pathways; induces chronic active gastritis	Chronic active gastritis (no malignancy); mild, localized inflammation without significant atrophy or metaplasia	• Allows study of specific virulence factors • Suitable for microbiota interaction studies	• Not a natural mouse pathogen (requires adapted strains) • Weak immunogenicity; loss of virulence factors over time	Virulence mechanisms and host-pathogen interactions	37,67
Hf-infected mice	Massive parietal cell loss triggers compensatory hyperproliferation and SPEM	Invasive submucosal cystic lesions (low malignant potential); robust inflammation with significant atrophy and metaplasia	• Natural mouse pathogen; strong colonization • Rapidly induces severe pathology, shortening experiment cycle	• Lacks CagA/VacA • Progression too rapid to capture early molecular events • Gender significantly influences response (typically females used)	Inflammation-driven carcinogenesis and atrophy mechanisms	67,68
Combination models						
MNNG/MNU + High Salt (NaCl)	Salt disrupts mucosal barrier, enhances carcinogen uptake, and upregulates pro-inflammatory cytokines	• MNNG: Dose-dependent adenocarcinoma in Wistar rats • MNU: Accelerates malignancy; increases adenocarcinoma incidence	• Mimics dietary risk factors • Effective at low doses • High tumor incidence	• Requires careful dose management to avoid salt toxicity	Synergistic carcinogenesis of diet and chemicals	69-71

Table 2 Continued

	Carcinogenic mechanisms	Induced pathology	Advantages	Limitations	Applications	References
MNU + Hp	Carcinogen effects are amplified during acute inflammation phase	Adenocarcinoma in Mongolian gerbils; strictly timing-dependent	• Replicates "Infection + Environment" etiology • Highlights critical window of susceptibility	• Protocol highly sensitive to experimental timing	Investigating interactions between infection and chemicals	[72,73]
Hp + High Salt (NaCl)	High salt weakens mucosal defense, facilitating bacterial colonization	Epithelial hyperplasia, parietal cell loss; enhanced Hp colonization	• Models early host-diet-pathogen maladaptation • Suggests dietary intervention strategies	• Typically induces precancerous lesions rather than invasive cancer.	Host-pathogen-diet interaction studies	[74]

CagA, cytotoxin-associated gene A; ENNG, N-ethyl-N'-nitro-N-nitrosoguanidine; GC, gastric cancer; GPMC, gastric precancerous conditions; Hf, *Helicobacter felis*; Hp, *Helicobacter pylori*; IM, intestinal metaplasia; MNNG, N-methyl-N'-nitro-N-nitrosoguanidine; MNU, N-methyl-N-nitrosourea; NaCl, sodium chloride; SPEM, spasmolytic polypeptide-expressing metaplasia; VacA, vacuolating cytotoxin A.

S. anginosus) associated with GC progression[79]. Zhou et al.[80] demonstrated significant enrichment of *S. anginosus* and *S. constellatus* during precancerous and early GC stages in a larger multicenter cohort of 1,043 subjects. Notably, fecal detection of these bacteria showed high sensitivity for early GC screening, suggesting the potential as non-invasive biomarkers. Fu et al.[81] used mouse models to demonstrate that *S. anginosus* promotes gastric inflammation, mucosal atrophy, and tumorigenesis *via* MAPK pathway activation. Subsequently, Yuan et al.[82] revealed that *S. anginosus* remodels the tumor immune microenvironment by metabolizing arginine-to-ornithine, thereby driving GC progression. Most recently, Zhou et al.[83] confirmed that *S. anginosus* promotes the progression of GC by causing metabolic reprogramming through the metabolite, methionine. In conclusion, these studies all underscored the crucial role of host-microbiota interactions in gastric carcinogenesis.

In addition to *S. anginosus*, other non-*H. pylori* bacteria have been implicated. For example, oral commensals, like *Fusobacterium nucleatum* and *Porphyromonas gingivalis*, can translocate to the stomach, promoting inflammation and tumor progression, while some *Lactobacillus* species and *Staphylococcus epidermidis* exhibit protective effects by attenuating *H. pylori* virulence and host inflammatory responses[84].

Germ-free (GF) mice can be used to completely eliminate the interference of endogenous microorganisms. Kwon et al.[85] transplanted the gastric microbiota of IM or GC patients into wild-type GF mouse models and successfully reproduced the main histopathologic features of precancerous lesions. Gnotobiotic mouse models have become a key tool to precisely analyze the functions of specific microbial members. This model enables researchers to purposefully introduce a single or a group of specific strains, thereby revealing the specific pathogenic or protective mechanisms in a controlled context[86,87].

With the deepening understanding of the dynamic interaction between the host and the microbiota, research models have evolved from focusing on a single pathogen to exploring complex ecosystems. Future research should aim to define microbial signatures within GPMC and GC, identify key non-*H. pylori* bacteria, and further use artificial intelligence (AI) and omics data to identify key microbial characteristics. Also, synthetic microbial communities (SynComs) with fully defined components can be constructed to study the interaction relationships among microorganisms and between microorganisms and the host, and to more accurately simulate the process of GC progression[88].

Xenograft models

Cell suspensions or tissue fragments are implanted into either immunodeficient (xenograft) or immunocompetent (allograft) hosts to establish GC models. While the lack of a

functional immune system in xenografts necessitates the use of immunocompetent models for evaluating immune checkpoint inhibitors and tumor-immune interactions, xenograft models remain the cornerstone for human tumor profiling[89,90]. These models are broadly categorized as heterotopic (e.g., subcutaneous) or orthotopic based on the implantation site. While heterotopic models, such as the subcutaneous approach, offer simplicity and ease of tumor monitoring, orthotopic implantation is recognized for superior clinical relevance because orthotopic implantation recapitulates the gastric TME and facilitates the study of spontaneous metastasis. The key features, advantages, limitations, and applications of these predominant surgical approaches are systematically compared in **Table 3**.

Cell line-derived xenografts models

Human GC cell lines are stable populations established through *in vitro* culture and monoclonal screening of primary tumor cells. These cells lines are commonly classified by degree of differentiation (e.g., moderate: NCI-N87 and MKN74; poor/undifferentiated: HGC-27 and MGC803), tumor origin (primary tumor *vs.* metastatic site), and pathologic subtype (e.g., adenocarcinomas, such as MKN45 and AGS). Some cell lines also exhibit metastatic tropism, such as MKN45, which preferentially disseminates to the liver and peritoneum.

Cell line-derived xenograft (CDX) murine model construction has historically relied on a limited number of mouse-derived GC cell lines. The earliest mouse-derived GC cell line was the murine forestomach carcinoma (MFC) line, which was established in 1987 by Qian et al.[32] through chemical induction of squamous cell carcinoma in the forestomach of inbred strain 615 mice. While MFC readily forms tumors and exhibits spontaneous lung metastasis in immunocompetent mice, the histologic features differ markedly from human GC subtypes and the unique genetic background of strain 615 limits its broader applicability. This finding highlights the need to develop GC cell lines compatible with more common inbred strains, such as C57BL/6 and BALB/c.

Table 3 Comparison of surgical approaches for xenograft GC models

Model	Surgical method	Key features	Advantages	Limitations	Applications	References
Subcutaneous	Injection of GC cell lines or implantation of tumor fragments into the flank/dorsal region	Encapsulated masses, usually palpable and with clear boundaries	• Simple, low cost, high reproducibility • Easy to monitor tumor growth	• Low metastatic potential • Lacks gastric microenvironment	Preliminary drug screening and *in vivo* pharmacokinetic studies	91,92
Orthotopic (cell suspension injection)	Injecting cell suspension into gastric wall	Mimics local invasion; spontaneously develop lymph node/liver metastasis	• Interacts with gastric stroma/vasculature • Moderate metastasis rate	• Technically demanding • Risk of cell leakage	Studying local invasion mechanisms and drugs targeting TME crosstalk	93,94
Orthotopic (SOI)	Suturing tumor fragments onto gastric serosa/submucosa	Maintains tissue architecture; highly metastatic	• Preserves tumor heterogeneity and stemness • Gold standard for constructing metastatic models	• Technically demanding • Requires imaging for monitoring	Studying metastatic drivers and anti-metastatic agents.	95-97
Intraperitoneal	Direct injection of GC cells into the peritoneal cavity	Forms ascites and disseminated nodules on peritoneum/organs	• Quickly generates PM • Reproducible for late-stage GC studies	• Bypasses early invasion steps • Non-spontaneous metastasis	Evaluating HIPEC and targeted drugs for malignant ascites	98-100
Systemic (intravenous/intracardiac)	Injecting cells *via* tail vein or heart	Hematogenous metastasis	• Specific homing to target organs • Rapid timeline	• Highly artificial • Lacks primary tumor	Investigating organ-specific metastasis and drugs targeting metastatic seeding	101,102

GC, gastric cancer; HIPEC, hyperthermic intraperitoneal chemotherapy; PM, peritoneal metastasis; SOI, surgical orthotopic implantation; TME, tumor microenvironment.

Yamamoto et al.[103] established the first transplantable GC cell lines (YTN2, YTN3, YTN5, and YTN16) for immunocompetent C57BL/6 mice in 2018, derived from MNU-induced gastric adenocarcinomas. Among these transplantable GC cell lines, YTN16 has particularly high invasiveness with frequent lung, lymph node, and peritoneal metastasis. YTN16 has become a widely used model due to the well-defined genetic background and responsiveness to targeted therapies[81,104,105]. More recently, Wang et al.[106] developed a gastric body adenocarcinoma model in BALB/c mice by combining MNU treatment with a high-salt diet, successfully establishing the MCC cell line. Tumors derived from MCC closely resemble the molecular characteristics of clinical diffuse-type GC, making this line especially valuable for studying TME interactions and immunotherapy strategies.

Although CDX models offer advantages, such as standardization, high throughput, and relatively low cost, CDX models present the following key limitations: lack of tumor specificity; limited representation of the TME; and a weaker correlation with patient tumor biology. As a result, complementary use of CDX and patient-derived xenograft (PDX) models has become an important strategy for constructing robust GC animal models.

PDX models and derivative models

PDX models are established by implanting human tumor tissue or patient-derived primary cells into immunocompromised hosts, followed by serial *in vivo* passaging[90]. Several patient-derived GC xenograft (PDGCX) models have been reported[107-110], demonstrating clear advantages over CDX models. PDX systems not only have a central role in personalized and precision medicine but also represent the most clinically relevant *in vivo* preclinical models for investigating novel therapeutic strategies.

One key advantage of PDX models is the ability to preserve the genetic heterogeneity and histologic features of primary tumors. Zhang et al.[108] established 32 stable PDX models from 207 GC surgical samples. Histologic and molecular analyses confirmed that these models retained the pathologic subtypes of the original tumors with key biomarkers (e.g., ERBB2, PTEN, and MET) remaining stable up to passage F12. This genetic stability is crucial for analyzing intratumoral heterogeneity and clonal evolution.

PDX models also provide a reliable platform for drug sensitivity testing and targeted drug screening. Zhang et al.[111] transplanted tumor tissues from 20 GC patients into NOG mice to establish PDX models for therapeutic evaluation. The models displayed strong sensitivity to oxaliplatin, fluorouracil, and capecitabine in early passages and remained responsive to capecitabine in later passages in a dose-dependent manner. MiniPDX was developed, enabling 7-day drug screening with high PDX concordance to guide personalized treatment for advanced GC and further enhance screening efficiency[112,113]. PDX platforms serve as patient "avatars," enabling dynamic, parallel testing of therapeutic regimens alongside actual clinical treatment to guide real-time decisions and overcome resistance.

However, a major limitation of standard PDX models is the absence of a functional immune system. To address this limitation, humanized PDX (Hu-PDX) models have been developed by reconstituting immunodeficient mice with human immune components (e.g., PBMCs or $CD34^+$ HSCs)[114]. Zhao et al.[115] developed a Hu-PDX model using HLA-matched human immune systems, which successfully replicated the tumor immune microenvironment and allowed for the evaluation of immune checkpoint inhibitors, like pembrolizumab. In addition to monotherapy, Luo et al.[116] utilized Hu-PDX models to demonstrate that the anti-angiogenic agent apatinib remodels the immunosuppressive tumor ecosystem by reducing tumor-associated neutrophil (TAN) recruitment, thereby synergistically enhancing the efficacy of anti-PD-1 immunotherapy. These models are currently the most advanced tools for evaluating the efficacy and toxicity of immunotherapies.

Further advances in patient-derived organoid (PDO) technology have led to the emergence of patient-derived organoid-based xenograft (PDOX) models, in which *in vitro* cultured PDOs are transplanted into immunodeficient mice to form *in vivo* xenografts. Zhao et al.[117] generated 57 organoids from 73 GC patients (78% success rate) in 2024 and used 5 to create PDOX models. The *in vivo* responses to chemotherapeutic drugs in these models were highly consistent with *in vitro* PDO results. Corso et al.[118] further demonstrated the utility of large-scale PDX platforms by transplanting tissues from 349 patients into NOD/SCID mice, successfully establishing 145 PDX models (42% success rate). This multi-level platform integrating tissue culture, organoids, and *in vivo* systems encompassed all Lauren histologic and TCGA molecular subtypes. Such large-scale, well-characterized biobanks generate the massive and diverse datasets essential for training AI models. The integration of histologic, molecular, and pharmacologic data from these platforms empowers AI to uncover complex patterns and significantly enhance the prediction of therapeutic outcomes.

In conclusion, while traditional CDX models offer a cost-effective route for basic screening, the inability to recapitulate tumor heterogeneity and the microenvironment severely limits the translational relevance. Standard PDX models remain the gold standard for preserving patient-specific tumor biology. Hu-PDX models, despite the complexity, are indispensable for immunotherapy research. In addition, PDOX models provide a scalable platform for high-throughput drug screening and generate the rich datasets essential for AI-driven discovery. Looking ahead, the field should prioritize optimizing engraftment methods and advancing next-generation models that robustly integrate the human TME, ultimately accelerating the path toward precision medicine.

Genetically engineered models

Advances in gene editing have facilitated the development of diverse transgenic, knockout, and knockin mouse models that enable the study of spontaneous GC tumorigenesis, metastasis, pathogenic gene discovery, and molecular subtype simulation. These models are considered among the most robust and informative tools for GC research (summarized in **Table 4**). When combined with *H. pylori* infection or chemical carcinogens, the models more effectively replicate the multifactorial nature of gastric carcinogenesis. However, the application is limited by high cost and the frequent reliance on single-gene alterations, which do not fully capture the complex, multigene interactions underlying human GC. Nevertheless, emerging technologies, such as CRISPR/Cas9 and Cre-loxP, have markedly improved the efficiency, precision, and versatility of these models, expanding the potential in both mechanistic studies and translational applications[150].

GC progression and animal models

Gastric premalignant conditions stage

In addition to the classical Correa cascade, which describes the progression from IM-to-GC, SPEM has emerged as a key focus in gastric metaplasia research due to the close association with cancer development. Current SPEM animal models are broadly divided into two categories (acute and chronic). Acute SPEM models are typically induced by chemical agents, such as DMP-777, L-635, or high-dose tamoxifen, which act by triggering rapid parietal cell loss and oxyntic atrophy. In contrast, chronic SPEM models are established primarily through *H. pylori* or *H. felis* infection, mimicking the human chronic inflammatory process and allowing progression to IM or dysplasia. The selection of an appropriate model therefore depends on the specific research context, a decision guided by the key comparative criteria summarized in **Table 5**.

Despite recent progress, SPEM research still faces significant challenges. First, there is limited clinical evidence to confirm the universality of mouse-derived findings in humans. Second, chemically induced acute models cannot adequately simulate the irreversible progression observed in clinical practice. Third, standardized criteria for pathologic marker detection and non-invasive screening biomarkers are lacking.

Future efforts should focus on establishing more stable, proliferative SPEM models that recapitulate clinical pathologic features. Key research priorities include elucidating the molecular mechanisms underlying SPEM cell differentiation and transformation, clarifying their interactions with *H. pylori* and the gastric microbiome, and identifying critical time windows for the reversibility of gastric mucosal lesions. Ultimately, refining the Correa cascade and developing drugs that specifically target and block distinct GPMC stages may enable early intervention in GC and potentially reverse the malignant progression.

Invasion, metastasis, and recurrence stage

Invasion and metastasis are fundamental biological characteristics of malignant tumors[157]. The liver and peritoneum are the most common metastatic sites for GC, together accounting for nearly 80% of all metastases and exerting a profound impact on the prognosis of patients with advanced disease[158].

Recurrence models are typically developed from pre-existing growth or metastasis models. These involve administering stage-specific treatments and subsequently monitoring the primary or metastatic sites for tumor recurrence. However, due to tumor heterogeneity and the limited availability of paired clinical specimens, most current models fail to exhibit highly aggressive phenotypes. Moreover, many models focus predominantly on metaplastic lesions and lack long-term monitoring of invasion or distant metastasis, leaving the malignant transformation potential uncertain. Therefore, developing clinically relevant models that faithfully reproduce the invasive phenotype of human GC remains essential. Among available systems, xenograft models are most frequently used for investigating GC metastasis and recurrence.

CDX models serve as important platforms for metastasis studies because of reproducibility and controllability. A major challenge in constructing these models is accurately recapitulating the invasive phenotype of human GC and reliably detecting tumor penetration through the muscularis mucosa. To visualize the metastatic process, Busuttil et al.[159] utilized GFP-luciferase–labeled GC cell lines (AGS, MKN45, and MKN28) to generate orthotopic models, enabling dynamic *in vivo* imaging of local invasion and hematogenous/lymphatic dissemination. Addressing the TME, Fujimori et al.[160] co-inoculated the murine GC cell line, YTN16, with myofibroblasts (LmcMF), successfully reconstructing the fibrotic stroma characteristic of peritoneal metastasis. In another study, Gao et al.[161] developed a peritoneal metastasis model by intraperitoneally injecting MKN-45-luc cells into BALB/c nude mice and demonstrated that combining lidocaine hydrochloride with paclitaxel produced significant synergistic anti-tumor effects by promoting apoptosis and suppressing migration and invasion. This finding highlights the potential of such models for preclinical evaluation of therapeutic strategies against GC with PM.

The establishment of PDX metastasis models depends on multiple factors, including tumor type, sampling site and quality, tumor aggressiveness, and the choice of immunocompromised host. In 1993, Furukawa et al.[97] first reported an orthotopic PDX model by transplanting intact human

Table 4 Comparison of common GEMMs

Model	Carcinogenic mechanisms	Induced pathology	Advantages	Limitations	Applications	References
INS-GAS transgenic	Insulin promoter-driven hypergastrinemia causes initial high acid, then parietal cell loss	Metaplasia, dysplasia, and invasive GC by 20 months; accelerated by Hp infection	• Faithfully recapitulates GC progression • High Hp susceptibility	Tumors confined to gastric corpus • Outcomes depend on genetic background	GC pathogenesis, therapeutic intervention, and microbiota–cancer interactions	33,119,120
Gastrin knockout	Gastrin deletion causes achlorhydria	Gastritis, atrophy, metaplasia, and antral carcinoma by 12 months; accelerated by Hp infection	• Proves carcinogenic role of low acid • Models Hp-negative carcinogenesis	• Mimics only acid-deficient subtypes	Carcinogenic mechanisms in Hp-negative patients	121-123
Tff1 knockout	Loss of TFF1 activates NF-κB and STAT3 pathways, promoting inflammation	Antral and pyloric adenocarcinoma; accelerated by Hp infection	• Does not require carcinogen induction	• Single-gene deletion simplifies human multigenic complexity	Epigenetic regulation, inflammatory signaling, and Gastrin-TFF1 interplay	124-129
H/K-ATPase:hIL-1β transgenic	hIL-1β expression activates NF-κB pathway, recruiting MDSCs and activating CAFs	Abnormal hyperplasia and carcinogenesis; accelerated by Hf infection	• Mimics the inflammation-to-cancer cascade. • Models TME	• Driven by single cytokine • Murine TME components differ from human	Epigenetics, TME, and IL-1RA evaluation	130,131
K19-Kras	K19-driven expression in isthmal progenitors causes hyperplasia and parietal cell loss	Oxyntic gland atrophy and mucinous metaplasia by 3 months, progressing to high-grade dysplasia with submucosal invasion by 20 months	• Pathology closely resembles Hf–induced GPMC • Unique expression of CXCL5, HB-EGF, and AR	• Long latency for invasion	*KRAS* signaling in intestinal metaplasia initiation	132-136
Mist1-Kras	Mist1^{+} stem cells identified as the origin of intestinal-type GC driven by Kras and Apc mutations	Complete transition from SPEM-to-IM	• Reversible by MEK inhibitors	• Short observation periods • Long-term efficacy unclear	Ras signaling in metaplasia; reversal strategies	137,138
Runx3 knockout	Enhances Wnt signaling activity, leading to aberrant expression of downstream targets	Intestinal transdifferentiation of the gastric epithelium; loss of chief cells with retained parietal cells	• Distinct from Hp–induced GC cascade • Models Wnt-driven pathogenesis	• Often induces a precancerous state	Non-inflammation-dependent mechanisms and Wnt signaling	139-143
Klf4 knockout	*Klf4* loss impairs epithelial barrier integrity, causing abnormal differentiation	Increased gastric epithelial cell proliferation; reduced parietal and chief cells	• Independent of the *Cdx2*-mediated intestinal metaplasia pathway	• Often induces a precancerous state	*Klf4* loss mechanisms; early tumorigenic events	144,145

Table 4 Continued

Model	Carcinogenic mechanisms	Induced pathology	Advantages	Limitations	Applications	References
Hip1r knockout	*Hip1r* deficiency causes apoptosis of parietal and zymogenic cells, resulting in SPEM	Spontaneous parietal cell apoptosis, chronic inflammation and subsequent SPEM	• Unique spontaneous apoptosis models	• Slower SPEM progression than chemical models • Unclear intestinal marker expression	Inflammatory cytokine-driven GPMC mechanisms	146-148
Amphiregulin knockout	AR deficiency accelerates acute oxyntic atrophy, resulting in SPEM	Fundic SPEM and progressing to IM and neoplastic lesions	• First model showing spontaneous fundic SPEM-to-IM progression	• Spontaneous progression can be lengthy	Molecular mechanisms and stepwise progression of GPMC	23,149

AR, *amphiregulin*; CAFs, cancer-associated fibroblasts; *Cdx2, caudal-type homeobox 2*; GC, gastric cancer; GEMMs, genetically engineered mouse models; GPMC, gastric premalignant conditions; HB-EGF, heparin-binding EGF-like growth factor; Hf, *Helicobacter felis*; *hIL-1β, human interleukin-1β*; *Hip1r, huntingtin-interacting protein 1-related*; Hp, *Helicobacter pylori*; IL-1RA, interleukin-1 receptor antagonist; IM, intestinal metaplasia; *INS-GAS, insulin-gastrin*; K19, keratin 19; *Klf4, kruppel-like factor 4*; MDSCs, myeloid-derived suppressor cells; MEK, mitogen-activated protein kinase; *Mist1, muscle intestine and stomach expression 1*; *Runx3, runt-related transcription factor 3*; SPEM, spasmolytic polypeptide-expressing metaplasia; *Tff1*, *trefoil factor 1*; TME, tumor microenvironment.

GC tissue into the stomach wall of nude mice. This achieved 100% tumor formation and metastasis with widespread dissemination to lymph nodes, liver, and lungs. In contrast, injecting cell suspensions resulted in only a 6.7% metastasis rate, underscoring the importance of preserving tumor integrity and employing orthotopic implantation to maximize metastatic potential. More recently, Li et al.[162] established PDX models that could be stably passaged up to 10 generations by subcutaneously implanting fresh GC tissue blocks from surgical resections into the inguinal, axillary, or dorsal regions of nude mice. These models exhibited high tumor formation and metastasis rates, particularly with inguinal implantation, making the models suitable for mechanistic studies of invasion and high metastasis-phenotype drug screening.

Tumor metastasis is strongly influenced by the intrinsic metastatic potential of tumor cells and the microenvironment in which the tumor grows[163]. PDX models faithfully preserve the biological characteristics of the primary tumor, making PDX models highly applicable for metastasis research. Although subcutaneous transplantation is technically straightforward, subcutaneous transplantation produces relatively low metastasis rates and may result in the loss of some tumor phenotypes. In contrast, orthotopic transplantation provides a more physiologically relevant environment by maintaining patient-derived stromal and immune components. Implantation of GC tissue or cells directly into the stomach allows modeling of the entire metastatic cascade, from local invasion and intravasation-to-distant metastasis formation, thereby more closely replicating the clinical metastatic process. In addition, PDX systems are invaluable for studying inter- and intra-tumoral heterogeneity, tumor evolution over time, and mechanisms of drug resistance[164].

Conclusion and future perspectives

In this review we have integrated modeling strategies, pathogenic mechanisms, and research contexts across the key stages of GC development, providing a systematic framework for mechanistic exploration and translational application. Specifically, environmental and inducible models are optimal for investigating early-stage disease and the inflammation-to-cancer transition. Genetically engineered mouse models (GEMMs) are indispensable for validating driver gene functions throughout tumor evolution and orthotopic PDX or PDOX systems serve as essential "avatars" for studying the mechanisms of late metastasis and drug resistance. Nevertheless, current approaches have notable limitations. Specifically, rodent systems are constrained by species-specific differences, chemically induced models require prolonged induction periods, and conventional xenografts fail to fully replicate the complexity of the human TME.

Table 5 Comparison of common SPEM mouse models

Modeling method	Carcinogenic mechanisms	Induced pathology	Advantages	Limitations	Applications	References
DMP-777	Inhibits neutrophil elastase, directly leading to parietal cell loss	Acute, reversible SPEM without inflammatory features	• Direct parietal cell loss model • No inflammatory interference • Fully reversible within 7–14 days	• Lacks inflammatory response • Dependent on gastrin and EGFR signaling • Does not progress to dysplasia	Study the direct parietal cell loss effects on SPEM and chief cell trans-differentiation mechanisms	151,152
High-dose tamoxifen	Induces parietal cell apoptosis *via* estrogen receptor, rapidly inducing chief cell trans-differentiation	Acute, reversible SPEM with minimal inflammation	• Rapid SPEM induction (3 days) • Fully reversible after 3 weeks	• Lacks strong inflammation • Dependent on estrogen receptor and IL-10 pathway • Requires combination models for carcinogenesis studies	Rapid reversible SPEM and chief cell trans-differentiation mechanisms	152,153
L635	Analog of DMP-777, does not inhibit neutrophil elastase, preserves inflammatory response	Acute SPEM with robust inflammation	• Models inflammation-associated SPEM • Rapid induction (3 days)	• Dependent on IL-33/13 pathway • Expensive and less accessible • Reversibility timeframe unclear	Inflammation-metaplasia link and inflammation-driven SPEM acceleration mechanisms	154,155
Hf infection	Long-term infection leads to parietal cell loss and chronic inflammation	Chronic SPEM progressing to dysplasia within 1 year	• Mimics natural human Hp progression • Models chronic inflammation-driven SPEM to dysplasia	• SPEM lacks typical human IM phenotypes • Develops deep cystic gastritis with low malignant potential • Does not fully model invasive/metastatic GC	Natural SPEM-to-dysplasia progression and long-term infection-driven carcinogenesis	68,156

EGFR, epidermal growth factor receptor; GC, gastric cancer; Hf, *Helicobacter felis*; Hp, *Helicobacter pylori*; IL, interleukin; IM, intestinal metaplasia; SPEM, spasmolytic polypeptide-expressing metaplasia.

To surmount these limitations, GC animal models are evolving from monotypic approaches toward complex ecosystems capable of deeply replicating the heterogeneity of the disease. Notably, an emerging THX mouse model recapitulates a human system with functional immunity, establishing a new foundation for realistically simulating the tumor immune microenvironment[165]. Double humanized BLT-mice, which integrate human immunity with gut microbiota, offer a robust platform for dissecting the "tumor-immune-microbiota" axis[166].

Future research should prioritize the development of models that encompass the entire pathologic continuum of GC with well-defined molecular markers delineating stage transitions and a competent immune microenvironment. Parallel to this, the convergence of AI with other cutting-edge technologies, including single-cell multi-omics and advanced gene editing, will be fundamental to building these precision models. Such an integrated approach will not only enable the design of subtype-specific therapeutic strategies but will also accelerate the translation of personalized medicine into clinical practice for gastric cancer.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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