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The impact of aberrant lipid metabolism on the immune microenvironment of gastric cancer: a mini review

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Gastric cancer (GC) remains one of the leading causes of cancer-related mortality worldwide, with limited responses to immune checkpoint blockade (ICB) therapies in most patients. Increasing evidence indicates that the tumor immune microenvironment (TIME) plays a crucial role in immunotherapy outcomes. Among various metabolic abnormalities in the TIME, dysregulated lipid metabolism has emerged as a critical determinant of immune cell fate, differentiation, and function. In this review, we comprehensively summarize the current understanding of the immune landscape in GC, focusing on how altered lipid metabolism reshapes immune cell populations—including tumor-associated macrophages (TAMs), dendritic cells (DCs), regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and cytotoxic $CD8^+$ T cells. We highlight key metabolic pathways such as fatty acid oxidation(FAO), cholesterol homeostasis, and lipid uptake that impact immune cell activity, contributing to immune evasion and therapeutic resistance. Importantly, we explore emerging therapeutic strategies targeting lipid metabolism, including inhibitors of cluster of differentiation 36 (CD36), fatty acid synthase (FASN), and sterol regulatory element-binding protein 1 (SREBP1) and discuss their synergistic potential when combined with ICB therapies. In conclusion, lipid metabolic reprogramming represents a promising yet underexplored axis in modulating antitumor immunity in GC. Integrating metabolic intervention with immunotherapy holds potential to overcome current treatment limitations and improve clinical outcomes. Future studies incorporating spatial omics and single-cell profiling will be essential to elucidate cell-type specific metabolic dependencies and foster translational breakthroughs.

KEYWORDS

gastric cancer, lipid metabolism, tumor immune microenvironment, CD8+ T cells, tumor-associated macrophages, immunotherapy resistance, fatty acid oxidation, immune checkpoint blockade

1 Introduction

According to GLOBOCAN 2022 statistics, in 2022, more than 968,000 new cases of gastric cancer (GC) were added, with nearly 660,000 deaths, ranking fifth globally both in terms of incidence and mortality. The region with the highest incidence rate is East Asia, which imposes a significant burden on cancer (1). Consequently, an urgent exploration and development of new therapeutic approaches has become imperative.

The tumor microenvironment (TME) is a complex system that can inhibit immune responses while promoting tumor progression. The composition of the TME differs across different tumor types, but its defining features include immune cells, stromal cells, vasculature, and extracellular matrix (2, 3). The complexity and dynamic interactions within the TME contribute significantly to the aggressive nature of GC and the development of therapeutic resistance (4). Therefore, understanding the intricate characteristics of the TME, particularly metabolic reprogramming within this milieu, is of substantial clinical importance for developing effective treatments for GC patients.

Metabolic reprogramming is widely recognized as a hallmark of cancer, allowing tumor cells to sustain proliferation, evade immune surveillance, and survive under stressful conditions. Among various metabolic alterations, abnormal lipid metabolism has emerged as a pivotal player in cancer progression, influencing energy metabolism, membrane biosynthesis, and signaling pathways (5–7). Cancer cells undergo significant lipid metabolic reprogramming, including increased lipid uptake, enhanced fatty acid synthesis (FAS), and elevated fatty acid oxidation (FAO). These alterations not only provide essential metabolic substrates but also enable cancer cells to resist oxidative stress, promoting tumor survival and resistance to conventional therapies (8).

Key enzymes involved in lipid metabolism, such as fatty acid synthase (FASN), ATP citrate lyase (ACLY), and stearoyl-CoA desaturase (SCD), are upregulated in GC (9–11), indicating their potential as therapeutic targets. Aberrant lipid metabolic pathways influence the recruitment, differentiation, and function of key immune cell populations including tumor-associated macrophages (TAMs), regulatory T cells (Tregs),and myeloid-derived suppressor cells (MDSCs), dendritic cells (DCs), CD8+ T cells,contributing to an immunosuppressive microenvironment that facilitates tumor progression.

Abbreviations: ACC, acetyl CoA carboxylase; ACLY, ATP citrate lyase; ACSLs, acyl-CoA synthetase long-chain family members; CAFs, cancer-associated fibroblasts; CD36, cluster of differentiation 36; CPT1, carnitine palmitoyl-transferase 1; DCs, dendritic cells; FAO, fatty acid oxidation; FAS, fatty acid synthesis; FASN, fatty acid synthase; FABP5, fatty acid-binding protein 5; GC, gastric cancer; ICIs, immune checkpoint inhibitors; LSR, lipolysis-stimulated lipoprotein receptor; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility complex; MIF, migration inhibitory factor; PPAR-γ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; SCD, stearoyl-CoA desaturase; SREBP1, sterol regulatory element-binding protein 1; TAMs, tumor-associated macrophages; TME, tumor microenvironment; Tpex, progenitor-exhausted T cells; Trm, tissue-resident memory T cells; Tregs, regulatory T cells.

2 Lipid metabolic pathways and molecular mechanisms

A key energy-generating pathway in lipid metabolism is mitochondrial fatty acid β-oxidation, which is mediated by carnitine palmitoyl-transferase 1 (CPT1), especially the isoform CPT1a (12, 13). This enzyme facilitates the transport of long-chain fatty acids to the mitochondria for oxidative breakdown and ATP production, particularly under nutrient-deprived conditions (14). Simultaneously, cancer cells exploit exogenous lipid sources through dietary uptake, with cluster of differentiation 36 (CD36) functioning as a major fatty acid translocase (15). CD36 is frequently overexpressed in malignant cells, contributing to enhanced fatty acid uptake, intracellular lipid accumulation, and increased metabolic plasticity (16–18). This metabolic architecture is tightly regulated by oncogenic signaling cascades, especially the PI3K/Akt/mTOR axis. This axis activates sterol regulatory element-binding protein 1 (SREBP1), a master transcriptional regulator of lipid biosynthesis (19, 20). When SREBP1 is activated, the expression of key enzymes involved in fat production, such as FASN and acetyl CoA carboxylase (ACC), is enhanced. This can promote *de novo* fat generation and support the promotion of membrane biogenesis and proliferation (21, 22). The uptake of extracellular lipids via CD36 and the lipolysis-stimulated lipoprotein receptor (LSR) is often upregulated in tumors and is also responsive to PI3K/mTOR signaling, reinforcing the lipid supply for cancer progression (23–25). Enzymes like acyl-CoA synthetase long-chain family members (ACSLs) activate imported fatty acids and channel them into biosynthetic and storage pathways, while lipogenesis induced by SREBP1 inhibits ferroptosis and improves tumor cell survival (20, 26). Uptake of lipids by CD36 enhances metastatic potential and contributes to adaptation to the TME (27). Additionally, reorganization of lipid metabolism can alter antigen presentation and inhibit T-cell activation, leading to impairment of immune surveillance (28). Phospholipid remodeling represents another critical branch of lipid metabolism. This metabolic adaptation highlights the key function of lipid metabolism in coordinating cellular bioenergetics with tumor invasiveness and immune escape, laying the mechanistic foundation for its involvement in the formation of an immunosuppressive TME (29).

3 Overview of the immune microenvironment in gastric cancer

TME of GC is composed of various immune cell subsets and non-immune components, and is characterized by prominent immunosuppressive features. Single-cell analyses have revealed a highly heterogeneous pattern of immune cell infiltration within the TME of GC. Immunosuppressive components such as Tregs,

MDSCs, and TAMs are widely distributed and are closely associated with ineffective antitumor immune responses (30–33). Tregs suppress $CD8^+$ T cell activity and the antigen presentation process through multiple mechanisms, serving as key regulatory factors in the progression of GC (34, 35). MDSCs exacerbate the immunosuppressive state by secreting inhibitory factors and modulating macrophage polarization (36). Moreover, M2 polarization of TAMs in GC has been shown to be closely associated with immune evasion and poor prognosis (37–39). Another key mechanism underlying the immunosuppressive TME is the upregulation of immune checkpoints, such as PD-L1 and the CD39/CD73 axis, which inhibit T cell effector functions and promote tumor immune evasion (40, 41). Studies have indicated that the TME in GC patients often exhibits a "cold tumor" phenotype—characterized by low immune cell infiltration and weak immune activation—which not only predicts poor prognosis but also correlates with low responsiveness to immunotherapy (42, 43).

Immune infiltration patterns exhibit dynamic changes across different GC subtypes and treatment contexts. Neoadjuvant chemotherapy can significantly remodel the TME by enhancing CD8+T cell infiltration and reducing immunosuppressive cells, highlighting the plasticity of the immune landscape (44, 45). High-throughput analyses and multiplex immunofluorescence have revealed complex interactions among different immune cells within the TME, such as exosome-mediated communication between TAMs and cancer cells (46, 47).

Furthermore, the degree of immune cell infiltration is closely associated with clinical outcomes. For instance, high PD-L1 expression often coexists with an "immune-excluded" infiltration pattern, suggesting that patients may benefit from immune checkpoint inhibitor therapy (48, 49). Key molecular features of the TME significantly shape immune infiltration and immunotherapy responses in GC, highlighting new avenues for enhancing antitumor immunity (50–52). Among these features, spatial metabolic heterogeneity — particularly lipid gradients within the TME — has recently gained attention as a critical factor influencing immune cell behavior.

4 Interactions between aberrant lipid metabolism and immune cells

4.1 TAMs

TAMs, one of the most abundant immune cells in the GC immune microenvironment, exhibit significant metabolic plasticity. Under the stimulation of various cytokines, macrophages can be polarized into two phenotypes with different functions: M1 macrophages, which have pro-inflammatory and tumor-inhibiting effects; And M2 macrophages, which have anti-inflammatory and tumor-promoting effects Their functional state is closely linked to their lipid metabolic program. In gastric cancer, scavenger receptors such as CD36 mediate the endocytosis of fatty acids and cholesterol from the tumor microenvironment, leading to intracellular lipid accumulation and promoting the establishment of a highly immunosuppressive TME (53, 54). This process further activates the peroxisome proliferator-activated receptor γ (PPAR-γ) signaling pathway, upregulating FAO, promoting TAM towards a m2 polarized phenotype, and enhancing its oncogenic function (55, 56). Moreover, lipid uptake promotes enhanced FAO, providing a stable energy supply for M2-polarized TAMs and augmenting their secretion of immunosuppressive factors such as IL-10 and TGF-β (57–59). These alterations collectively contribute to the formation of a microenvironment that favors tumor survival and immune evasion (60, 61). Mechanistically, lipid uptake via CD36 facilitates intracellular fatty acid accumulation, which activates PPAR-γ signaling and upregulates key enzymes of FAO, such as CPT1A.

Further studies have revealed that the metabolic state of TAMs is a key determinant of their spatial distribution and functional heterogeneity. For example, lipid-rich TAMs are predominantly located in hypoxic regions, where they respond to tumor-derived factors such as IL-34 and signals associated with p53 inactivation, exhibiting enhanced immunosuppressive capabilities (62, 63). At the metabolic level, lipid metabolic reprogramming is closely regulated by the TRAF3/STAT6 pathway, which governs key transcriptional programs involved in the polarization process (64). Meanwhile, signaling molecules such as CD40 have been shown to promote the reprogramming of TAMs toward an antitumor phenotype by remodeling fatty acid and glutamine metabolism, highlighting the potential of metabolic interventions in reshaping TAM function (65). Overall, lipid uptake and metabolism determine the fate of TAMs, representing a critical regulatory axis within the GC immune microenvironment and a promising therapeutic target for future treatment strategies (66). These findings highlight the central role of TAM lipid metabolism in promoting immune evasion and progression of gastric cancer.

4.2 Dendritic cells

DCs within the GC immune microenvironment is often markedly suppressed by dysregulated lipid metabolism. In gastric cancer, this metabolic dysfunction contributes to impaired tumor antigen presentation and weakened immune surveillance.The lipid-rich tumor environment leads to lipid accumulation in DCs, particularly the formation of lipid droplets enriched with cholesterol and triglycerides, which significantly impairs their antigen-presenting capacity (67, 68). Lipid overload not only diminishes the expression of major histocompatibility complex (MHC) class I and II molecules but also suppresses the expression of costimulatory molecules such as CD80 and CD86, thereby limiting T cell activation (69, 70). Studies have shown that Epstein-Barr virus–associated GC exacerbates antigen presentation impairment by secreting exosomes that interfere with DC maturation (70). Moreover, tumor-induced lipid metabolic reprogramming can suppress mitochondrial function and glucose metabolism in DCs, driving them toward an immunotolerant phenotype (67, 68). A decline in cross-presentation capacity is another critical defect of lipid-laden DCs, particularly impairing

their ability to elicit CD8$^+$ T cell responses (71, 72). Some studies have reported that lipid accumulation hinders the ability of DCs to uptake and process extracellular antigens, thereby weakening their effectiveness in activating tumor-specific T cells (73, 74). Furthermore, Tregs form immunosuppressive complexes with DCs through a CXCR3-mediated chemotactic mechanism, further limiting the ability of DCs to activate CD8+ T cells (75). In recent years, engineered dendritic cell (DC) systems have been developed to bypass the metabolic impairments of natural DCs, offering new avenues for tumor vaccines and targeted immunotherapy (76, 77). Therefore, targeting lipid metabolic regulatory pathways is considered a potential strategy to restore DC immune function and enhance immune responses in gastric cancer (78, 79).

4.3 Tregs and MDSCs

Tregs are abundantly infiltrated in the GC immune microenvironment and rely on lipid metabolism to maintain their stability and immunosuppressive function. Studies have shown that within the tumor environment, Tregs gain an energetic advantage by enhancing FAO, which sustains their Foxp3 expression and suppressive capacity (80, 81). PD-1 deficiency disrupts the metabolic stability of Tregs, suggesting that their metabolic adaptability is a critical factor in the establishment of immune tolerance (80). Moreover, fatty acid-binding protein 5 (FABP5) and the SIRT1–CX3CL1 axis play important roles in regulating lipid metabolism in Tregs, influencing their distribution within the TME and their immunosuppressive capacity (82, 83). In lipid-rich microenvironments, Tregs exhibit enhanced stability and activity, representing one of the major obstacles to the efficacy of immune checkpoint inhibition therapy (84, 85).

Similar to Tregs, MDSCs exhibit potent immunosuppressive properties regulated by lipid metabolism. In high-lipid microenvironments, they sustain their survival through FAS and cholesterol metabolism, while secreting a range of immunosuppressive factors (29, 86). Ginger polysaccharide–induced lipid metabolic disruption can promote apoptosis of MDSCs, indicating that targeting lipid metabolism holds potential for enhancing immune responses (86). Within the GC TME, MDSCs cooperate with Tregs to establish a metabolically coupled immunosuppressive network (87, 88). Recent studies have shown that cancer-associated fibroblasts (CAFs) influence the metabolic activity of MDSCs through CD36 and the secretion of macrophage migration inhibitory factor (MIF), further exacerbating immune evasion (87). In summary, targeting lipid metabolism has emerged as a key strategy for modulating the functions of Tregs and MDSCs and overcoming immune tolerance (29, 85).

4.4 CD8$^+$ T cells

CD8$^+$ T cells are the central effector cells in antitumor immune responses, and their functional state is significantly influenced by dysregulated lipid metabolism within the TME. In the GC microenvironment, fatty acid uptake and cholesterol metabolism reshape the metabolic programming of CD8$^+$ T cells, leading to metabolic imbalance, enhanced exhaustion phenotypes, and reduced cytotoxic function (89). Tumor cells secrete lipid metabolism–regulating factors such as SCD1 and FABP5, which elevate levels of free fatty acids and oxidized lipids in the TME. This induces the accumulation of reactive oxygen species (ROS) in CD8$^+$ T cells, leading to lipid peroxidation and mitochondrial damage (90). This process is accompanied by the upregulation of inhibitory receptors such as PD-1 and TIGIT, ultimately leading to T cell exhaustion and the loss of sustained cytotoxic activity (91). Moreover, excess cholesterol can accumulate in the membranes of CD8$^+$ T cells, disrupting immunological synapse formation and TCR signaling, thereby further suppressing their effector functions (92).

Studies have also indicated that certain lipid metabolic pathways exert bidirectional regulatory effects on CD8$^+$ T cells. Tissue-resident CD8$^+$ T cells rely on FAO to sustain energy supply and long-term survival; however, in the nutrient-deprived and competitive TME, this metabolic dependency may actually constrain the sustained activation of their effector functions (89). Under high-lipid conditions, tumor cells compete with CD8$^+$ T cells for nutritional substrates, leading to energy deprivation in CD8$^+$ T cells. This results in a state of "functional starvation," characterized by reduced expression of effector molecules such as Granzyme B and IFN-γ (27, 91). Therefore, targeting lipid metabolic pathways—such as CD36 inhibition, FAO blockade, or cholesterol metabolism modulation—is considered a promising strategy to restore CD8$^+$ T cell function and enhance the efficacy of immunotherapy (90, 93) (Figure 1).

5 Clinical and therapeutic implications

Lipid metabolic reprogramming is not only a key mechanism in shaping the TME of GC, but also offers multidimensional therapeutic targets for clinical intervention. High expression of key lipid metabolic molecules such as CD36, FASN, and SREBP1 is closely associated with the infiltration of immunosuppressive cells and T-cell exhaustion, and is considered one of the major contributors to immunotherapy resistance (94–96). For instance, Li et al. found that lipid metabolic imbalance can promote symbiotic signaling pathways between CAFs and TAMs, which significantly impairs the efficacy of immune checkpoint inhibitors (ICIs) (97). Emerging lipid-targeted strategies —such as FASN inhibitors, FAO pathway blockers, and cholesterol metabolism modulators—are being actively explored to enhance CD8$^+$T cell function, inhibit TAM polarization, and reduce Treg-mediated immunosuppression (94, 98, 99). Moreover, lipid metabolism–related genes have also been identified as potential predictive biomarkers of immune response. Genes such as RGS2, APOD, and MTTP have demonstrated promising prognostic and therapeutic response prediction value in multiple studies (94, 96, 98).

Combination therapy strategies are emerging as a key approach to overcoming the bottlenecks of immunotherapy in GC Several clinical trials—such as ATTRACTION-2, ATTRACTION-4, KEYNOTE-859, KEYNOTE-061 and CheckMate-649—have validated the efficacy of combining ICIs with chemotherapy (100–104). Combination

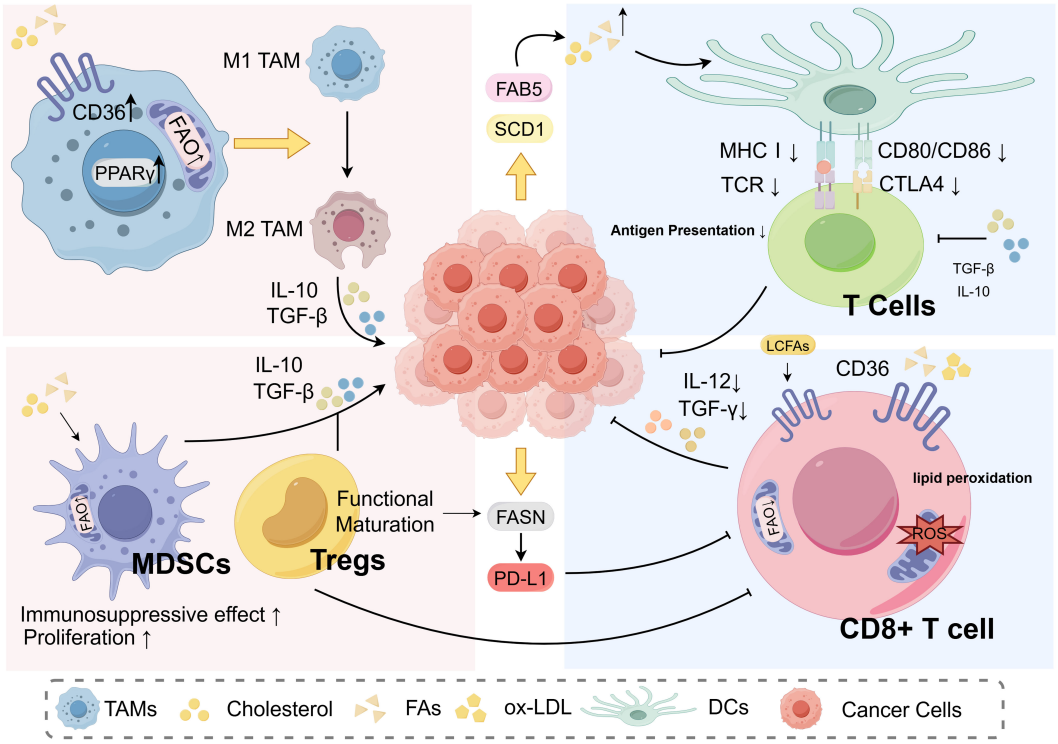

FIGURE 1
Interactions between aberrant lipid metabolism and immune cells.

strategies involving CD36 antagonists or cholesterol synthase inhibitors have significantly enhanced antitumor immune responses in preclinical models (94). Meanwhile, lipid metabolism–based immune subtyping approaches are increasingly being employed to guide the selection of GC patients for immunotherapy (101, 105). In summary, the role of lipid metabolism in precision immunotherapy for GC is becoming increasingly prominent. Existing clinical trials combining immune checkpoint inhibitors with chemotherapy have demonstrated heterogeneous outcomes, which may partially reflect underlying metabolic states of the tumor immune microenvironment (106–110). Aberrant expression of lipid metabolism–related molecules such as FASN, CD36, and SREBP1 has been associated with immune cell exhaustion, Treg enrichment, and impaired dendritic cell function, suggesting their potential value as both therapeutic targets and predictive biomarkers (111–114). Integrating lipidomic analysis into future clinical trial designs may enhance stratification strategies and optimize combination regimens to overcome resistance (Table 1).

6 Research gaps and future perspectives

Although the role of lipid metabolism in regulating the immune microenvironment of GC has been progressively elucidated, many gaps remain in understanding its mechanistic network. Current research primarily focuses on classical lipid metabolism regulators such as CD36 and FASN, while the roles of non-coding RNAs and RNA modifications (e.g. m^6A) in the cross-regulation of lipid metabolism remain largely underexplored (115–117). Moreover, how lipid metabolism specifically affects different immune cell subsets—such as tissue-resident memory T cells (Trm) and progenitor-exhausted T cells (Tpex)—remains insufficiently investigated at the single-cell resolution level (118, 119). Most current mechanistic studies are based on *in vitro* cell experiments and traditional animal models, with a lack of application of emerging technologies—such as spatial transcriptomics, spatial metabolomics, and single-cell lipidomics—for constructing a "functional lipid map" within the immune microenvironment (120, 121).

In future research, a primary focus should be the expanded systematic screening of lipid metabolism regulators, including transporters, enzymes, and intermediate metabolites, to evaluate their immunological effects (122, 123). Secondly, integrating clinical cohorts to perform lipid metabolic phenotyping and establishing a biomarker system capable of predicting immunotherapy response and resistance risk will be critical for advancing personalized treatment (124–126). Moreover, constructing *in vitro* microenvironment models—such as organoid–immune cell co-

TABLE 1 Clinical trials of immunotherapy-based combination strategies in gastric cancer.

Trial	Phase	Drugs	Actual enrollment	Study period	Reference	Lipid metabolism/ immune remodeling findings
NCT02872116 (CHECKMATE-649)	III	Nivolumab + Ipilimumab or Nivolumab in Combination With Oxaliplatin + Fluoropyrimidine vs Oxaliplatin + Fluoropyrimidine	2031	May 27, 2020- May 31, 2024	(100)	↑ $CD8^+$ T cells, ↓ PD-L1 immune evasion; lipid modifications regulate PD-L1.
NCT02746796 (ATTRCTION-04)	II/III	SOX/Capecitabine + Oxaliplatin with vs without Nivolumab	724	March 7, 2017 – May 10, 2018	(101)	↑ $CD8^+$ T cells; enhanced tumor microenvironment immune activation.
NCT03675737 (KEYNOTE-859)	III	Pembrolizumab+ Chemotherapy vs Placebo + Chemotherapy	1579	November 8, 2018 – September 28, 2024	(102)	↑ PD-L1 expression, immune activation linked to lipid gene co-signatures.
NCT03878472	II	Camrelizumab + Apatinib + S-1 ± Oxaliplatin	25	April 1, 2019 – May 31, 2024	(105)	↑ $CD8^+$ T cells, ↓ PD-L1 immune evasion.
NCT04082364 (MAHOGANY)	II/III	Combination Margetuximab, Retifanlimab, Tebotelimab, and Chemotherapy	81	September 30, 2019 - December 2023	(106)	↑ T-cell activation via PD-1 and LAG-3 blockade; HER2–PD-L1 immune crosstalk implicated.
NCT03335540 (ADVISE)	I	Nivolumab + Ipilimumab vs Nivolumab	20	May 7, 2018 – August 25, 2021	(107)	↑ Immune markers in low/ intermediate PD-L1 tumors; ↑ T-cell and macrophage activation.
NCT03662659 (RELATIVITY-060)	II	Relatlimab + Nivolumab + XELOX/FOLFOX/SOX vs. Nivolumab + XELOX/ FOLFOX/SOX	274	October 16, 2018 – January 16, 2024	(108)	↑ T-cell activation via PD-1 and LAG-3 blockade
NCT04908566	II	PD-1 inhibitor + mFOLFIRINOX vs. mFOLFIRINOX	30	August 2023 – May 2025	(109)	↑ $CD8^+$ T and NK cells, ↓ macrophages and $FOXP3^+$ Tregs; dynamic immune remodeling predicts response
NCT04997837	III	Chemotherapy + PD-1 inhibitor + Radiotherapy VS Chemotherapy	433	July 21, 2021 – July 21, 2027	(110)	Radiation-induced PD-L1 upregulation
NCT03615326 (KEYNOTE-811)	III	Pembrolizumab/Trastuzumab/ Chemotherapy vs Trastuzumab/Chemotherapy	698	October 5, 2018 - March 20, 2024	(111)	↑ T-cell activation; HER2–PD-L1 crosstalk enhances immune response with pembrolizumab.
NCT02589496	II	Pembrolizumab	45	March 26, 2016 – December 2021	(113)	↑ Immune activation; metabolism pathways and epigenetic features linked to tumor microenvironment score (TMEscore) predicting ICB response.
NCT04182724 (KEYNOTE-061)	II	PD-1 inhibitor + albumin-bound paclitaxel + apatinib	43	July 11, 2019 – October 13, 2022	(114)	↑ PD-L1 expression; VEGFR inhibition and immune activation via PD-1 blockade.
NCT02267343 (ATTRACTION-2)	III	Nivolumab vs Placebo	493	October 2014 – January 2021	(115)	↑ PD-L1–dependent immune response; lipid metabolism not reported.
NCT05008783	III	Cadonilimab + Oxaliplatin + Capecitabine (XELOX) vs. Placebo + Oxaliplatin + Capecitabine (XELOX)	610	September 17, 2021 – October 18, 2025	(116)	↑ PD-L1 expression; enhanced immune activation via dual PD-1/ CTLA-4 blockade.

↑, upregulated; ↓, downregulated.

culture systems—or developing novel drug delivery platforms targeting lipid metabolism will help bridge the gap between basic research and clinical application in metabolic immune regulation (127). Building on this foundation, conducting multicenter prospective clinical studies to evaluate the efficacy and safety of lipid metabolism–targeted interventions combined with immunotherapy will be a key pathway toward the clinical translation of metabolism-based immunotherapies (128, 129).

7 Conclusion

Lipid metabolism plays a central regulatory role in the TME of GC. Lipid competition between tumor cells and immune cells not only reshapes energy metabolism patterns but also alters immune cell functional states, inducing immunosuppressive phenotypes such as M2 polarization of TAMs, impaired antigen presentation by DCs, enhanced Treg functionality, and exhaustion of $CD8^+$ T cells (30, 32, 34). Lipid metabolic reprogramming mechanisms—including CD36-mediated lipid uptake, enhanced FAO, and cholesterol accumulation—have been shown to play critical roles in GC progression and immune evasion by regulating immune checkpoint expression, immune cell metabolic adaptation, and the secretion of immunosuppressive factors (40, 48, 101). Targeting lipid metabolic pathways—such as FASN, CPT1A, CD36, or cholesterol metabolism—can enhance immunotherapeutic responses and alleviate the immunosuppressive nature of the TME, demonstrating promising translational potential (123). However, the cell-specific functions of lipid metabolism across different immune cell subsets, its spatial heterogeneity, and the interplay between metabolic and epigenetic regulation axes remain to be further investigated (119, 130, 131). Future research should integrate emerging technologies such as spatial transcriptomics, single-cell lipidomics, and multi-omics analyses, while establishing clinical cohorts to explore predictive biomarkers and novel strategies for metabolism-targeted therapies (127, 132).

Author contributions

SC: Writing – original draft, Writing – review & editing. WC: Writing – original draft. TX: Writing – original draft. JL: Writing – original draft. JY: Writing – original draft. YH: Writing – original draft, Writing – review & editing. SQ: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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