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Correlation between dyslipidaemia and gastric cancer: pathogenesis to prevention and treatment strategies

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Abstract

As the sixth most common cancer in the world, the development of gastric cancer (GC) is influenced by many factors. Recent studies have revealed a strong association between dyslipidaemia and GC. In this paper, the relationships between dyslipidaemia and GC are discussed in depth. We review the development of GC through the mechanisms of the inflammatory response, signalling pathways, and apolipoprotein function, and the intersecting targets of atherosclerosis and GC are explored. The synergistic effects of *Helicobacter pylori* infection and dyslipidaemia on the development of GC are also analysed, and the potential value of statins in the prevention and treatment of GC is discussed. In this review, we systematically investigated the relationship between dyslipidaemia and GC to provide new ideas for GC prevention and treatment.

Keywords Dyslipidaemia, Gastric cancer, Apolipoproteins, Atherosclerosis, Statins

Introduction

The sixth most prevalent type of cancer worldwide is gastric cancer (GC), and the primary risk factors include both environmental and genetic factors, including dietary habits, smoking status, sex, advanced age, family history of GC, and *Helicobacter pylori* (*H. pylori*) infection [1]. *H. pylori* infection is directly associated with the risk of GC, and eradicating *H. pylori* can significantly reduce the incidence of GC [2]. In recent years, dyslipidaemia has also been recognized as an important risk factor for GC, which is significantly correlated with the development of GC and directly and indirectly affects the development of GC through *H. pylori* [3, 4].

The risk of GC is closely associated with dyslipidaemia. Triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC) are typically elevated in individuals with dyslipidaemia, whereas high-density lipoprotein cholesterol (HDL-C) is typically decreased, and changes in these lipid markers are significantly correlated with GC development and progression [5–7]. Apolipoproteins (APOs), as important structural components of plasma lipoproteins, are involved in lipid metabolism and transportation and are considered potential targets and markers for GC treatment and prevention [8–10]. Dyslipidaemia promotes the development of atherosclerosis and is a significant risk factor for it [11]; in recent years, studies have shown that patients with

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atherosclerosis have an increased risk of GC, that the prevalence of atherosclerosis in patients with GC is significantly greater than that in the general population, and that there is a close connection between the two diseases at both the clinical and molecular levels [12, 13]. Atherosclerosis and GC have multiple intersecting targets, and interventions involving these targets is expected to positively impact the treatment of both diseases. Statins are primarily used to lower cholesterol levels and prevent the risk of heart disease. However, recent studies have shown that they may also have a role in cancer prevention and treatment [14, 15], with statin use reducing the incidence of GC by as much as 30% [16, 17] and improving the survival of GC patients [18].

Given the importance of dyslipidaemia in the development of GC, summarizing the relevant studies can help provide systematic insights and strategies for its prevention, diagnosis, and treatment.

Current status of research on gastric cancer and dyslipidaemia

Epidemiology, risk factors, and associations with dyslipidaemia in gastric cancer patients

One of the most prevalent malignant tumours worldwide is GC, with an annual incidence rate of more than 1 million, ranking sixth in the world, and a mortality rate ranking second in the world. GC cases are mainly concentrated in the regions of Asia, Africa, South America, and Eastern Europe, among which China ranks first in the world in terms of new cases of and deaths from GC [19–21]. *H. pylori* infection is a significant risk factor for GC, and almost all patients with GC are infected with *H. pylori*. Moreover, gastric cardia cancer is also associated with overweight and gastroesophageal reflux disease injury [22]. Recent research has demonstrated a strong correlation between dyslipidaemia and the onset of GC. In individuals with gastrointestinal malignancies, TG and HDL-C may be valuable indicators of visceral obesity [23]. APOs, important lipoproteins, are potential targets and biomarkers of GC and impact the prognosis of GC patients [9].

Epidemiology of dyslipidaemia and its association with cancer

Dyslipidaemia is a condition in which the plasma levels of TC, LDL-C, and TG are elevated and the levels of HDL-C are reduced. It is a known cardiovascular disease (CVD) risk factor [24]. Differences in lipids exist among different ethnic groups, such that black individuals have lower average levels of TC and TG and higher levels of HDL-C than white individuals do [25]. In the United States, approximately 4.51 million people died from high LDL-C in 2020, a 19% increase in the number of deaths since 2010 [26]. Nearly a quarter of adults in South Korea were diagnosed with hypercholesterolemia in 2020, and the prevalence continues to increase through 2022 [27]. In the Asia-Pacific region, the prevalence of high TC, high LDL-C, low HDL-C, and high TG varies by nation [28]. Among Chinese adults aged 40 years and over, the overall prevalence of dyslipidaemia was 43%, with similar rates found in rural and urban locations. However, compared with rural individuals, urban individuals were more likely to have low HDL-C. Both rural and urban dwellers had high rates of individuals with increased LDL-C and TC [29].

According to these statistics, the prevalence of dyslipidaemia has been increasing annually, resulting in several illnesses that pose a significant risk to human health. The relationship between dyslipidaemia and the incidence of cancer has drawn increasing attention in recent years, and more research has addressed this relationship. Among the cancer types examined are colorectal, ovarian, gastric, and cervical. These findings indicate a strong link between the development of these malignancies and dyslipidaemia [3, 30–32].

Dyslipidaemia and gastric cancer development

Dyslipidaemia is defined as abnormal plasma concentrations of lipids and lipoproteins that deviate from expected values. A growing body of research has demonstrated that dyslipidaemia and aberrant lipid metabolism are key drivers of carcinogenesis [33–37]; for example, elevated LDL-C and TC and decreased HDL-C increase the levels of inflammatory mediators, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). These modifications promote tumour cell proliferation and angiogenesis while decreasing tumour cell apoptosis, thereby increasing cancer risk [6, 38].

Cholesterol and TG, which are insoluble in water, must bind to proteins to form lipoproteins to be transported and function in the body. These proteins, such as APOs, bind to cholesteryl esters, TG, free cholesterol, and phospholipids, promoting lipoprotein formation and functional expression [39]. In addition, lipid components may act as antagonists or agonists of transcription factors and regulate cell cycle progression, affecting cell proliferation, migration, and apoptosis, thus playing important roles in the development and progression of diseases such as cancer [40, 41].

Dyslipidaemia and gastric cancer: mechanisms and clinical significance

HDL exerts anti-inflammatory and antioxidant functions by inhibiting the oxidative modification of LDL, endothelial cell (EC) activation, and monocyte migration and by blocking the proinflammatory effects of oxidized low-density lipoprotein (ox-LDL) [42]. A scavenger receptor called CD36 can identify and attach to ox-LDL.

Sarcoma tyrosine kinase (SRC), c-Jun amino-terminal kinase (JNK), Rac (GTPase) proteins, and nuclear factor-kB (NF-κB) are among the downstream signalling pathways that are activated when these two molecules bind. These signalling pathways can increase LDL uptake and oxidative processes and produce proinflammatory cytokines [43]. LDL-C particles activate platelets and damage the vascular endothelium, triggering cellular inflammation, especially as smaller LDL-C particles are more likely to penetrate vascular endothelial cells, leading to more severe oxidative damage and cancer progression [44]. Modified lipoproteins (e.g., ox-LDL) further impair endothelial function when bound to proteoglycans in the extracellular matrix of the vascular endothelium [36]. In addition, the activation of endothelial cells (ECs) and the binding of lipoproteins to proteoglycans recruit lipoprotein granules, monocytes, B lymphocytes, T lymphocytes, and other immune cells to secrete a range of cytokines and inflammatory factors, such as IL-8, E-selectin, P-selectin, vascular cell adhesion molecule-1 (VCAM), and intercellular adhesion molecule-1 (ICAM), which contribute to the entry of monocytes into the intima of the vessel wall and their differentiation into M1 and M2 macrophages in a microenvironment rich in growth factors and proinflammatory cytokines [45–47]. Through scavenger receptors, M1-type and SMC-derived macrophages quickly identify and phagocytose ox-LDL, including CD36, transform into foam cells, and secrete cytokines that influence the systemic inflammatory response [48]. Adipose tissue also produces the proinflammatory cytokines TNF-α and IL-6, which are crucial for inflammatory reactions [42]. Furthermore, anti-inflammatory cytokines and chemokines are produced by activated M2-type macrophages, initiating effective anti-inflammatory regulatory processes crucial for reducing inflammation and healing injured tissues. The inflammatory cytokines TNF-α, IL-1, IL-6, and IL-18 are characteristic of GC [49]. By triggering the NF-κB signalling pathway and promoting the release of inflammatory proteins through its isoforms IL-1a and IL-1β, IL-1 stimulates carcinogenesis and development in a chronic inflammatory environment. IL-1β stimulates GC cell proliferation via the tyrosine kinase pathway, activating the VEGF signalling pathway, increasing angiogenesis, and encouraging tumour growth, IL-1α stimulates endothelial cell proliferation and angiogenesis [50]. Furthermore, myeloid-derived suppressor cells (MDSCs) secrete more IL-6 and TNF-α when IL-1β stimulates the NF-κB signalling pathway [49]. By activating the JAK2/STAT3 signalling pathway and phosphorylating STAT3, IL-6 promotes the proliferation and angiogenesis of tumour cells by triggering the production of oncogenes and transcription factors (such as cFOX, TRF-1, and Bcl2). Additionally, IL-6 enhances lymph node invasion and liver metastases, encouraging B cells to differentiate into plasma cells [51]. Like IL-6, tumour-associated macrophages (TAMs) release IL-18, promoting tumour growth [52]. *H. pylori* infection is one of the important causative factors of GC, and the TNF-α-inducible protein it produces can bind to the cell surface, activate the NF-κB signalling pathway, and induce cancerous transformation of normal tissues [53]. In addition, the chronic inflammatory response induced by hypertriglyceridaemia may promote carcinogenesis by increasing tumour cell proliferation [54] (Fig. 1).

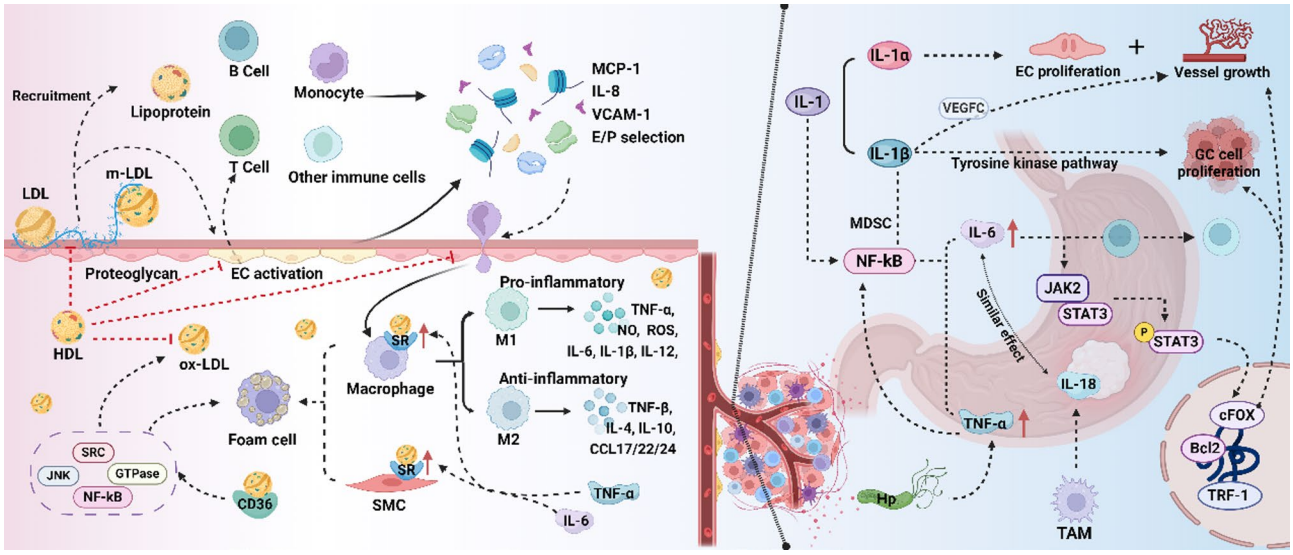

Fig. 1 Mechanism linking dyslipidaemia and gastric cancer. The left side of the figure shows the inflammatory mechanisms associated with HDL and LDL both inside and outside the vasculature, which in turn drive the activation of relevant signalling pathways and cytokine release. The right side of the figure shows the mechanisms associated with representative inflammatory factors involved in gastric cancer progression and angiogenesis

The interactions and signalling of these cytokines in the tumour microenvironment not only promote tumour progression but also further exacerbate the aggressiveness and metastatic ability of the tumour by activating multiple signalling pathways and regulating the function of immune cells. In recent years, dyslipidaemia has been found to be closely related to the occurrence and development of GC. Although the specific mechanism has not been completely clarified, clinical trials have demonstrated a significant correlation between the two factors [3, 55, 56]. Owing to the atypical symptoms of early GC, most patients are already in the progressive stage when they are first diagnosed. Although surgery can significantly improve the survival rate of patients with early-stage GC, the postoperative recurrence rate is high and the prognosis is poor [57, 58]. Therefore, targeting these inflammatory cytokines and their signalling pathways has become a potential antitumour therapeutic strategy. Second, in addition to timely screening and early diagnosis, preventive means of controlling dyslipidaemia are vital for improving the prognosis of GC patients.

Dyslipidaemia and gastric cancer: the bridging role of apolipoproteins

Dyslipidaemia triggers a wide range of diseases that are mediated and accomplished primarily through lipoproteins. Lipoproteins are the main form of lipids in the blood and are formed by APOs binding to TG, cholesteryl esters, free cholesterol, and phospholipids. APOs are important protein components of lipoproteins that are responsible for binding and transporting lipids to various body tissues for metabolism and utilization. Typically, APOs fall into the following categories: A, B, C, D, E, H, or L. APOA1, APOA2, APOA4, APOA5, APOB-48, APOB-100, APOC1, APOC2, APOC3, APOC4, APOD, APOE, APOH, APOL1, APOL2, APOL3, APOL4, APOL5, APOL6, APOM, APOO, and APOJ are among the 22 members of the human apolipoprotein gene family [59]. They have four primary functions: participating in lipoprotein structural composition, acting as ligands for lipoprotein receptors, directing lipoprotein formation, and acting as activators or inhibitors of enzymes involved in lipoprotein metabolism. APOs can regulate macrophage polarization, alter the immune microenvironment of tumours, modulate tumour inflammation and immune responses, and play key roles in tumour progression, invasion, and metastasis [39, 60]. Because dysregulation of lipid metabolism is a known characteristic of carcinogenesis, APOs, which have different roles and vary in serum lipoprotein composition, size, and associated apolipoprotein types, are being studied [60, 61].

The primary protein component of HDL, APOA1, is necessary to transfer cholesterol and possesses anti-inflammatory and antioxidant properties. HDL-C inhibits the proliferation, migration, and invasion of cancer cells. Research has indicated a positive correlation between a high APOA1 level and a favourable pathological response (pR) among GC patients. In contrast, the APOB level is negatively correlated with a pR, and the ratio of APOB to APOA1 is also negatively correlated with a pR in GC patients. In patients with advanced gastric cancer (AGC), the level of APOA1 is decreased and APOB is increased [62]. The preoperative serum APOB to APOA1 ratio has been utilized as a prognostic factor for GC, and a high APOB/APOA1 ratio is linked to lower overall survival (OS) in GC patients. It might be a standalone prognostic factor for GC [63]. A gastric adenomatous polyp (GAP) is a precancerous lesion of GC. Serum APOA1 and APOB are independent risk factors for GAP. Notably, the positive correlation between serum APOA1 levels and incidence in patients with gastric polyps indicates that APOA1 might be crucial in diagnosing GAP. It is a potential biomarker for assessing early cancer diagnosis and cancer risk more accurately [64].

A significant protein component of low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), and celiac disease is APOB. It plays a key role in lipoprotein synthesis by mediating microsomal triglyceride transfer protein (MTTP) [65]. Intestinal metaplasia (IM) is a precancerous lesion of GC. In the IM, the expression level of APOB is high, which contributes to increased lipid uptake by infiltrating macrophages, which induces gastric carcinogenesis by promoting the formation of a lipid microenvironment. The inhibition of APOB expression slows the deterioration process of the IM [65]. High APOB levels are directly associated with a high risk of GC. Its expression is regulated by the hepatocyte nuclear factor 4 A (HNF4A) gene, and high expression of HNF4A often leads to a poor prognosis in GC patients [66, 67].

Apolipoprotein C1 (APOC1) expression is strongly linked to a poor prognosis and is considerably higher in the T2, T3, and T4 stages of GC than in the T1 stage [68]. Zinc finger protein 460 (ZNF460) promotes the development of GC by binding to the APOC1 promoter, facilitating its transcription and accelerating epithelial–mesenchymal transition (EMT) [69]. In addition, APOBEC3B in the catalytic polypeptide-like C (APOBEC) family of apolipoprotein B mRNA editing enzymes can promote the proliferation of GC cells and is a key factor in the development of GC [70]. In gastric adenocarcinoma (STAD) tissues, APOBEC2 expression is significantly downregulated, and APOBEC2-positive patients can benefit from postoperative adjuvant chemotherapy [8] (Fig. 2).

High apolipoprotein D (APOD) expression in GC is closely associated with a worse patient prognosis, making it a potential target for GC therapy [10]. According to previous studies, GC tissues have substantially higher

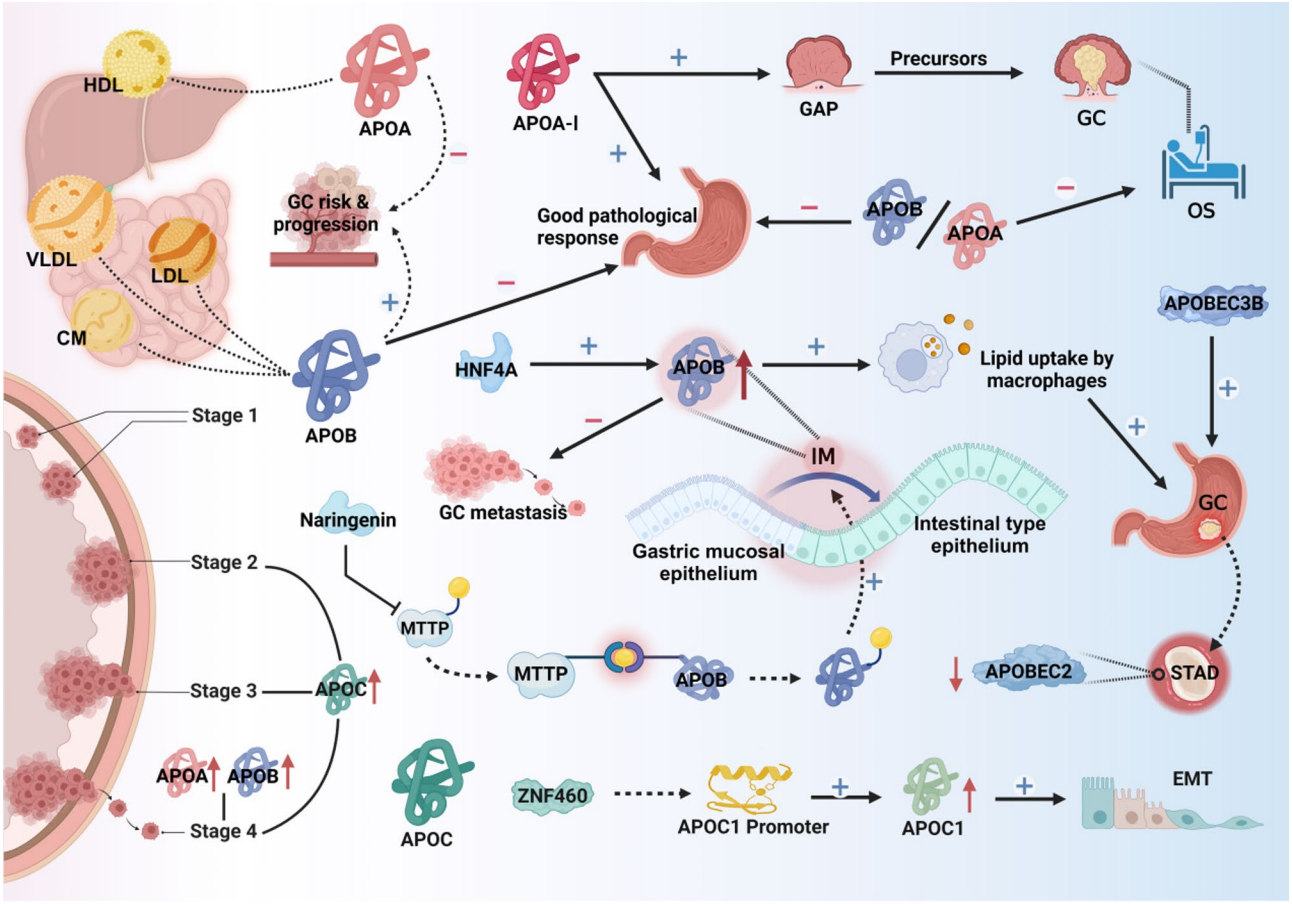

Fig. 2 Relationships between APOA, APOB, APOC and gastric cancer. From top to bottom, the diagram shows the mechanisms linking APOA, APOB, APOC and gastric cancer. "+" stands for "promotion", and "-" stands for "inhibition". The bottom left corner depicts the changes in the three lipoproteins in each stage of gastric cancer

levels of APOD protein expression than nearby normal tissues do [71]. In addition, APOD was positively correlated with macrophage infiltration (CD68) and the WNT signalling pathway (WNT2B) and is a downstream target regulated by necrotic apoptosis-related genes [72]. The expression of APOD, a putative biomarker of hypoxia implicated in the immune response, was inversely correlated with tumour purity, tumour mutation load (TMB), and microsatellite instability (MSI). In addition, APOD, a marker gene of immune senescence, is associated with the immune senescence process in GC [73]. APOD also has a strong positive correlation with multidrug resistance [74]. In the GC microenvironment, APOD expression is highest in fibroblasts. It is correlated with APOD and PDK4 expression in myofibroblasts and fibroblasts, and APOD participates in the immune response as a potential biomarker of hypoxia in fibroblasts [75–77]. High fibroblast APOD expression facilitates tumour growth and immune evasion in the GC microenvironment, as demonstrated by single-cell analysis and immunohistochemistry (IHC) labelling [10]. Additionally, there was a positive correlation between APOD, fewer activated mast cells, and more T helper 1 (Th1) cells [73]. APOD expression is lower in primary gastric tumour tissues than in liver metastatic tissues [78]. The APOD gene encoding the HDL component promotes cell migration by interacting with growth factors [79].

The apolipoprotein E (APOE) expression level and its function in GC have received extensive attention. Research has demonstrated that tumour tissues exhibit noticeably greater levels of positive APOE expression than normal tissues do [80]. By attaching itself to the LRP1 and LRP8 receptors of melanoma cells, tumour-secreted APOE prevents the recruitment of invasive and metastatic endothelium cells [81]. In addition, APOE is considered one of the significant regulatory proteins for *H. pylori* infection of gastric cells and may play an important role in the development of *H. pylori*-induced gastropathy [82]. Notably, ApoE is delivered by macrophages to the lipoprotein receptor of cancer cells, which results in the release of TGF-β from tumour cells and the inhibition of CD8 + T-cell activity. These findings suggest that macrophages that contain ApoE have an immunosuppressive effect. This immunosuppressive function is

particularly significant in metastatic GC. ApoE-hyperexpressing macrophages are present mainly in metastatic GC, whereas in primary GC and normal tissues, they are underexpressed; moreover, serum ApoE levels are elevated in patients with metastatic GC, and ApoE expression levels are higher in liver, ovarian, and peritoneal metastatic samples than in primary tumours [83]. Exosomes generated from tumour-associated macrophages (TAMs) facilitate GC cell motility by delivering functional APOE [84]. In addition, elevated APOE expression in GC patients was associated with reduced overall survival, suggesting that APOE is an important prognostic molecule with immunomodulatory functions [9] (Fig. 3).

In conclusion, APOs significantly impact the development, metastasis, incidence, and prognosis of GC. They also influence the pathological process of GC through a variety of mechanisms, including the control of lipid metabolism, the immunological response, invasion, and cell migration. These APOs could be potential therapeutic targets in addition to being GC indicators (Table 1).

Relationship between LDL-C and gastric cancer

LDL-C is the main form of cholesterol carried in the blood, and its key apolipoprotein is apolipoprotein B-100 (APOB-100). Each LDL-C particle contains one APOB-100 molecule. In the case of infection or inflammation, LDL-C forms many small, dense particles [39]. Elevated levels of LDL-C play a key role in the development of cardiovascular disease but are also significantly associated with the risk of GC [96]. Therefore, reducing LDL-C levels has been an important goal in preventing and treating GC [97].

In GC patients, changes in LDL-C levels are correlated with tumour malignancy and progression. LDL-C levels are generally high in GC patients, especially in stage I and II patients [1]. In neuroendocrine-immunostratified gastric cancer (GCNEI), which encompasses mixed adeno-neuroendocrine carcinoma (MANEC) and neuroendocrine carcinoma (NEC), the distribution of LDL-C levels significantly differed; specifically, patients with GCs that expressed neuroendocrine (NE) markers but had no NE morphology (GC-NENM) presented a decrease in LDL-C levels; in contrast, patients with GCs that contained an NEC component of gastric cancer (GC-NEC) presented significantly elevated LDL-C levels in all pathological stages of GCNEI. The probability of developing GC-NEC is positively related to LDL-C levels [23]. Furthermore, elevated LDL-C levels have been linked to a greater likelihood of having an advanced tumour stage [7].

Relationships between HDL-C, TG, and TC and gastric cancer

In individuals with GC, low preoperative HDL-C levels are linked to a poor prognosis; the lower the HDL-C level is, the greater the likelihood of GC development and malignancy. GC patients have reduced HDL-C levels, and male patients often have higher HDL-C levels than female patients. In patients with advanced gastric cancer (AGC), HDL-C levels are further reduced, suggesting a

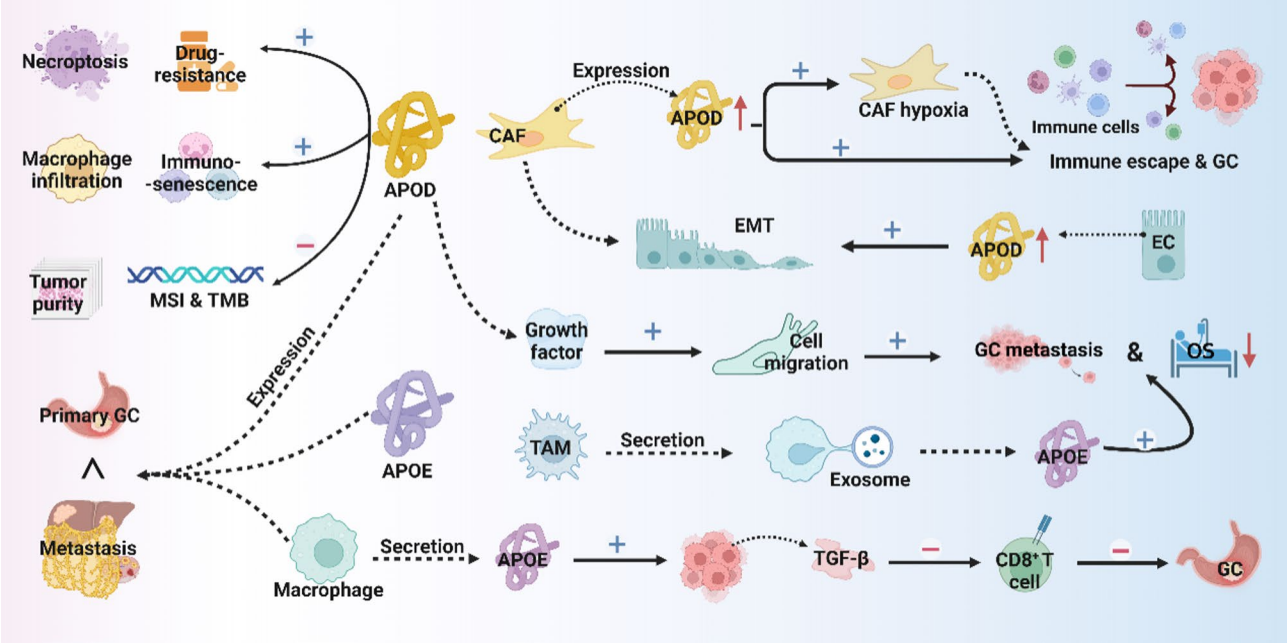

Fig. 3 Relationships between APOD, APOE and gastric cancer. From top to bottom, the diagram shows the mechanisms of APOD, APOE and gastric cancer. "+" stands for "promotion", and "-" stands for "inhibition"

Table 1 Summary of studies related to apos and GC. The table summarizes the relevant studies on apolipoproteins and gastric cancer and lists the relevant studies

APOs	Year	Conclusions and Implications	Ref
APOA	2021	Low ApoA-I levels are associated with GC risk.	[1]
	2023	ApoA-I correlates with GC pathological response.	[62]
	2018	ApoB/ApoA-I ratio linked to GC survival.	[63]
	2022	APOA2 is a prognostic biomarker for Cldn6high GC.	[85]
APOB	2024	APOB linked to intestinal metaplasia (IM) progression.	[65]
	2024	High APOB in IM tissue linked to GC progression.	[67]
	2021	Low APOB linked to GC progression.	[86]
	2023	Lipid metabolism modulation may improve GC prognosis.	[87]
APOD	2024	High APOD linked to poor GC prognosis.	[10]
	2023	High APOD linked to poor GC prognosis.	[71]
	2022	APOD impacts GC microenvironment.	[72]
	2024	APOD expression rises with age, linked to GC development.	[73]
	2021	APOD dysregulation correlates with poor GC prognosis.	[74]
	2023	APOD promotes GC through multiple signalling pathways.	[75]
	2024	APOD and related genes can be used to assess GC prognosis.	[76]
	2023	APOD expression changes linked to GC hypoxia and prognosis.	[77]
	2024	APOD plays a significant role in GC metastasis.	[78]
	2021	APOD predicts GC prognosis effectively.	[79]
	2023	APOD plays a significant role in the progression of GC.	[88]
	2023	High levels of APOD are associated with poor prognosis in GC.	[89]
	2024	APOD as a risk score can predict the outcome of GC.	[90]
	2021	APOD impacts GC microenvironment.	[91]
	2022	APOD plays a significant role in the progression of GC.	[92]
	2024	APOD predicts GC outcome effectively.	[93]
APOE	2020	High APOE linked to poor GC prognosis.	[80]
	2023	High APOE linked to poor GC prognosis.	[81]
	2021	High APOE in *H. pylori*-associated GC.	[82]
	2024	APOE impacts GC microenvironment.	[83]
	2024	APOE is highly expressed in GC tissue.	[94]
	2023	High APOE linked to poor GC prognosis.	[95]

negative correlation with the severity of GC [1]. Approximately 20–35% of patients with neuroendocrine-immunostratified gastric cancer (GCNEI) have lower levels of HDL-C and TG, and the lower the levels are, the greater the risk of developing different GCNEI subtypes, which is also linked to a greater chance of developing a tumour larger than 5 cm [7].

The risk of GC is considerably increased by increased dietary TC intake, and the TG/HDL-C ratio predicts 5-year death in GC patients on its own [6]. Serum lipid levels and TNM stage were significantly correlated in GC patients. Patients with early-stage T disease had greater TC levels. Patients in stages I and II, as well as those in stage N0, had higher levels of TG and TC. Serum TG and TC levels were significantly greater in patients with N0 stage disease and stages I and II disease, but TC levels were greater in male patients with T1 and T2 stages. Serum TC levels were increased in female patients in phases T1 and T2 [1]. Early GC and AGC patients had significantly different TC levels, and GC patients' serum TC levels were inversely related to the progression of GC; high TC levels were typically linked to a favourable prognosis for GC patients [98].

In summary, low levels of HDL-C and TC are usually associated with a high risk and progression of GC, while changes in TG levels may also affect the prognosis of patients with GC.

Intersecting targets of dyslipidaemia, atherosclerosis, and gastric cancer

Dyslipidaemia is an important risk factor for atherosclerosis, and abnormal lipid metabolism leads to vascular endothelial cell damage and promotes the onset and development of atherosclerosis [11]. The close association between atherosclerosis and GC is reflected in clinical observations and supported at the molecular biology level [12]. Patients with atherosclerosis have an increased risk of developing GC, and the prevalence of atherosclerosis is significantly greater in patients with GC than in the general population [13]. These two diseases have a specific correlation, possibly related to common risk factors or molecular mechanisms. A review of

the relevant literature revealed multiple intersecting targets between atherosclerosis and GC, including CHI3L1, MMP9, MMP12, MMP7, CXCL10, PLEK, HMOX1, and CD163. The expression of these targets is upregulated in atherosclerosis and GC, and these targets work together through multiple signalling pathways to promote disease progression. These findings provide new ideas and potential targets for future therapeutic strategies, and interventions targeting these shared intersecting targets may positively impact the treatment of atherosclerosis and GC (Table 2).

Helicobacter pylori and dyslipidaemia: dual risk factors for gastric cancer

Over half of the world's population is infected with the bacterium *H. pylori*, which is closely linked to gastritis, ulcers, and GC. The consequences of infection vary from person to person, with 25% of infected individuals likely to develop ulcer complications and 1% of infected individuals likely to develop GC [127]. *H. pylori* infection is not only strongly associated with the development of GC but is also significantly associated with changes in blood lipid levels, particularly elevated levels of TC and LDL-C, as well as lowered levels of HDL-C, an abnormality that continues to influence the development and progression of GC [128, 129].

Studies have shown that dyslipidaemia and *H. pylori* infection are independent risk factors for gastric adenomatous polyps (GAPs), which are precancerous lesions of the stomach [64]. Individuals who test positive for *H. pylori* have at least twice the risk of developing GC than those who test negative, and the decreasing trend in the prevalence of GC coincides with the decreasing trend in the prevalence of *H. pylori* infection in the population [130].

H. pylori-infected individuals commonly have dyslipidaemia, which includes higher TC, TG, and LDL levels and lower HDL levels. According to a study by Shimamoto et al., there was a negative correlation between HDL levels and *H. pylori* infection and a positive correlation with TC, TG, and LDL levels [131]. A study by Nigatie et al. also demonstrated that patients with *H. pylori* infection had significantly higher TG, TC, and LDL levels than uninfected patients did [132]. According to a study by Tali et al., individuals with *H. pylori* infection had a noticeably increased prevalence of high LDL, low HDL,

Table 2 Intersecting targets of atherosclerosis (AS) and GC. The table summarizes eight targets at the intersection of atherosclerosis and gastric cancer and lists their associated signalling pathways and related conclusions for the reader

Target	Dis.	Signalling pathways	Conclusion	Ref
CHI3L1	GC	IL-13Rα2, CD44, NF-κB, TGF-β	Promotes GC invasion and metastasis.	[99–102]
	AS	MAPK, PKB/Akt, Wnt/β-, PI3K/Akt, JAK/STAT	Exacerbates plaque inflammation.	[102–105]
MMP9	GC	Wnt/β-catenin/MMP9, TGF-β1/ERK, c-Jun/MMP-9, LAPTM4B-35/MMP-9	Promotes GC invasion and metastasis.	[106–108]
	AS	TLR4MMP2/MMP9, ERK/MMP9, NF-κB, AP-1, MAPKs, ROS-ERK-MMP9, C5a-MMP1/MMP9, EGFR-ERK/AKT	Affects plaque stability and promotes acute coronary syndrome.	[109–111]
MMP12	GC	PI3K/Akt/mTOR, MAPK/ERK, Hedgehog	Closely related to the prognosis of GC.	[112]
	AS	PI3K/AKT, MAPK, NF-κB	Reduces atherosclerotic plaques.	[113, 114]
MMP7	GC	PI3K/Akt/mTOR, MAPK/ERK	Promotes GC invasion and metastasis.	[115)
	AS	CSE/H2S, E-cadherin/β-catenin	Promotes thrombus formation and plaque rupture.	[116]
CXCL10	GC	PI3K/AKT, NF-κB	Promotes GC invasion and metastasis.	[117]
	AS	NF-κB, MAPK	Exacerbates plaque instability.	[118]
PLEK	GC	PLEKHA, PI3K/Akt/mTOR, MAPK/ERK, PLEK2	Promotes the survival and proliferation of GC cells.	[119, 120]
	AS	PI3K/AKT, NF-κB, TNF-α	Exacerbates intimal inflammation and cell infiltration.	[121]
HMOX1	GC	Keap1/Nrf2/HMOX1	Closely related to the prognosis of GC.	[122]
	AS	HMOX1/LDHB	Increases plaque instability and cardiovascular risk.	[123]
CD163	GC	PI3K/AKT/mTOR, NF-κB	Associated with lower OS and DFS.	[124]
	AS	NF-κB, HIF1α/VEGF-A, VEGF-A/VEGFR2	Promotes plaque progression and rupture risk.	[125, 126]

hypercholesterolemia, and hypertriglyceridaemia [4]. Eradication of *H. pylori* infection resulted in a significant decrease in the prevalence of dyslipidaemia among GC patients [97]. These findings suggest that *H. pylori* infection is closely associated with the development of GC and further contributes to the development of GC by affecting lipid levels. Therefore, eradicating *H. pylori* infection may be one of the key measures to reduce the risk of GC and improve the prognosis of patients with GC.

Advances in statins and gastric cancer research

Statins are among the most widely and intensively studied drugs and are known for their excellent risk–benefit ratio [133]. Furthermore, lovastatin, the first statin, has been known for its exceptional effectiveness since it was initially used in clinical settings in 1987. These medications have long been the subject of medical research and are primarily used to reduce cholesterol and lower the risk of heart disease. Atorvastatin, rosuvastatin, pravastatin, pitavastatin, simvastatin, and fluvastatin are the six statins available on the international market [14]. Statins such as atorvastatin, simvastatin, and pravastatin have been linked in studies to a decreased risk of GC [134]. The effectiveness of statins in controlling cardiovascular health is already widely acknowledged, and an increasing amount of data also points to their possible function in preventing and treating cancer [135, 136]. Statins exert their anticancer effects through various mechanisms, including reducing inflammation, inhibiting cell proliferation, hindering angiogenesis, and promoting apoptosis. They are not only remarkably effective in preventing specific types of cancer but also significantly reduce cancer incidence and mortality [14, 137].

Antitumour mechanisms and clinical significance of Statins

By blocking 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), a crucial enzyme in the production of cholesterol, statins lower blood cholesterol levels, and the decrease in intracellular cholesterol levels prompts the upregulation of LDL receptors on the surface of hepatocytes, which improves the clearance of LDL [138]. In addition, cholesterol reduction and mevalonate pathway inhibition help to counteract cancer cell proliferation, migration, and metastasis and promote apoptosis [139, 140]. The primary source of acetyl-coenzyme A (acetyl-CoA), the starting material for the mevalonate (MVA) route, is pyruvate, the byproduct of glycolysis, which undergoes a decarboxylation process. This route involves condensing three molecules of acetyl-CoA to create 3-hydroxyglutaryl-CoA, which is subsequently converted to mevalonate by HMG-CoA reductase (HMGCR). This phase is the rate-limiting step of the pathway [141]. Following mevalonate kinase phosphorylation, mevalonate is transformed into isopentenyl pyrophosphate (IPP), a crucial step in the production of geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP). Geranyl pyrophosphate synthase (GGPPS) and farnesyl diphosphate synthase (FDPS) catalyse these processes [142–144]. A key mechanism of statin therapy for cancer is the inhibition of HMGCR, which depletes mevalonate (MVA), IPP, FPP, and GGPP in cells; disrupts the activity of Ras and Rho family GTPases; lowers the concentrations of GGPP and FPP; and decreases RAS and Rho isoprenylation, signalling, and DNA synthesis [145–148]. According to previous studies, simvastatin inhibits the β-catenin and Yes-associated protein (YAP) signalling pathways. It reduces the activity of GGPP and RhoA, inhibiting the proliferation, migration, and invasion of the GC cell lines MKN45 and MGC803 [149]. Interleukin 33 (IL-33) is a cytokine that is considered a key initiator of chronic inflammation and carcinogenesis. High expression of IL-33 in GC tissues activates the inflammatory microenvironment through the TBK1-IRF3 signalling pathway, promotes infiltration of tumour-associated macrophages (TAMs) and other immune cells, and exacerbates tumour progression. Statins are capable of blocking the TBK1–IRF3–IL-33 signalling pathway. The IRF3–IL-33 signalling axis effectively reduces the production of inflammatory factors; reduces the proliferation, survival, and invasive ability of tumour cells; alters the tumour microenvironment; and thus inhibits tumour progression [2]. These findings may provide a new strategy for preventing and treating GC and other related cancers (Fig. 4).

The multiple roles of statins in gastric cancer management

Statins have shown significant potential for reducing the risk of GC and improving patient survival. Several studies have demonstrated that long-term use of lipid-lowering drugs prevents the development of gastrointestinal cancers and that the use of statins reduces the incidence of GC and improves patient survival [18, 150, 151]. For example, a recent meta-analysis confirmed the positive effects of statins in reducing the incidence of GC and improving survival [152]. In addition, statin use enhances overall survival (OS) in cancer patients undergoing surgery and adjuvant chemotherapy on a dose–by–dose basis while reducing mortality from GC [145, 152].

A recent meta-analysis indicated that statins provide greater protection against GC in Asian populations than in Western populations, which is likely attributable to differences in body size and genetics that influence drug metabolism. Furthermore, both the cumulative dose and the duration of use, particularly when the duration of use exceeds 2 years, are associated with a reduced risk of GC [17]. A Korean study revealed that statin patients had a lower risk of GC when their LDL-C levels were lower [34]. Statin use for at least six months was found to be

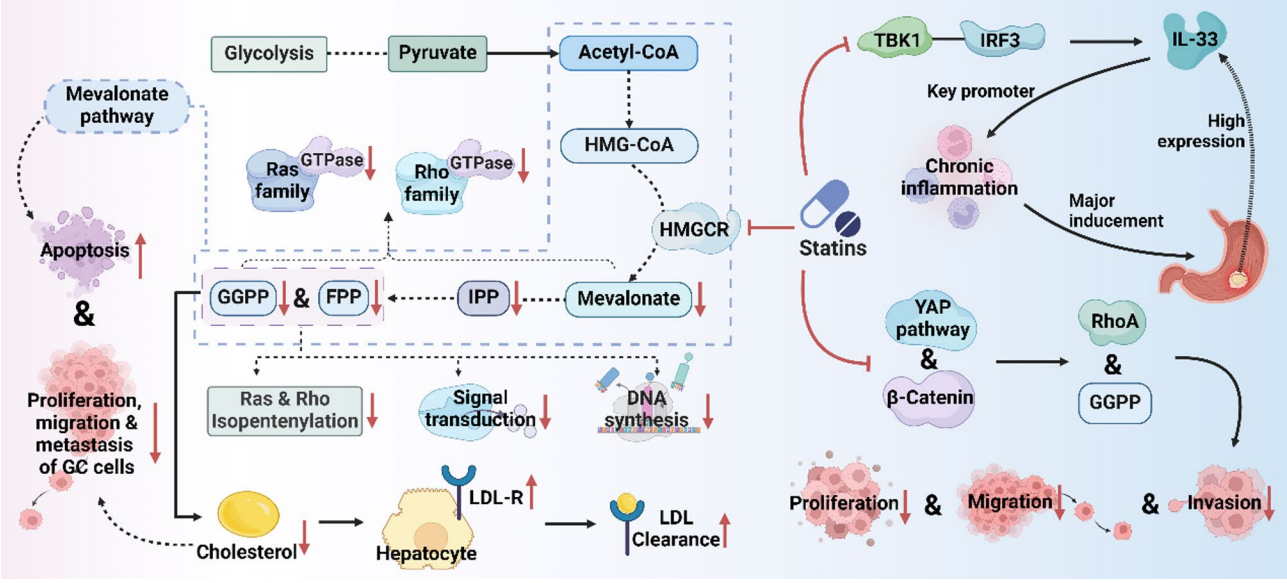

Fig. 4 Antitumour mechanisms of statins. The left side of the figure mainly shows the mechanism related to the ability of statins to increase LDL clearance by inhibiting HMGCR via inhibition of the mevalonate pathway, thereby reducing the proliferation, migration and metastasis of gastric cancer cells and promoting apoptosis. The right side shows that statins inhibit the TBK1–IRF3–IL-33 signalling pathway and the β-catenin and YAP signalling pathways and reduce the activity of GGPP and RhoA, thereby reducing the invasion, migration and spread of gastric cancer cells

significantly associated with a lower incidence of gastric, colorectal, and oesophageal cancer as well as a lower cancer mortality rate following diagnosis in another large-scale investigation [153]. In addition, among both men and women, those who used statins more frequently had the lowest incidence of GC, especially among women, with a corresponding increase in GC as statin use declined [134]. The long-term administration of statins reduces the risk of GC in patients with *H. pylori* eradication. It is mainly protective against noncardia cancers, and its effect is positively correlated with dose and duration [154]. These findings demonstrate that statins not only are crucial for managing cardiovascular disease but also hold promise as versatile strategies for preventing and treating GC and other related cancers. Existing studies are limited in providing conclusive evidence, largely due to inadequate control of confounders and limited follow-up duration. Future research should focus on large-scale randomized controlled trials (RCTs) with extended follow-up periods, diverse ethnic representations, and uniform standardized methodologies to comprehensively evaluate the role of statins in GC prevention and establish a scientific foundation for their potential use in this context.

Conclusions and outlook

Dyslipidaemia is strongly associated with GC development. Elevated LDL-C levels are correlated with increased GC risk, whereas HDL-C, TG, and TC levels are inversely related. These results offer a novel perspective on GC management. Future research should define lipid thresholds and their quantitative links to GC risk to refine lipid management strategies. The development of GC risk prediction models that integrate lipid levels with demographic and familial factors could enhance individualized risk assessment and early intervention, potentially reducing incidence rates. APOs are implicated in GC progression through diverse mechanisms and signalling pathways, making them promising biomarkers and therapeutic targets. Investigating APO interactions with cancer cell receptors and intracellular signalling could foster the development of targeted therapies such as monoclonal antibodies or small-molecule inhibitors, advance early diagnosis and treatment, and improve patient outcomes. Additionally, dyslipidaemia-induced atherosclerosis and gastric cancer share multiple targets involved in disease progression via shared pathways. Targeting these factors could benefit both conditions. Future research should construct an atherosclerosis-gastric cancer molecular network model, employing bioinformatics to identify common targets such as inflammatory genes and oxidative stress proteins. In vitro and in vivo studies should validate the roles of these targets and explore joint intervention strategies. The development of multitarget therapies may improve patient health and reduce health care burdens.

H. *pylori* infection is closely associated with GC development and is significantly linked to dyslipidaemia. By modulating blood lipid levels and influencing relevant signalling pathways, statins can reduce GC risk and increase survival rates, making them valuable tools in GC prevention and treatment. Future research warrants

multicentre, large-sample randomized controlled trials to clarify the efficacy and safety of different statin types and doses for patients at various GC stages and to develop precise usage guidelines. Additionally, studies should explore the synergistic mechanisms of statins with antibiotics in combination therapy alongside *H. pylori* eradication, aiming to increase eradication rates and lower the risk of GC recurrence.

Overall, dyslipidaemia is an important risk factor for the development of GC. Therefore, routine monitoring of blood lipid levels, prevention and management of dyslipidaemia, and improved adherence to and effectiveness of dyslipidaemia management may be helpful in reducing the incidence of GC. For example, promoting healthy lifestyles, including a rational diet, regular exercise, smoking cessation and alcohol restriction, can prevent dyslipidaemia at the source. Moreover, providing dyslipidaemia patients with graded management, as well as personalized diet, exercise guidance and medication advice, is highly important. Currently, relevant research is still ongoing. In future research, more specific and precise molecular mechanisms between dyslipidaemia and GC should be explored from the perspective of clinical practice, and different ethnic groups in different countries should be targeted. Thus, more progress can be made in the prevention of GC, as well as in the discovery of diagnostic biomarkers and therapeutic targets.

Abbreviations

GC	Gastric cancer
APO	Apolipoprotein
H. pylori	*Helicobacter pylori*
TG	Triglycerides
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
TC	Total cholesterol
HDL-C	High-density lipoprotein cholesterol
CVD	Cardiovascular disease
IL	Interleukin
TNF-α	Tumour necrosis factor-alpha
EC	Endothelial cell
ox-LDL	Oxidized low-density lipoprotein
SRC	Sarcoma tyrosine kinase
JNK	c-Jun amino-terminal kinase
GTPase	Guanosine triphosphatase
NF-κB	Nuclear factor-kB
VCAM	Vascular cell adhesion molecule-1
ICAM	Intercellular adhesion molecule-1
SMC	Smooth muscle cell
MDSC	Myeloid-derived suppressor cell
JAK2	Janus kinase 2
STAT3	Signal transducer and activator of transcription 3
cFOX	C-Forkhead box protein
TRF-1	Telomeric repeat binding factor 1
Bcl2	B-cell lymphoma-2
TAM	Tumor-associated macrophages
pR	Pathological response
AGC	Advanced gastric cancer
OS	Overall survival
GAP	Gastric adenomatous polyp
VLDL	Very low-density lipoprotein
MTTP	Microsomal triglyceride transfer protein
IM	Intestinal metaplasia
HNF4A	Hepatocyte nuclear factor 4 A
APOC1	Apolipoprotein C1
ZNF460	Zinc finger protein 460
EMT	Epithelial–mesenchymal transition
APOBEC3B	Apolipoprotein B mRNA editing enzyme catalytic subunit 3B
APOBEC	Apolipoprotein B mRNA-editing enzyme catalytic polypeptide
STAD	Stomach adenocarcinoma
WNT	Wingless-related integration site
WNT2B	Wnt family member 2B
MSI	Microsatellite instability
PDK4	Pyruvate dehydrogenase kinase 4
IHC	Immunohistochemistry
Th1 cell	T helper 1 cell
LRP	Low-density lipoprotein receptor-related protein
TGF-β	Transforming growth factor-β
APOB-100	Apolipoprotein B-100
GCNEI	Neuroendocrine-immunostratified gastric cancer
MANEC	Mixed adeno-neuroendocrine carcinoma
NEC	Neuroendocrine carcinoma
NE	Neuroendocrine
GC-NENM	No NE morphology
GC-NEC	NEC component of gastric cancer
AGC	Advanced gastric cancer
CXCL10	Chemokine (C-X-C motif) ligand 10
CHI3L	Chitinase 3-like protein 1
MMP	Matrix metalloproteinase
PLEK	Pleckstrin
HMOX1	Heme oxygenase-1
CD	Cluster of differentiation
HMGCR	3-hydroxy-3-methylglutaryl coenzyme A reductase
Acetyl-CoA	Acetyl-coenzyme A
MVA	Mevalonate
IPP	Isopentenyl pyrophosphate
GGPP	Geranylgeranyl pyrophosphate
FPP	Farnesyl pyrophosphate
GGPPS	Geranyl pyrophosphate synthase
FDPS	Farnesyl diphosphate synthase
YAP	Yes-associated protein
MKN45	Human gastric cancer cell line
MGC803	Human gastric cancer cell line
IRF3	Interferon regulatory factor 3
TBK1	TANK-binding kinase 1
MCP-1	Monocyte chemoattractant protein-1
m-LDL	Modified-low density lipoprotein
B cell	B lymphocyte
T cell	T lymphocyte
NO	Nitric oxide
ROS	Reactive oxygen species
CCL	C-C Motif chemokine ligand
SR	Scavenger receptor
VEGFC	Vascular endothelial growth factor C
MDSC	Myeloid-derived suppressor cell
CM	Chylomicron
MSI	Microsatellite instability
TMB	Tumor mutational burden
CAF	Cancer-associated fibroblasts
LDL-R	Low-density lipoprotein receptor
AS	Atherosclerosis
DFS	Disease-free survival

Author contributions

Wu T contributed to the original draft preparation; Zhang LN also contributed to manuscript writing while overseeing the project; Tian J and Lu YY contributed to the image collection drawing; Yang Y and Yang X participated in the literature collection; Jin PH and Gu YH revised the manuscript; and all authors wrote, read, and approved the final manuscript—the reasons for designating Wang XK and Yi L as co-corresponding authors are two-fold. Wang XK and Yi L were the corresponding authors of this manuscript because they discussed and selected topics together and developed the framework of the entire manuscript; after the first draft was completed, they revised and improved the manuscript together and jointly guided the completion of this manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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