Metabolic heterogeneity and functional diversity of cancer-associated fibroblasts in gastric cancer (Review)

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Abstract. Gastric cancer (GC) remains a major global health challenge characterized by poor prognosis and high mortality rates, despite advances in anticancer therapies. Increasing evidence indicates that GC is a highly stromal-rich tumor, with cancer-associated fibroblasts (CAFs) serving as key stromal components of the tumor microenvironment (TME). CAFs exhibit substantial metabolic heterogeneity, such that distinct CAF subtypes demonstrate intrinsic differences and dynamic remodeling in glucose, lipid and amino acid metabolism. This metabolic reprogramming represents not only functional diversity but also an adaptive response to microenvironmental stressors, including tumor-derived signals, hypoxia, nutrient fluctuations and oxidative stress. Through these adaptations, CAFs engage in extensive crosstalk with tumor and immune cells, thereby contributing to microenvironmental remodeling. Due to their critical role and abundance in GC, CAFs have emerged as promising therapeutic targets. The present review summarizes the origins, characteristics and heterogeneity of CAFs in GC and discusses their interactions with the TME. In addition, it summarizes the metabolic heterogeneity of CAFs, explores potential metabolism-targeted therapeutic strategies and outlines the broader impact of CAFs on the TME.

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Abbreviations: CAFs, cancer-associated fibroblasts; TME, tumor microenvironment; ECM, extracellular matrix; NFs, normal fibroblasts; MSCs, mesenchymal stem cells; EMT, epithelial-mesenchymal transition; iCAFs, inflammatory CAFs; mCAFs, matrix-associated CAFs; apCAFs, antigen-presenting CAFs; pCAFs, proliferative CAFs; myCAFs, myofibroblastic CAFs; eCAFs, ECM CAFs; TAMs, tumor-associated macrophages; glyCAFs, glycolytic CAFs

Key words: CAFs, TME, gastric cancer, metabolic heterogeneity, functional diversity

Contents

1. Introduction

Gastric cancer (GC) remains one of the most lethal malignancies worldwide. According to Global Cancer Observatory estimates, GC accounts for ~1 million new cases and 650,000 deaths annually, with a disproportionately high disease burden in China, which accounts for 44.1% of global GC cases and >50% GC-associated mortalities (1). Despite a global decline in incidence of 42% (range: 35-49%) from 1990-2021 (2), which may be attributed to *Helicobacter pylori* control, lifestyle shifts and broader screening access, GC remains the fifth most common cancer and the fourth leading cause of cancer-associated mortalities worldwide, with a poor prognosis and a 5-year survival rate of <10% (3). GC exhibits marked epidemiological variation, with the highest incidence rates observed in Eastern Asia, South America and Eastern Europe, although >50% all new cases occur in developing countries (4,5). In addition, GC is 2-3 times more common in men compared with women (6).

The pathogenesis of GC involves a complex interplay between host and environmental factors, including genetic predisposition (encompassing inherited traits and epigenetic modifications), infections, dietary habits and environmental exposures (7). Furthermore, *Helicobacter pylori* infection is a well-established major risk factor for GC, along with smoking, alcohol consumption and high salt intake (8). Therefore, further investigation into the mechanisms underlying GC progression, in addition to the identification of novel therapeutic targets and the development of innovative therapeutic agents, remains essential.

Cancer-associated fibroblasts (CAFs) form a crucial tumor-promoting component of the GC microenvironment. Dense CAF infiltration and associated fibrosis are hallmark pathological features of GC, particularly in undifferentiated

subtypes. CAFs maintain dynamic bidirectional communication with both cellular and extracellular matrix (ECM) components that are strongly associated with immunosuppressive phenotypes and poor prognosis in GC (9,10). In addition, CAFs can regulate angiogenesis, provide metabolic support and may contribute to therapeutic resistance in GC (Fig. 1) (11). As a result, CAFs have emerged as promising therapeutic targets in GC.

Targeting CAFs may disrupt the tumor microenvironment, overcome treatment resistance and inhibit metastasis, thereby enhancing the efficacy of existing therapies and providing novel treatment options for patients with refractory disease. However, CAF-targeted therapies face several challenges, including the pronounced heterogeneity of CAFs, presence of functionally distinct or even opposing subpopulations and the lack of specific biomarkers, all of which hinder the development of precise therapeutic strategies (12,13). The present review focuses on GC and comprehensively examines the characteristics of CAFs, with particular emphasis on their heterogeneity, especially metabolic heterogeneity and the functional diversity arising from these features.

2. Origins and heterogeneity of CAFs

CAFs originate from multiple cell types (Fig. 2). Previous studies have shown that CAFs in GC can arise from tissue-resident fibroblasts [normal fibroblasts (NFs)], mesenchymal stem cells (MSCs), gastric submucosa-MSCs, bone marrow (BM)-MSCs and epithelial cells (14-16). In a mouse model of GC induced by *Helicobacter felis*-associated inflammation, ≥20% CAFs were revealed to originate from MSCs and BM-MSCs (17). Studies have also demonstrated that TGF-β stimulation serves a critical role in driving the transformation of MSCs and normal NFs into CAFs (18,19). In addition, in gastritis induced by *Helicobacter pylori* infection, TGF-β has been shown to induce epithelial-mesenchymal transition (EMT) in epithelial cells, thereby promoting their conversion into CAFs (20,21). Pericytes can also differentiate into CAFs (22).

CAFs exhibit substantial heterogeneity due to their diverse cellular origins, which can lead to functionally distinct subpopulations (Fig. 2). A variety of biomarkers, including α-smooth muscle actin (α-SMA), fibroblast activation protein (FAP), S100 calcium binding protein A4 (S100A4), podoplanin, caveolin-1, mevalonate kinase, CD10 and complement C5a receptor 2, have been identified for CAFs (23). However, these markers lack specificity because they are typically expressed only in certain CAF subsets or are also expressed by non-CAF cell types. In addition, their expression patterns vary across different tumor types, necessitating the use of multiple markers for accurate CAF identification (24,25). Advances in single-cell RNA sequencing (scRNA-seq) technology have helped addressing this challenge. In a recent study of human GC samples, six distinct CAF subtypes were identified: i) Inflammatory CAFs (iCAFs); ii) pericytes; iii) matrix-associated CAFs (mCAFs); iv) antigen-presenting CAFs (apCAFs); v) smooth muscle cells; and vi) proliferative CAFs (pCAFs). iCAFs exhibited enhanced immune-related activities, including complement activation and chemokine-mediated inflammatory responses. By contrast, apCAFs and pCAFs are typically enriched in type I IFN signaling and chemokine production. mCAFs are involved in angiogenesis, wound healing and ECM regulation (26). Additional CAF subtypes identified in GC include myofibroblastic CAFs (myCAFs), which are located adjacent to cancer cells and exhibit high α-SMA expression (27). ECM CAFs (eCAFs), located in the distal stroma, are characterized by the high expression of invasion-related genes, such as *MMP14*, lysyl oxidase-like 2 and periostin *(POSTN)*. These CAFs promote metastasis not only through ECM remodeling but also by recruiting M2-like tumor-associated macrophages (TAMs) (28). The application of scRNA-seq has advanced the understanding of CAF heterogeneity and developmental trajectories in GC.

3. Metabolism in CAFs

Emerging evidence has revealed that the functional heterogeneity of CAFs is closely associated with their metabolic plasticity (29,30). As key architects of the tumor microenvironment (TME), CAFs can actively orchestrate the reprogramming of major metabolic pathways, including glucose, amino acid and lipid metabolism. These metabolic alterations fundamentally determine their functional states and thereby influence tumor progression.

Glucose metabolism. Glucose is the primary source of cellular energy and is metabolized through glycolysis, the pentose phosphate pathway and the tricarboxylic acid (TCA) cycle (Fig. 3). Amongst these pathways, glycolysis has been the most extensively studied. Glycolysis is an oxygen-independent metabolic process that converts glucose into pyruvate in the cytoplasm. Under aerobic conditions, normal cells typically transport pyruvate into the mitochondria for oxidative phosphorylation (OXPHOS). By contrast, tumor cells preferentially utilize glycolysis even in the presence of sufficient oxygen. This metabolic phenotype is known as aerobic glycolysis or the Warburg effect (31). Notably, accumulating evidence indicates that CAFs can also undergo aerobic glycolysis, resembling the metabolic behavior of tumor cells (32,33). In certain tumor types such as pancreatic cancer and melanoma, the metabolic profile of CAFs shifts from OXPHOS to glycolysis (34,35). In GC, Kogure *et al* (36) showed that highly metastatic GC cells shift CAF metabolism from OXPHOS to aerobic glycolysis, as indicated by increased glycolytic gene expression and reduced OCR. These glycolytic CAFs (glyCAFs) secrete lactate into the TME, which is subsequently taken up by tumor cells and utilized to support OXPHOS via oxidation to pyruvate by LDH, entering the mitochondria to fuel the TCA cycle and generating electrons for the ETC to drive ATP synthesis. This metabolic coupling model is referred to as the 'reverse Warburg effect', although its physiological relevance remains a subject of ongoing debate (32).

Previous studies have established glyCAFs to be emerging biomarkers of malignancy, potential indicators of tumor aggressiveness and patient prognosis. CAFs can originate from NFs, which primarily rely on OXPHOS as their main energy-producing pathway, utilizing the mitochondrial TCA cycle to fully oxidize substrates (such as glucose and glutamine) for ATP generation. Compared with NFs, CAFs undergo a marked metabolic shift from OXPHOS to glycolysis, driven

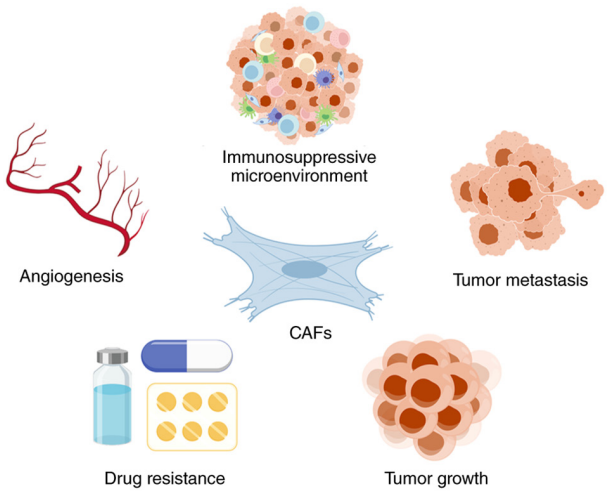

Figure 1. Tumor-promoting effects of CAFs. CAFs exert multiple pro-tumorigenic functions, including the induction of angiogenesis, promotion of tumor proliferation and metastasis, establishment of an immunosuppressive microenvironment and mediation of therapy resistance. CAFs, cancer-associated fibroblasts.

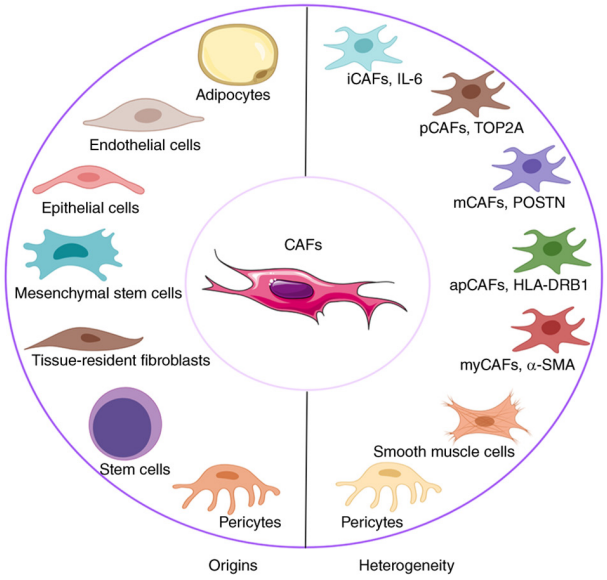

Figure 2. Origins and heterogeneity of CAFs. CAFs can originate from multiple cell types, including adipocytes, endothelial cells, epithelial cells, mesenchymal stem cells, resident fibroblasts and pericytes. Based on phenotypic and functional characteristics, CAFs can be further classified into distinct subtypes, including iCAF, pCAF, mCAF, apCAF and myCAF, some of which share phenotypic features with smooth muscle cells and pericytes. CAFs, cancer-associated fibroblasts; iCAFs, inflammatory CAFs; mCAFs, matrix-associated CAFs; apCAFs, antigen-presenting CAFs; pCAFs, proliferative CAFs; myCAFs, myofibroblastic CAFs; TOP2A, DNA topoisomerase II α; POSTN, periostin; HLA-DRB1, major histocompatibility complex, class II, DR β1; α-SMA, α-smooth muscle actin.

by complex interactions within the TME (35,37). Co-culturing with colon cancer cells has been shown to induce fibroblasts to undergo metabolic reprogramming toward glycolysis and to express markers characteristic of myCAFs and iCAFs (38). Specifically, in GC, Kogure *et al* (36) previously revealed that fibroblasts co-cultured with peritoneal highly metastatic GC cell line 44As3 exhibited distinct expression patterns

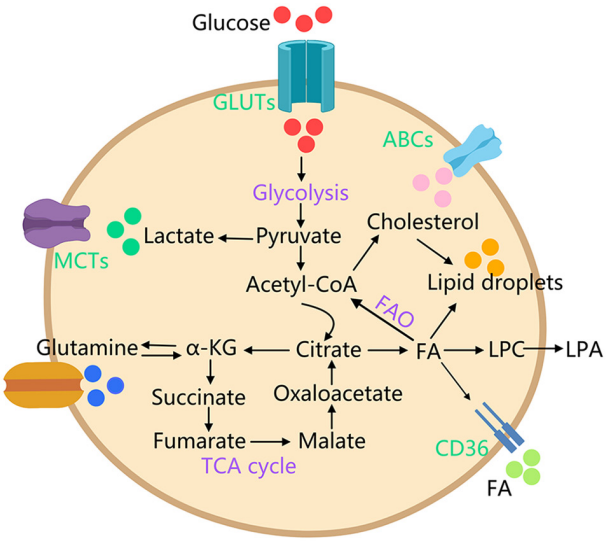

Figure 3. Metabolism of glucose, amino acids and lipids in CAFs. Glucose is taken up by CAFs through GLUTs, converted into lactate through glycolysis and exported through MCTs. FAs are transported through CD36, where a portion undergoes FAO to generate acetyl-CoA and ATP, whilst others are utilized for cholesterol synthesis, lipid droplet formation or LPA production. Amino acids (such as glutamine) enter the TCA cycle, where they are oxidized for energy production or utilized for anabolic metabolism. CAFs, cancer-associated fibroblasts; GLUTs, glucose transporters; FAO, fatty acid oxidation; acetyl-CoA, acetyl coenzyme A; FA, fatty acids; LPC, lysophosphatidylcholine; TCA, tricarboxylic acid; LPA, lysophosphatidic acid; MCT, monocarboxylate transporters; α-KG, α-ketoglutarate; ABC, ATP-binding cassette.

of glycolysis-related genes [such as lactate dehydrogenase A *(LDHA)* and enolase 2], accompanied by altered glucose uptake, lactate production and oxygen consumption, compared with those co-cultured with the low-metastatic parental cell line HSC-44PE, collectively indicating a pronounced shift toward glycolysis. In another study, Gu *et al* (39) demonstrated that GC cell-derived exosomes can induce the differentiation of MSCs into CAFs, during which nuclear pyruvate kinase M1/2 *(PKM)* is persistently upregulated, resulting in NF-κB p65 activation, sustained transcription of IL-6 and IL-8 and the resulting CAF-conditioned medium enhances GC cell proliferation. These findings suggest that glyCAFs represent a characteristic feature and potential therapeutic target in GC. In addition, hexokinase 2, a critical rate-limiting enzyme in glycolysis, has also been reported to be upregulated in tumor-induced CAFs (40).

Beyond tumor-derived signals, hypoxia is another key driver of glycolytic reprogramming in CAFs. Hypoxia induces metabolic reprogramming in NFs and promotes their transition into CAFs, a process characterized by the elevated expression of hypoxia-associated factors, such as carbonic anhydrase 9 and VEGF (41,42). A previous study has also shown that compared with those in NFs, CAFs in GC exhibit significantly increased expression levels of hypoxia-regulated genes, including *POSTN*, bone morphogenetic protein 4, matrix remodeling-associated 5 and *LBH*, the expression levels of which are associated with GC aggressiveness and poorer prognosis (43). Furthermore, hypoxia-inducible factor-1α (HIF-1α), an oxygen-sensitive subunit that is degraded under normoxic conditions and stabilized under hypoxia, promotes the expression of glycolysis-related genes such as *PKM* and

LDHA, and serves as a central regulator of the metabolic shift in CAFs (44). This is mediated by suppressing mitochondrial function and oxygen consumption. Therefore, current evidence indicates that the glycolytic phenotype of CAFs is maintained through multiple mechanisms, including HIF-1α signaling and the epigenetic reprogramming of glycolytic enzymes (44). Consequently, targeting hypoxia-related proteins and signaling pathways to inhibit the formation of glyCAFs has emerged as a promising therapeutic strategy in cancer treatment, with potential applicability in GC. However, this approach has several limitations. Hypoxia-related proteins (such as members of the HIF family) are also involved in various physiological processes, such as angiogenesis and erythropoiesis, where their systemic inhibition may result in off-target toxicity (45). In addition, CAF subtypes differ in their dependence on hypoxia signaling. Therefore, single-target strategies may affect only specific CAF populations (including myCAFs), whereas other subtypes may persist and continue to promote tumor progression. Inhibition of hypoxia signaling may also induce the metabolic reprogramming of CAFs from glycolysis toward OXPHOS or fatty acid oxidation (FAO), thereby maintaining their tumor-promoting functions (44,46). CAFs secrete abundant ECM components, forming a dense stromal barrier that impedes drug penetration and limits access to CAFs.

Lactic acid is a major end-product of glycolysis secreted by CAFs and is a key mediator of metabolic crosstalk between CAFs and cancer cells. It has been suggested that lactic acid released by CAFs can serve as an energy source for adjacent cancer cells (47), thereby reprogramming tumor metabolism and enhancing invasive potential (48). Simultaneously, lactic acid contributes to the establishment of an immunosuppressive microenvironment, by impairing T-helper 1 cell function whilst promoting regulatory T cell (Treg) differentiation (49). Notably, CAFs not only secrete lactic acid but can also utilize it. Kitamura *et al* (50) previously demonstrated that CAFs highly express monocarboxylate transporter 1, enabling them to import and metabolize lactic acid, thereby supporting their growth and establishing a symbiotic relationship with cancer cells. Beyond serving as a metabolic substrate for CAFs, lactic acid also promotes their differentiation. Andreucci *et al* (51) reported that lactic acid acts as a potent inducer of CAF differentiation, by driving the conversion of adipocytes into CAF-like cells (such as myofibroblasts), possibly via upregulation of IL-6, IL-1β and TGF-β1, which may account for the activation. Therefore, targeting the lactic acid shuttle between cancer cells and CAFs may represent a promising therapeutic strategy.

Lipid metabolism. Lipids are multifunctional molecules that serve as signaling mediators, energy sources and regulators of various cellular processes. They encompass a diverse range of molecular species, where current evidence suggests that the major lipid classes involved in cancer progression include fatty acids, glycerides, sphingolipids, glycerophospholipids and cholesterol (Fig. 3) (52,53). Compared with NFs, CAFs exhibit enhanced lipid metabolic activity and greater lipid droplet accumulation, characteristics that are closely associated with their phenotype and function (54).

To the best of our knowledge, despite the abundance of CAFs in GC, studies investigating their lipid metabolism remain limited. A recent scRNA-seq analysis revealed substantial metabolic heterogeneity among CAF subtypes (55). In this study, iCAFs are primarily associated with fatty acid metabolism, whereas myCAFs favor more carbohydrate metabolism, particularly the TCA cycle and OXPHOS. More detailed investigations have identified a distinct CAF subpopulation termed 'lipid-type CAFs', which differs from myCAFs, iCAFs and apCAFs. This subtype exhibits a unique transcriptomic profile, enriched in ATP-binding cassette transporter- and adipogenesis-related genes and displays distinct lipid metabolic characteristics (56). Lipid-type CAFs establish metabolic symbiosis with tumor cells by supplying essential lipids, including phospholipids, fatty acyl groups (primarily long-chain polyunsaturated fatty acids), cholesterol esters, oleic acid and ceramides, to support energy production and biosynthesis, particularly under glucose-deficient conditions (57-59). In addition, myCAFs can secrete abundant lysophosphatidylcholine (LPC), which can be taken up by cancer cells and converted into phosphatidylcholine to maintain membrane integrity (60).

Fatty acids form the fundamental component of complex lipids and can be metabolized through a multitude of processes, primarily involving cellular uptake, β-oxidation and *de novo* synthesis. CD36 is a fatty acid translocase that mediates the uptake of exogenous fatty acids. Recently, a CD36-high CAF subtype has been identified within the TME of colorectal cancer. These CAFs participate in complex metabolic interactions with cancer and immune cells, where their elevated abundance is associated with shorter overall survival (61). Inhibition of CD36 has been shown to suppress tumor growth of hepatocellular carcinoma, enhance immune activity and improve the efficacy of immunotherapy (62). However, the role of CD36 appears to be context-dependent. In lung metastasis models, CD36 expression decreases during the transition of fibroblasts into CAFs, whereas in breast cancer, loss of CD36 enhances ECM production and promotes tumor invasiveness (63,64). Carnitine palmitoyltransferase 1 (CPT1) is a key rate-limiting enzyme in FAO. In GC, a $CPT1C^+$ CAF subtype has been revealed to promote the formation of a matrix-rich and immunosuppressive microenvironment, where high infiltration by these cells is associated with poor survival and resistance to chemotherapy. Notably, CPT1 expression differs substantially between CAFs and tumor cells, with CAFs exhibiting high CPT1 expression and tumor cells showing low CPT1 expression. This differential expression facilitates a metabolic shift toward lipid utilization in CAFs, preserves glucose availability for tumor cells and promotes tumor progression (65). These characteristics make CPT1 a particularly attractive therapeutic target among lipid metabolism-related proteins. Concurrently, apolipoprotein D and ATP citrate lyase are upregulated in CAFs within GC. These proteins in CAFs may contribute to tumor progression and have been identified as independent prognostic risk factors (66,67). Therefore, targeting lipid metabolism in CAFs may inhibit tumor progression by restricting metabolic support to cancer cells and remodeling the TME.

Amino acid metabolism. Amino acids are critical for tumorigenesis, serving not only as sources of energy and biosynthetic precursors but also as regulators of cellular functions (68,69).

In addition, they provide essential nitrogen and carbon to serve as alternative fuels under conditions of glucose deprivation (Fig. 3).

CAFs frequently reprogram their metabolism to meet the metabolic demands of tumor cells (70). Previous studies have shown that CAFs can support tumor cells by synthesizing essential nutrients, including glutamate, glutamine, cysteine, alanine and nucleosides (71-73). CAFs in GC have been shown to secrete lysyl oxidase (LOX), which activates the TGF-β signaling pathway in GC cells, thereby promoting insulin-like growth factor 1 expression and enhancing GC cell migration, EMT and glycolysis (74). In addition, amino acids supplied by CAFs can be taken up by tumor cells to mitigate drug-induced damage and contribute to therapeutic resistance. Zhu *et al* (75) reported that CAF-derived cysteine is taken up by pancreatic ductal adenocarcinoma cells, thereby conferring resistance to ferroptosis and mediating cisplatin resistance. Similarly, CAFs can release glutathione and its metabolites, which reduce cisplatin accumulation in ovarian cancer cells and promote chemoresistance (76).

Glutamine is a crucial nutrient for tumors. Under nutrient-limited conditions, tumor cells frequently rely on CAF-derived glutamate and glutamine for proliferation. Previous studies have demonstrated that CAFs highly express genes involved in glutamine synthesis (such as glutamate-ammonia ligase) and amino acid transferases (including glutamic-oxaloacetic transaminase 1/2 and branched chain amino acid transaminase 1), enabling them to produce and transport glutamine to support tumor growth and resistance to stress (77,78). Beyond direct secretion, CAFs can enhance glutamine uptake by cancer cells through the upregulation of key transporters. CAFs have been shown to promote glutamine uptake in lung cancer cells by increasing the expression of transporters SLC38A2 and SLC7A5 (79,80) and metabolic enzymes alanine/serine/cysteine transporter 2 and glutaminase (71). In addition, a metabolic symbiosis cycle has been previously reported, where CAFs supply glutamine to tumor cells, whilst cancer cells provide ammonia generated from glutamine catabolism to CAFs for amino acid synthesis (81). Although this study did not use GC models, its findings may also apply to GC. miR-105 is aberrantly expressed in GC and involved in tumor progression, while MYC, a key GC driver, regulates metabolism in CAFs. Thus, this mechanism has potential translational relevance for GC. Targeting glutamine metabolism in CAFs to deprive tumors of metabolic support has therefore emerged as a promising therapeutic strategy, including the use of inhibitors of glutamine synthesis or transport and combination treatment approaches.

Autophagy is a fundamental cellular process that is essential for maintaining metabolic homeostasis. By serving as a source of amino acids, it enables CAFs to potentially support tumor cell nutrition. A study has previously shown that under nutrient-deprived conditions, autophagy serves as a critical mechanism for replenishing intracellular amino acid pools through the degradation of cellular proteins. In CAFs, regulation of mitophagy by *ATG3* or *ATG5* can promote proline biosynthesis and alter ornithine and citrulline concentrations, thereby promoting CAF activation (82). Although this mechanism was demonstrated in PDAC, it also applies to GC, where CAFs may activate autophagy to generate amino acids under specific conditions. In addition, as previously described, ammonia functions not only as a nitrogen source for CAFs but also as an inducer of autophagy, stimulating the secretion of nutrients, such as glutamine (83,84).

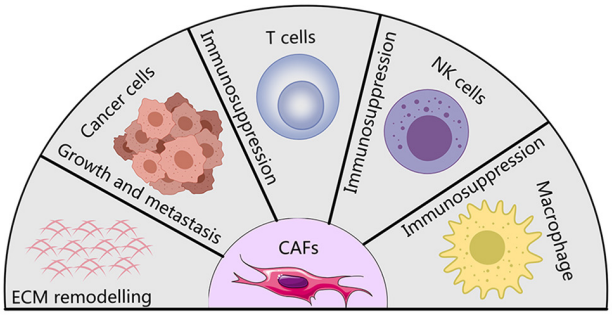

Figure 4. Communication between CAFs and the TME. CAFs are involved in multiple aspects of tumor development, including ECM remodeling, tumor proliferation and metastasis and the induction of immunosuppression involving T cells, NK cells and macrophages. CAFs, cancer-associated fibroblasts; TME, tumor microenvironment; ECM, extracellular matrix; NK, natural killer; PD-L1, programmed cell death 1 ligand 1; FSTL-1, follistatin-like 1; S100A4, S100 calcium binding protein A4; LOX, lysyl oxidase; BGN, biglycan; CLDN18.2, claudin 18.2.

4. Crosstalk and functions between CAFs and TME

As a key component of the TME in GC, CAFs actively remodel the microenvironment through direct intercellular communication and the secretion of bioactive molecules that alter TME properties (Fig. 4). CAFs orchestrate ECM remodeling not only by depositing structural proteins (such as collagens and periostin), but also by secreting enzymes (including MMPs and LOX) that mediate matrix degradation and cross-linking (85-87). CAFs regulate cancer cells through paracrine signaling (TGF-β, C-X-C motif chemokine ligand 12 and growth arrest specific 6) (19,88), direct interactions of surface proteins (S100A4/claudin 18.2) (89) and filamentous protrusions that engage cancer cells (ROR2/WNT5A) (90). CAFs are key drivers of an immunosuppressive microenvironment, as reflected by a significantly lower response to immunotherapy in patients with high CAF infiltration (20.9%) compared with those with low infiltration (53.2%) (91).

Analyses have revealed multifaceted crosstalk between CAFs and TAMs (Fig. 4). Specifically, they appear to be positively correlated, exhibit spatial overlap (such as eCAFs with $CD163^+$ TAMs) (28) and engage in functional reciprocity, in which CAFs secrete factors that polarize M2 macrophages and may even undergo phenotypic interconversion (92-95). In addition, CAFs can contribute to cytotoxic T cell inhibition and Treg enhancement (Fig. 4). CAFs interact with $CD8^+$ T cells to induce dysfunction through the secretion of inhibitory factors (96-98). Certain CAF subtypes also exhibit tumor-suppressive properties. apCAFs, characterized by high major histocompatibility complex class II expression, are frequently located near tertiary lymphoid structures and promote T cell activation, thereby enhancing anti-tumor immunity (99).

5. Challenges and future perspectives

Although the important role of CAFs in tumor therapy has been increasingly recognized, the development of effective therapeutic strategies targeting CAFs remains a formidable challenge.

CAF functional heterogeneity represents a core obstacle to targeted therapy. CAFs comprise functionally opposing subpopulations: myCAFs are predominantly pro-tumorigenic, whereas certain iCAFs or apCAFs may exert tumor-suppressive effects (100,101). Therefore, broad-spectrum depletion may eliminate pro-tumor CAFs but also damage beneficial subsets, potentially accelerating tumor progression.

The lack of specific CAF markers impedes clinical translation. Common markers (such as FAP or α-SMA) are not exclusive to CAFs, leading to potential off-target toxicity (102,103). In addition, the dynamic and heterogeneous expression of markers across CAF subpopulations makes it difficult for a single marker to capture all pro-tumor CAFs (100,104). Compounding this challenge, CAF composition varies across cancer subtypes. Luminal A breast cancer is enriched in CAF-S2, HER2-positive tumors in CAF-S4 and triple-negative breast cancer in CAF-S1 or CAF-S4, with these subsets defined by fibroblast activation protein, integrin β1/CD29, αSMA, fibroblast-specific protein 1/FSP1, platelet-derived growth factor receptor β, and caveolin-1 expression (105). This heterogeneity further increases the complexity of therapeutic targeting of CAFs. Similarly, diffuse-type gastric cancer (DGC) and intestinal-type gastric cancer (IGC) are two distinct subtypes of GC. IGC predominantly induces CAFs with high α-SMA expression (myCAFs), whereas DGC tends to induce CAFs characterized by high expression of senescence markers such as SA-β-gal and p16 (sCAFs) (106).

Furthermore, CAF metabolism is highly dynamic and can shift in response to microenvironmental cues (such as hypoxia, pH, lactate concentration and inflammatory cytokines) in addition to therapeutic pressure. Specifically, myCAFs tend to rely on aerobic glycolysis, whereas iCAFs may predominantly depend on OXPHOS. These states can also then interconvert under certain conditions, leading to metabolic reprogramming. iCAFs can transdifferentiate into myCAFs upon TGF-β stimulation (107). Such metabolic plasticity compromises the long-term efficacy of strategies based on static metabolic markers.

Similar to challenges associated with CAF surface markers, most CAF-enriched metabolic enzymes or transporters (for example, glucose transporter 1, LDHA, monocarboxylate transporter 4 and carnitine palmitoyltransferase 1A) are also expressed in NFs, immune cells or tumor cells, making targeted intervention prone to off-target toxicity and systemic metabolic disturbances (108-110). In addition, CAFs are not metabolically isolated. Their metabolites (such as lactate, ketone bodies, glutamine or exosomes) support tumor cell growth and reprogram immune cells (such as Tregs and tumor-associated macrophages). This metabolic coupling suggests that inhibition of a single CAF metabolic pathway may have limited efficacy due to compensatory adaptations in tumor or immune cells and may even induce unintended pro-tumor effects (57,111).

Despite these challenges, targeting CAFs remains an attractive therapeutic strategy, particularly in GC, where CAFs are key components of the TME and contribute to drug resistance and poor clinical outcomes (11,112). The present review highlights the heterogeneity of CAFs in GC and their dynamic interactions with cellular and non-cellular components of the TME, with a focus on metabolic diversity and plasticity.

Tumor cells must adapt to a nutrient-deprived TME to survive. In this process, CAFs undergo metabolic reprogramming, including aerobic glycolysis, lipid metabolism and amino acid metabolism, to generate metabolites that support tumor cell proliferation and biosynthesis. Recent advances in single-cell sequencing, spatial transcriptomics, proteomics, metabolomics and multiplex immunofluorescence are accelerating the identification of CAF subpopulations and their interaction networks within the TME. Targeted therapies against CAFs are emerging as novel strategies for GC treatment.

CAFs exhibit remarkable heterogeneity. The present review focused on their metabolic heterogeneity and interplay with the TME. Distinct TMEs harbor CAF subpopulations with divergent metabolic phenotypes, and CAFs can undergo metabolic reprogramming in response to microenvironmental cues, exerting differential effects on the TME. Elucidating this metabolic heterogeneity is critical for understanding their complex roles in tumor progression. Moreover, the heterogeneity and plasticity of CAFs pose substantial challenges to targeted therapies, underscoring the urgent need for further research to facilitate clinical translation.

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Authors' contributions

QF drafted the article and created the figures. NL, JW and SY contributed to the collection of literature and the initial drafting of portions of the manuscript. WX revised the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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