Role of metabolic reprogramming of cancer-associated fibroblasts in tumor development and progression (Review)

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Abstract. The occurrence and development of tumors is affected by tumor cells themselves and various components of the tumor microenvironment (TME). Among these, cancer-associated fibroblasts (CAFs), the main stromal component, can differentiate from different cell types and play an important role in the TME. The present review summarized the role of the metabolic reprogramming of CAFs in tumor development and progression. As the rapid growth of tumors is a process inseparable from energy supply and the TME is characterized by hypoxia and nutrient deficiencies, metabolic reprogramming can reverse the effects of a lack of energy supply in the TME. Studies have found that CAFs can affect tumor proliferation, migration, invasion, metastasis and drug resistance by changing metabolic patterns. The present review promoted research on the metabolic reprogramming of CAFs and emphasized the importance of considering the heterogeneity and plasticity of CAFs in the TME, which will lead to the development of more effective therapeutic strategies that target specific metabolic pathways in CAFs, potentially improving the efficacy of cancer treatments and overcoming drug resistance.

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Abbreviations: Akt, protein kinase B; CAF, cancer-associated fibroblast; CRC, colorectal cancer; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; Gln, glutamine; HCC, hepatocellular carcinoma; iCAF, inflammatory CAF; IL, interleukin; MAPK, mitogen-activated protein kinase; NF, normal fibroblast; PDAC, pancreatic ductal adenocarcinoma; PI3K, phosphoinositide 3-kinase; TCA, tricarboxylic acid cycle; TGF-β1, transforming growth factor beta 1; TME, tumor microenvironment

Key words: cancer-associated fibroblasts, metabolic reprogramming, tumor, glycolysis, lipid, amino acid

Contents

1. Introduction

As a systemic disease, tumor occurrence and development are dictated primarily by tumor cells but also by other components. This concept originated from the 'seed and soil' principle proposed by Stephen Paget in 1889 (1). The 'seeds' are the tumor cells and the 'soil' is the other component of the tumor microenvironment (TME) that maintains the growth of tumor cells. The TME is composed of tumor and nonmalignant cells and an extracellular matrix (ECM). Nonmalignant cells include immune, stromal and vascular cells (2). Cancer-associated fibroblasts (CAFs) are the predominant cell type (3). Several previous studies have found that CAFs, in addition to supporting the TME, promote tumor development and progression by eliciting changes that include the secretion of cytokines, release of exosomes and alteration of metabolic patterns (4-7). As an important communication hub in the TME, CAFs can interact with tumor cells and other cellular components to participate in tumor development and progression (8). Therefore, it is important to understand the role of CAFs in these processes.

Tumor development and progression require a high nutrient supply to meet the energy requirements of the abnormal growth and proliferation of tumor cells and tumor and stromal cells change their metabolic patterns to facilitate these processes (9). Under aerobic conditions, normal cells produce ATP through oxidative phosphorylation via the tricarboxylic acid cycle (TCA) (10), whereas tumor cells obtain energy through aerobic glycolysis, which is known as the 'Warburg effect' (11). In the TME, tumor cells alter other metabolic patterns, such as the lipid (12) and amino acid (13) metabolism. Thus, metabolic reprogramming is a hallmark of cancer (14).

There is metabolic coupling between tumor cells and the surrounding CAFs (15), with anabolism and catabolism dominating tumor cells and CAFs, respectively, suggesting a symbiotic relationship in the TME (16). Contrary to the tumor metabolic model, CAFs feed tumor cells with high-energy 'fuels' such as lactic acid, generated glycolysis, via is the 'reverse Warburg effect' (17). Additionally, CAFs undergo various metabolic changes, such as lipid and amino acid metabolism reprogramming. Therefore, this review aimed to summarize the specific role of metabolic reprogramming of CAFs in tumor development and progression. To this end, a comprehensive search in the PubMed database was performed using the following query: ('Metabolic Reprogramming') AND ('Cancer-Associated Fibroblasts') AND ('Cancer' OR 'Tumor' OR 'Neoplasm') AND ('Cancer Progression' OR 'Tumor Progression' OR 'Neoplasm Invasiveness'). The selection of literature focused on effective research from the last decade that has substantially influenced the field.

2. Heterogeneity of CAFs

Source of CAFs. There are multiple sources of CAFs in the TME (Fig. 1). CAFs are mainly produced by activating normal fibroblasts (NFs) (18). Previous studies have found that various regulatory factors, such as cytokines and signaling pathways, can participate in tumor progression and development through transforming growth factor beta 1 (TGF-β1), which is involved in the activation of NFs (19) and the activation of various pro-inflammatory fibroblast-derived cytokines, such as interleukin (IL)-1, IL-6 and tumor necrosis factor (20-22). Furthermore, previous studies revealed that the Notch vascular endothelial growth factor-related signaling pathways can mediate CAF activation (23) and ECM remodeling, which is conducive to the generation and maintenance of CAFs (24). Physiological factors such as reactive oxygen species (ROS) and metabolic disorders stimulate the activation of CAFs (25). Additionally, unlike other types of cancer, NFs in pancreatic and liver cancers have a unique name, known as 'stellate cells.' Activated pancreatic and hepatic stellate cells are transformed into CAFs (26-28).

Other cell types can be converted into CAFs. Bone marrow mesenchymal stem cells differentiate into CAFs by recruitment through the TGF-β-Smad signaling pathway (29-31). Additionally, epithelial (32), endothelial (33) and macrophage (34,35) cells can be converted into CAFs through epithelial-mesenchymal transition (EMT), endothelial-mesenchymal transition and macrophage-myofibroblast transition, respectively. For example, Dulauroy *et al* (36) found that when acute tissue injury occurs, the primary sources of CAFs are perivascular cells expressing disintegrin and metalloproteinase 12(+). In breast cancer, human adipose tissue-derived stem cells can be transdifferentiated into CAFs via the TGF-β1-Smad3 signaling pathway (37). Androgen receptor-associated protein 55 expression in stromal smooth muscle cells in prostate cancer has been implicated in CAF formation (38). Thus, CAFs are heterogeneous.

Biomarkers of CAFs. In the TME, unlike tumor and immune cells, CAFs have various biomarkers that are not specific (39). Vimentin is a biomarker for resting fibroblasts (40). As CAFs are derived from various cell precursors, activated CAFs retain some of the functions of the cells or tissues of origin; therefore, there are differences in the molecular expression of CAFs. Common biomarkers of activated CAFs include fibroblast-activating protein, α-smooth muscle actin, fibroblast-specific protein 1 and platelet-derived growth factor receptors (41). CAFs should be identified by combining multiple biomarkers owing to the non-specificity of activated molecular markers of CAFs. For example, Hu *et al* (42) performed a functional analysis of CAF heterogeneity in tumor tissues of patients with non-small cell lung cancer and identified CAF subtypes using CAF biomarkers. The identified CAF subtypes were distinguished as follows: The first was mainly characterized by high expression of hepatocyte growth factor and fibroblast growth factor 7, low expression of phospho-Smad2 and a strong protective effect on tumors; the second was mainly characterized by high expression of fibroblast growth factor 7, low expression of hepatocyte growth factor and phospho-Smad2 and a moderate protective effect on tumors; and the third was mainly characterized by high expression of phospho-Smad2, low expression of hepatocyte growth factor and fibroblast growth factor 7 and a minimum protective effect on tumors.

Subtypes of CAFs. CAFs are characterized by phenotypic heterogeneity and plasticity (43) and single-cell (sc)RNA-seq can be used to distinguish between CAF subtypes by detecting cellular heterogeneity (44). Previous studies named the CAF subtypes according to the function of a unique gene set (45-50) (Fig. 2). Therefore, the present review summarized the common CAF subtypes and their functions in different types of cancer. A previous study found that pancreatic stellate cells could differentiate into two subtypes of CAFs: Inflammatory CAFs (iCAFs) and myofibroblast CAFs. Myofibroblast CAFs were observed near tumor cells and exhibited upregulated expression of α-smooth muscle actin, while iCAFs detached from tumor cells and mainly secreted IL-6, IL-11, platelet-derived growth factor receptor α and other inflammatory mediators, while α-smooth muscle actin expression was not increased (45). iCAFs and myofibroblast CAFs are the most common CAF subtypes among multiple types of cancer (51), with similar genetic characteristics but distinct functional properties (52). A previous study on pancreatic ductal adenocarcinoma (PDAC) explored the specific mechanism of subtype heterogeneity of CAFs. Biffi *et al* (53) used organoids and mouse models to reveal that CAFs generate iCAFs through IL-1-induced leukemia inhibitory factor expression and the Janus kinase/signal transducer and activator of transcription downstream signaling pathway, while TGF-β can antagonize this process by downregulating IL-1 receptor, type I expression and promoting the differentiation of CAFs into myofibroblast CAFs. Subsequently, Elyada *et al* (46) discovered a new subtype of CAFs in PDAC that express major histocompatibility complex class II and CD74 but not the classical costimulatory molecule, called 'antigen-presenting CAF.' The three subtypes are interchangeable. Wang *et al* (54) compared tumor heterogeneity among patients with PDAC with different degrees of fibroproliferation and found that there is a new subtype of CAFs a with highly activated metabolic state in patients with loose PDAC, which mainly plays a role in tumor development and progression by

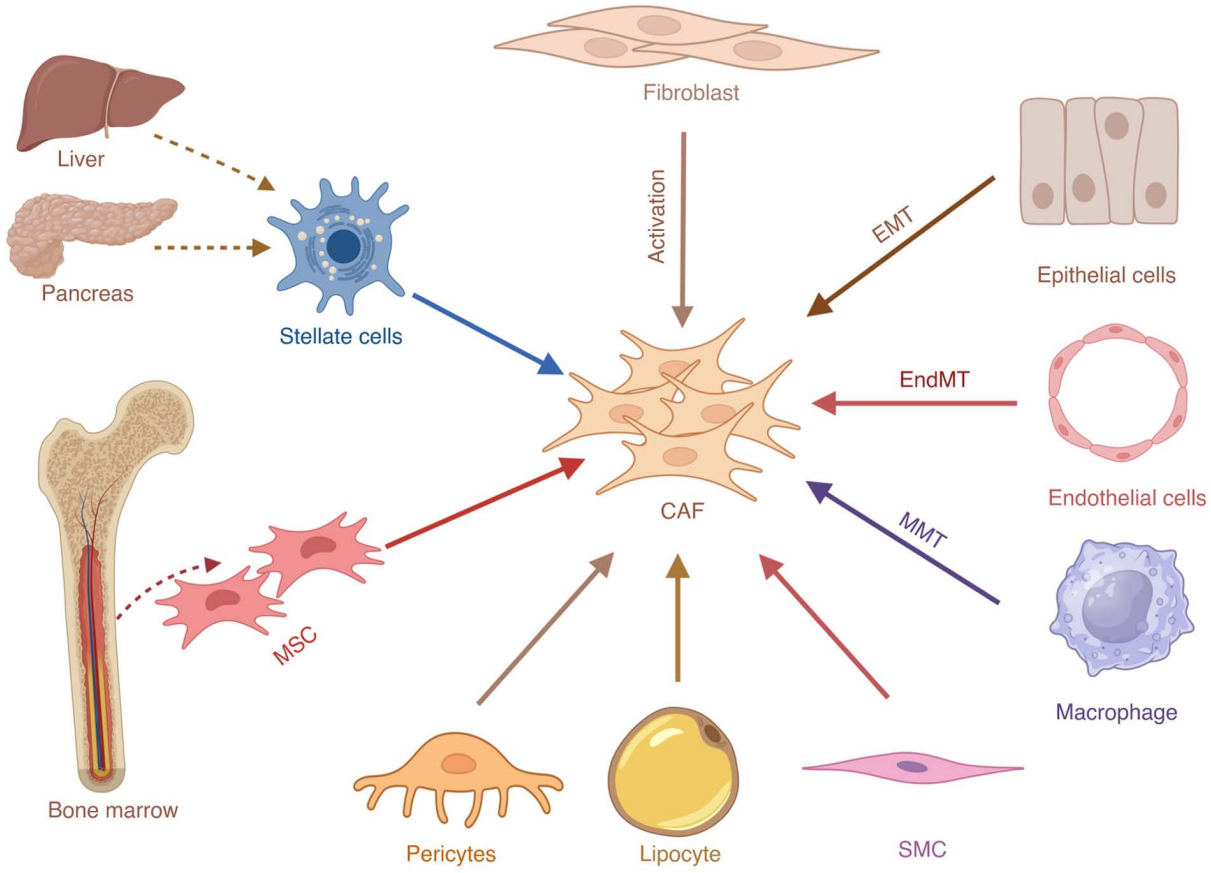

Figure 1. Illustration of the multiple cellular sources of CAFs. The primary source of activated CAFs is NFs. Additionally, the remaining cell types can differentiate into CAFs in various ways to participate in tumor progression. For example, bone marrow mesenchymal stem cells differentiate into CAFs through recruitment. Epithelial and endothelial cells and macrophages can be converted to CAFs through EMT, endothelial-mesenchymal transition and macrophage-myofibroblast transition, respectively. Smooth muscle cells and adipocytes are transdifferentiated into CAFs. (Created in BioRender. Li, R. (2025) https://BioRender.com/s03n609.) CAF, cancer-associated fibroblast; NF, normal fibroblast; EMT, epithelial-mesenchymal transition; MMT, mesothelial-to-mesenchymal transition; EndMT, endothelial-to-mesenchymal transition; MSC, mesenchymal stem cell; SMC, smooth muscle cells.

enhancing glycolytic metabolism. Additionally, Niu *et al* (55) found a lipid-rich subtype of CAFs in SET domain-containing 2-deficient PDAC that is involved in tumor progression by providing lipids for mitochondrial oxidative phosphorylation through the ATP-binding cassette, sub-family A, member 8a transporter, suggesting that PDAC is a tumor type with significant metabolic changes.

Other types of cancer have their own CAF subtypes. For example, Lambrechts *et al* (56) compared normal and tumor lung tissues to identify multiple stromal cell subtypes in the TME of patients with lung cancer. Subsequently, Cords *et al* (47) investigated the prognosis-relevant CAF subtypes in non-small cell lung cancer, including tumor-like CAFs, matrix CAFs, iCAFs and interferon-response CAFs. Among them, tumor-like CAFs and matrix CAFs were associated with poor prognosis, whereas iCAFs and interferon-response CAFs exhibited improved prognosis. Additionally, in gastrointestinal cancer, differences in the CAF subtypes were observed within tumor tissues at different sites. For example, Li *et al* (48) identified two CAF subtypes in gastric cancer, ECM CAFs and iCAFs, with ECM CAFs being a newly discovered subtype of CAF with high periostin expression. Roulis *et al* (49) identified a rare CAF subtype, 'pericryptal Ptgs2-expressing fibroblasts,' in the intestinal mesenchyme, which is involved in the progression of colorectal cancer (CRC). Rare CAF subtypes have been identified in breast cancer. Bartoschek *et al* (50) detected vascular, m, cycling and developmental CAF subtypes with different origins in mesenchymal cells in a mouse breast cancer model. A previous breast cancer study (57) analyzed the CAF subtypes using spatial transcriptomics and proteomics and found steady-state, mechanoresponsive and immunomodulatory CAF superclusters. The differences in the CAF subtypes between these two breast cancers may be due to differences in ethnicity and experimental techniques used. Notably, Ma *et al* (58) analyzed the CAF subtypes in six types of cancer and found that metabolic reprogramming occurs in subtypes of CAFs other than metabolic state CAFs. For example, matrix CAFs were enriched in fatty acid biosynthesis. Therefore, the role of CAFs in the TME may depend on metabolic reprogramming (Fig. 2).

3. Metabolic reprogramming of CAFs

In the TME, metabolic reprogramming is not limited to altering a single metabolic mode, but to the interaction of the entire metabolic network, including glucose, lipid and amino acid metabolism (59). CAFs are primary regulators of tumor

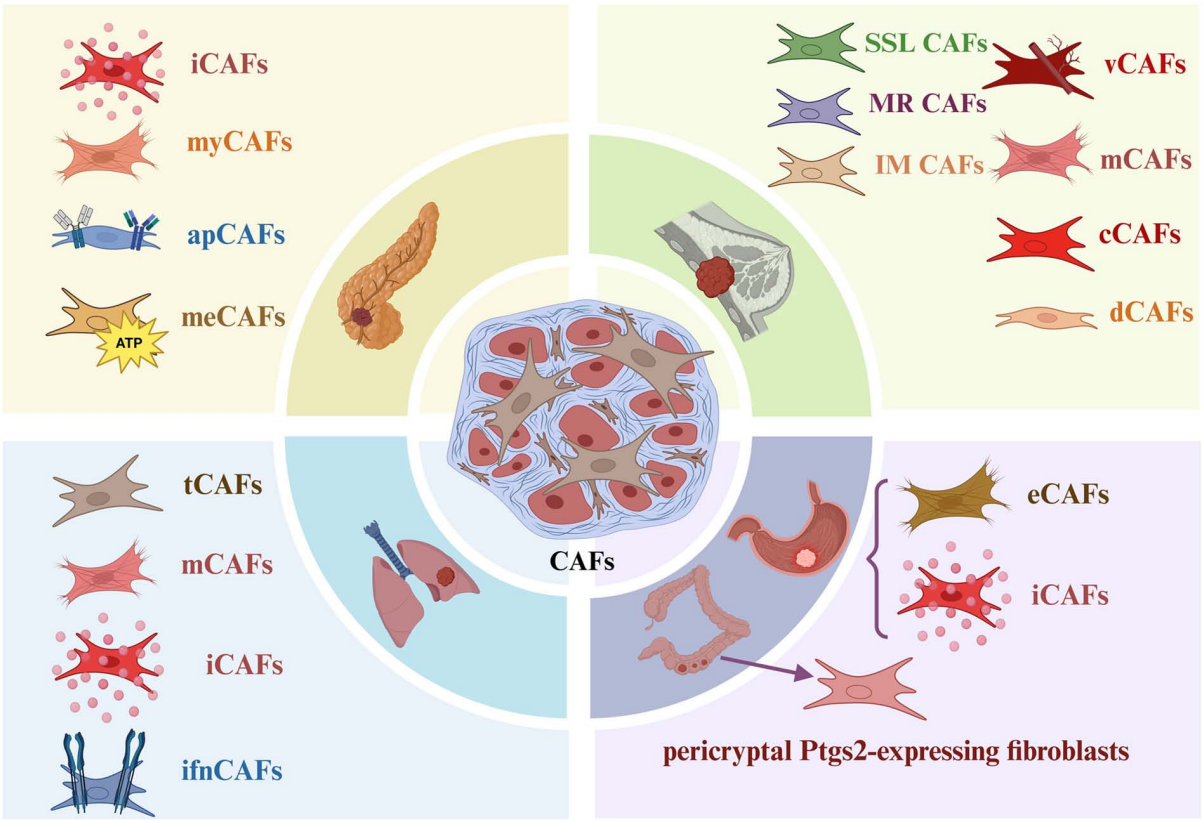

Figure 2. Summary of functional CAF subtypes predominantly found in PDAC and non-small cell lung, gastrointestinal and breast cancers. (Created in BioRender. Li, R. (2025) https://BioRender.com/24ea6hh.) CAF, cancer-associated fibroblast; PDAC, pancreatic ductal adenocarcinoma; iCAFs, inflammatory CAFs; myCAFs, myofibroblast CAFs; apCAFs, antigen-presenting CAFs; meCAFs, metabolic CAFs; tCAFs, tumor-like CAFs; mCAFs, matrix CAFs; ifnCAFs, interferon-response CAFs; eCAFs, extracellular matrix CAFs; vCAFs, vascular CAFs; mCAFs, matrix CAFs; cCAFs, cycling CAFs; dCAFs, developmental CAFs; SSL CAFs, steady state-like CAFs; MR CAFs, mechanoresponsive CAFs; IM CAFs, immunomodulatory CAFs.

metabolism (60); accordingly, the present study has summarized the mechanisms of metabolic reprogramming in CAFs (Fig. 3).

Reverse 'Warburg effect'. Even under normoxia, CAFs preferentially convert glucose to lactate via aerobic glycolysis, a phenotype driven by factors such as TGF-β and exacerbated by hypoxia. TGF-β1 enhances glucose uptake by upregulating glucose transporter 1 (GLUT1) via Smad2/3, p38 mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) activation. Under hypoxia, hypoxia-inducible factor-1α (HIF-1α) directly activates GLUT1 transcription (61) and inhibition of prolyl hydroxylase-mediated hydroxylation stabilizes HIF-1α (62). For example, hypoxic gastric cancer cells upregulate circNRIP1 acts as a sponge for miR-138-5p, relieving HIF-1α inhibition and enhancing glycolysis (63). HIF-1α can also be stabilized by TGF-β1 or platelet-derived growth factor, which downregulate isocitrate dehydrogenase 3α via miR-424, causing α-ketoglutarate depletion and prolyl hydroxylase 2 inhibition (64). Furthermore, TGF-β1 and HIF-1α augment glycolytic flux by upregulating key enzymes, hexokinase 2, 6-phosphofructo-2-kinase/fructose-2,6-bis-phosphatase 3 and pyruvate kinase M2 (65-67).

Mitochondrial dysfunction is a key driver of the metabolic shift from oxidative phosphorylation to aerobic glycolysis in CAFs, a process regulated by multiple mechanisms. ROS are critical mediators of mitochondrial retrograde signaling (68). External stimuli, such as radiation, damage mitochondria, elevating ROS levels that progressively harm both the fibroblast nucleus and mitochondria (69). Dysregulated mitochondrial calcium homeostasis also plays a role in ovarian cancer; specifically, overexpression of mitochondrial calcium uptake 1 inhibits pyruvate dehydrogenase, blocking pyruvate entry into the TCA cycle and enhancing glycolysis (70). Additionally, Sung *et al* (71) showed that triple-negative breast cancer cells overexpress integrin β4 and secrete it via exosomes, which CAFs internalize. This triggers c-Jun and AMP kinase phosphorylation, activates BNIP3L-mediated mitophagy and induces hyperglycolysis with excessive lactate secretion.

Lactate, the end product of CAF glycolysis, reinforces its own production through multiple positive feedback mechanisms, promoting a glycolytic metabolic network (72). Intracellularly, lactate catalyzes histone lysine lactylation to upregulate glycolytic genes (73) and stabilizes HIF-1α. For example, Kozlov *et al* (74) showed that lactate reduces prolyl hydroxylase phosphorylation and increases ROS, thereby stabilizing HIF-1α, boosting transcription and protein levels of glycolytic enzymes and driving the shift from oxidative phosphorylation to glycolysis in fibroblasts. Lactate also binds its G-protein coupled receptor GPR81, activating downstream signaling in an autocrine manner to further enhance glycolysis (75). Specifically, lactate, acting via GPR81, reduces intracellular cAMP levels, thereby inhibiting protein kinase A

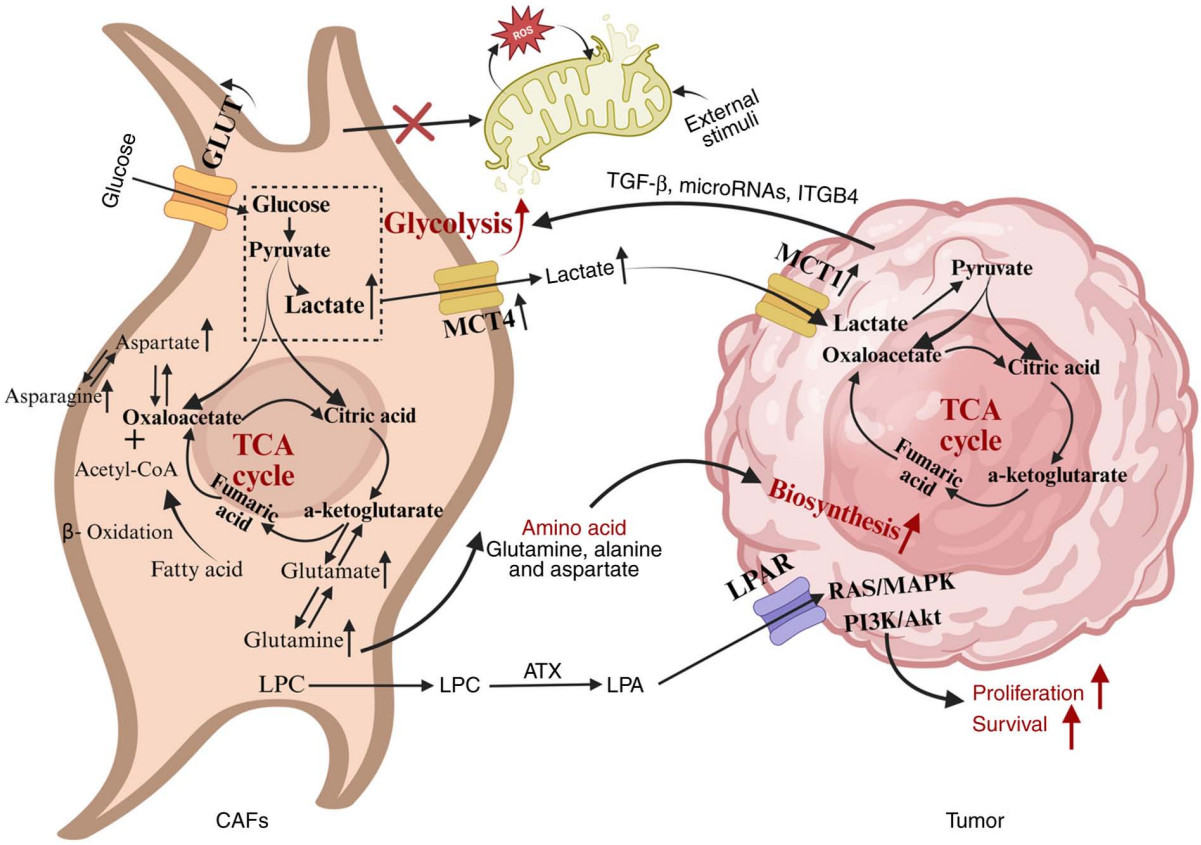

Figure 3. Metabolic crosstalk between CAFs and tumor cells. CAFs. CAF, cancer-associated fibroblast; GLUT, glucose transporter; TCA cycle, tricarboxylic acid cycle; MCT, monocarboxylate transporter; TGF-β, transforming growth factor-beta; ITGB4, integrin subunit beta 4; LPC, lysophosphatidylcholine; ATX, autotaxin; LPA, lysophosphatidic acid; LPAR, lysophosphatidic acid receptor; RAS, rat sarcoma; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; Akt, Protein Kinase B (Created in BioRender. Li, R. (2025) https://BioRender.com/wuur2w0).

activation. This process suppresses protein kinase A-induced ubiquitination of HIF-1α, leading to its stabilization (76,77). Lactate can also activate the PI3K/Akt signaling pathway via GPR81, which promotes the translocation of GLUT1 to the plasma membrane and activates glycolytic enzymes (78). Extracellularly, lactate within the TME can also enhance glycolysis through various mechanisms. For instance, lactate efflux acidifies the surrounding microenvironment, activating matrix metalloproteinases 2 and 9 to degrade the ECM. This process releases latent TGF-β, which then activates the TGF-β receptor/PI3K signaling pathway to synergistically enhance glycolysis (79).

Amino acid metabolism. Glutamine (Gln) is central to amino acid metabolic reprogramming in CAFs. CAFs exhibit a pronounced dependency on Gln; Gln-sensing activates the TRAF6-p62 complex, driving Akt2-mediated polarization and invasion (80). In triple-negative breast cancer (81), estrogen activates the G-protein-coupled estrogen receptor in CAFs, initiating a cAMP/protein kinase A/CREB signaling axis that upregulates Gln synthetase, which increases Gln synthesis. CAFs then catabolize Gln into metabolites readily taken up by tumor cells. For example, in PDAC, tumor cells stimulate pancreatic stellate cells to undergo autophagy, degrading cellular proteins to produce non-essential amino acids such as alanine, which tumor cells take up as an alternative carbon source to fuel the TCA cycle (82).

ECM remodeling is critical for tumor invasion and CAFs are the main producers of ECM components. They facilitate ECM production by using Gln for *de novo* proline synthesis, enabled by high expression of the rate-limiting enzyme pyrroline-5-carboxylate reductase 1 (83,84). Proline also contributes to other aspects of tumorigenesis (85). Under stress conditions such as glucose deprivation, proline, glutamine and their derivatives serve as alternative energy sources. Mitochondrial proline dehydrogenase/proline oxidase degrades proline into glutamate, which is subsequently converted to α-ketoglutarate for TCA cycle entry. This pathway also generates pyrroline-5-carboxylate, ATP and ROS. Moreover, ornithine, glutamate and proline interconvert dynamically.

CAFs also highly express arginase, dominating arginine metabolism to create an immunosuppressive microenvironment. In PDAC, hypoxia induces arginase II in CAFs, converting arginine to ornithine. Local arginine depletion impairs tumor-infiltrating T-cell function and fosters immunosuppression (86).

Lipid metabolism. Lipid metabolic reprogramming in CAFs drives tumorigenesis. Upstream signaling factors, including TGF-β and lysophosphatidic acid, initiate this reprogramming and trigger downstream events (87). To meet the high lipid demands of both CAFs and tumor cells, CAFs acquire lipids via exogenous uptake and endogenous *de novo* synthesis. They overexpress transporters such as CD36, which mediates

Table I. Specific mechanisms by which metabolic reprogramming of CAFs promotes tumor proliferation.

First author/s, year	Type of tumor	Metabolic mode	Activating factors	Mechanism	(Refs.)
Martinez-Outschoorn *et al*, 2014/Becker *et al*, 2020	Breast, prostate, and head and neck cancers	Glycolysis	Anoxia/Inflammatory factors	ROS/HIF-1α/ NF-κB Axis	(101/103)
Fiaschi *et al*, 2012	Prostate cancer	Aerobic glycolysis	Cancer cell-CAF contact	HIF1-SIRT3 Axis	(102)
Li *et al*, 2020	Breast cancer	Glycolysis	Exosomes	SNHG3/miR-330-5p/ PKM Axis	(104)
Zhang *et al*, 2020	Oral squamous cell carcinoma	Glycolysis	ITGB2	PI3K/AKT/mTOR Pathway	(105)
Yang *et al*, 2016	Ovarian carcinoma	Amino acid metabolism	Nutrient scarcity in the TME	Glutamine Anabolic Pathway	(107)
Linares *et al*, 2017	Prostate cancer	Amino acid metabolism	P62 deficiency	P62/ATF4 Axis	(108)
Mishra *et al*, 2018	Prostate cancer	Amino acid metabolism	Androgen signaling deprivation therapy	RASAL3/Ras/Axis Macropinocytosis	(109)

AFT4, activating transcription factor 4; CAFs, cancer-associated fibroblasts; HIF-α, hypoxia-inducible factor 1-α; mTOR, mammalian target of rapamycin; NFκB, nuclear factor-κB; PKM, pyruvate kinase M; RASAL3, RAS-activating protein-like 3; ROS, reactive oxygen species; SIRT3, sirtuin 3; SNHG3, small nucleolar RNA host gene 3.

fatty acid and oxidized LDL uptake in triple-negative breast cancer (88) and hepatocellular carcinoma (89) and members of the fatty acid transport protein family (90). When exogenous lipids are scarce, CAFs upregulate *de novo* synthesis enzymes; for example, 17β-estradiol (E2)/G1 activates epidermal growth factor receptor-extracellular signal-regulated kinase 1/2 signaling to upregulate fatty acid synthase expression and lipid production (91). A key outcome is lipid droplet formation to nourish tumor cells. Under hypoxia, HIF-1α induces stearoyl-CoA desaturase 1, expanding lipid droplet stores (92). Lipid droplets release free fatty acids for mitochondrial β-oxidation and CAFs transfer lipids via exosomes to support tumor progression (93).

Various products generated from CAF lipid metabolic reprogramming can also act on tumor cells. Lipid signaling molecules, for instance, can bind to specific receptors on the surface of CAFs, activating them and promoting their conversion to a pro-tumorigenic phenotype. TGF-β stimulates sphingosine kinase 1 to produce sphingosine-1-phosphate, which then binds to sphingosine-1-phosphate receptors 2 and 3, leading to p38 MAPK phosphorylation. This drives differentiation of CAF cells and their secrete of factors that promote ovarian cancer cell invasion (94). In PDAC, activated pancreatic stellate cells secrete large quantities of lipids, particularly lysophosphatidylcholine that is hydrolyzed to lysophosphatidic acid by the autocrine enzyme autotaxin, which in turn promotes the proliferation and migration of PDAC cells by activating the Akt2 signaling pathway (95). Under persistent pathological stimulation, human pancreatic stellate cells upregulate cyclooxygenase-2 to produce prostaglandin E2, which modulates the pro-fibrotic activity of the cells via the EP4 subtype of the prostaglandin E2 receptor (96). Furthermore, products such as ketone bodies and fatty acids generated by CAFs serve as important energy sources for tumor cells. For example, under conditions of Cav-1 loss or serum starvation, CAFs activate ketogenic enzymes to secrete ketone bodies, which are then transported into cancer cells via MCT1 to drive mitochondrial biogenesis and promote tumor progression (97).

4. Role of metabolic reprogramming of CAFs in tumor development and progression

Metabolic reprogramming of CAFs promotes tumor proliferation. Tumor cell proliferation can be monitored using the Ki-67 proliferation index employing immunohistochemistry or the mitotic count using hematoxylin and eosin staining (98). Tumor cell proliferation is central to carcinogenesis; the faster its proliferation, the higher the degree of tumor malignancy (99). In the TME, tumor cells promote their own proliferation and other components, such as CAFs, are also involved in this process (100). Additionally, metabolic reprogramming may affect the survival of cancer stem cells (99). Therefore, the role of the metabolic reprogramming of CAFs in tumor cell proliferation are summarized in Table I. CAFs can participate in tumor cell proliferation by reprogramming glucose metabolism through various regulatory factors. A previous study found that in various types of cancer, such as breast and prostate cancers, there is a metabolic coupling between CAFs and tumor cells. The specific mechanism is that tumor cells drive glycolysis in CAFs through HIF1-α and nuclear factor-κ-B to produce mitochondrial fuels such as lactic acid, ketone bodies, fatty acids, glutamine and

Table II. Specific mechanisms by which metabolic reprogramming of CAFs promotes tumor migration.

First author/s, year	Type of tumor	Metabolic mode	Activating factors	Mechanism	(Refs.)
Liu *et al*, 2020	Hepatocellular carcinoma	Aerobic glycolysis	ECM Stiffness	MAPK-YAP Pathway	(115)
Wu *et al*, 2020	Nasopharyngeal carcinoma	Aerobic glycolysis	Extracellular vesicle-packaged LMP1	NF-κB p65 Pathway	(116)
Gong *et al*, 2020	Colorectal cancer	Lipid metabolism	Elevated FASN Expression	Lipid Trafficking	(117)
Wang *et al*, 2024	Hepatocellular carcinoma	Lipid metabolism	Lipid metabolism	CD36-dependent Signaling Hub for CAF Activation	(118)
Sun *et al*, 2019	Breast cancer	Glycolysis	Anoxia	Oxidized ATM-Orchestrated Glycolytic Reprogramming	(119)
Shan *et al*, 2017	Pancreas cancer	Aerobic glycolysis	Aerobic glycolysis	Unidirectional Lactate Shuttle from CAFs to Cancer Cells	(120)
Mestre-Farrera *et al*, 2021	Epithelial tumor	Amino acid metabolism	TGFβ-Snail1	TRAF6-p62-Akt2 Axis	(80)

Akt2, protein kinase B 2; ATM, Ataxia-Telangiectasia Mutated; CAF, cancer-associated fibroblast; ECM, extracellular matrix; FASN, fatty acid synthase; LMP1, latent membrane protein 1; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; Snail1, Zinc finger protein SNAI1; TGFβ, transforming growth factor beta; TRAF6, tumor necrosis factor receptor associated factor 6; YAP, yes-associated protein.

other amino acids, which provide nutrients for tumors and participate in tumor growth (101). This phenomenon has been confirmed in prostate cancer (102). A previous study on breast cancer (103) have found that isolated CAFs exhibit a glycolytic phenotype and produce lactate and pyruvate; when the consumption of lactate production is inhibited, the metabolic pattern of CAFs is altered, thereby hindering tumor growth. A previous study (104) explored the specific mechanism of the glycolytic phenotype expressed by CAFs in breast cancer; small nucleolar RNA host gene 3 in exosomes secreted by CAFs can increase pyruvate kinase M expression by positively regulating its expression, then transitioning to a pro-glycolytic phenotype. Additionally, in oral squamous cell carcinoma, the high expression of integrin subunit β 2 in CAFs can lead to the regulation of the PI3K-serine-threonine kinase-mammalian target of the rapamycin signaling pathway, enhancement of the glycolytic pathway, increase in the secretion of lactic acid and promotion of tumor cell proliferation (105).

Other metabolic patterns of CAFs change tumor cell proliferation. CAFs can synthesize amino acids through the TCA to provide carbon and nitrogen sources for tumor cells and participate in tumor cell proliferation (106). For example, in ovarian cancer, CAFs promote Gln production by upregulating the Gln anabolic pathway. Gln is absorbed by ovarian cancer cells and converted to glutamate by glutaminase, thereby maintaining tumor cell proliferation (107). P62-deficient CAFs can also produce asparagine by activating glucose carbon flux through the pyruvate carboxylase-asparagine synthase cascade, which is involved in tumor growth as a nitrogen source for stromal and tumor epithelial proliferation (108). Additionally, crosstalk exists between amino acid metabolism in tumor cells and CAFs that promote tumor proliferation. A prostate cancer study (109) demonstrated that epigenetic silencing of CAFs can drive macropinocytosis-mediated Gln synthesis. This promotes tumor cell proliferation by increasing the TCA flux after Gln is absorbed by tumor cells. Lipids are the basis of tumor proliferation. However, there is no study confirming the effect of lipid metabolism in CAFs on tumor cell proliferation and further exploration is needed.

Metabolic reprogramming of CAFs promotes tumor migration and invasion. The directed migration or invasion of the tumor into adjacent tissues, which is the initial stage of tumor metastasis, is a hallmark of cancer (110). This process involves tumor cells gaining the ability to actively move and migrate directionally to adjacent noncancerous tissues, known as the 'invasion front (margin)', wherein they approach the edge of adjacent noncancerous tissues (111); tumor cells then cross the adjacent basement membrane and invade surrounding tissues through EMT (112). Previous studies have revealed that the metabolic reprogramming of CAFs can participate in tumor migration and invasion (Table II). During tumor formation, tumors act on tumor cells by generating various forces that cause dynamic changes in behavior (113,114). In this manner, ECM hardness can affect hepatocellular carcinoma migration. The specific mechanism involves a hardened ECM that upregulates aerobic glycolysis through the MAPK-Yes-associated protein signaling cascade (115). In nasopharyngeal carcinoma, the extracellular vesicles package Epstein-Barr virus-encoded latent membrane protein 1 that activates NFs, which transform into CAFs and activated CAFs undergo aerobic glycolysis and autophagy, promoting tumor migration and formation of a premetastatic microenvironment (116). This process alters the lipid metabolism patterns. For example, Gong *et al* (117) found that fatty acid synthase in CAFs in CRC was markedly increased compared with that in NFs and that small-molecule

Table III. Specific mechanisms by which metabolic reprogramming of CAFs promotes tumor vascularization.

First author/s, year	Type of tumor	Metabolic mode	Activating factors	Mechanism	(Refs.)
Bonuccelli *et al*, 2010	Breast cancer	Aerobic glycolysis	Caveolin-1 deficiency	Glycolysis-Angiogenesis Axis	(126)
Li *et al*, 2022	Oral squamous cell carcinoma	Glycolysis	Glycolysis	PGC-1α/PFKFB3-Angiogenesis signaling axis	(128)
Zhou *et al*, 2018	Hepatocellular carcinoma	Lipid metabolism	miR-21-Enriched Exosomes	PDK1/Akt pathway	(129)
Hsu *et al*, 2023	Colorectal cancer	Lipid metabolism	KRAS	TFCP2-BMP4/WNT5B Axis	(130)
Verginadis *et al*, 2022	Melanoma and pancreatic tumors	Amino acid metabolism	ATF4	ATF4-Col1a1 Axis	(131)

AFT4, activating transcription factor 4; Akt, protein kinase B; BMP4, bone morphogenetic protein 4; Cola1, Collagen, type I, alpha 1; KRAS, Kirsten rat sarcoma viral oncogene homologue; PDK1, 3-phosphoinositide-dependent protein kinase-1; PFKFB3, 6-phospho-fructo-2-kinase/fructose-2,6-biphosphatase 3; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1alpha; TFCP2, transcription factor CP2; WNT5B, Wnt Family Member 5B.

metabolites of CAFs could promote the migration of CRC cells. In the TME, tumor cells secrete cytokines that activate quiescent fibroblasts. Moreover, activated CAFs exhibit increased active lipid levels, increased lipid content and lipid phagocytosis and thereby promote tumor cell migration through CD36 lipid metabolism reprogramming (118).

Tumor invasion includes multiple processes, such as promotion of EMT occurrence, ECM remodeling and enhanced angiogenesis and lymphangiogenesis (Table II). For example, it has been found that CAFs in breast cancer can enhance glycolysis, which produces lactate. This involves oxidizing ataxia-telangiectasia mutated kinase, which further activates the TGFβ1/MAPK signaling pathway and affects the mitochondrial activity of tumor cells to promote tumor invasion (119). The levels of key enzymes mediating aerobic glycolysis, such as lactate dehydrogenase B and pyruvate kinase M2 in CAFs in pancreatic cancer are increased, enhancing aerobic glycolysis and promoting pancreatic cancer cell invasion through 'tumor-stromal' metabolic coupling (120). Additionally, CAFs are Gln-dependent and when Gln is deficient, serine-threonine kinases regulate the migration and invasion of CAFs into Gln-rich regions, thereby promoting tumor epithelial cell invasion into adjacent tissues (80). ECM sclerosis is linked to Gln metabolism and forms a metabolic network in which various fuel sources promote tumor invasion (106).

Metabolic reprogramming of CAFs promotes tumor neovascularization. In the TME, the proliferation and differentiation of tumor cells require adequate oxygen and nutrients from blood vessels (121). Therefore, tumor neovascularization is closely related to the occurrence and development of tumors. Tumor neovascularization is the creation of blood vessels based on the original capillaries or post-capillary venules (122,123). This process involves the interaction of multiple growth factors and signaling pathways (124). Metabolic reprogramming of CAFs is a key factor in angiogenesis (Table III), including changes in multiple metabolic pathways, such as glucose, lipid and amino acid metabolism (125). In breast cancer, caveolin-1-deficient CAFs can upregulate the expression of glycolytic enzymes, provide energy through paracrine means and promote tumor angiogenesis (126). Fructose-2,6-biphosphatase 3, a metabolic enzyme that regulates glucose metabolism, is involved in glucose metabolism in CAFs in oral cancer to promote the growth of tumor tissues (127) by enhancing the pro-angiogenic phenotype (128). Additionally, hepatic stellate cells, which are unique to HCC, can be transformed into CAFs under the influence of tumor cells, induce abnormal lipid metabolism and secrete angiogenic cytokines to participate in the occurrence and development of tumors (129). In CRC, the oncogenic Kirsten rat sarcoma viral oncogene homolog activates transcription factor CP2 to upregulate bone morphogenetic protein 4 and wingless-type mammary tumor virus integration-site family member 5B adipogenesis factors, converting CAFs into lipid-rich CAFs, producing vascular endothelial growth factor A and stimulating tumor angiogenesis (130). Verginadis *et al* (131) found a strong correlation between activating transcription factor 4 in melanoma and pancreatic tumors and glycine and proline levels, the main amino acids of collagen. Activating transcription factor 4-deficient CAFs has been found to inhibit angiogenesis.

Metabolic reprogramming of cancer-associated fibroblasts promote tumor metastasis. Tumor metastasis is the leading cause of antineoplastic therapy failure and mortality in most patients with cancer (132). Tumor cells leave their primary organs to colonize and grow in distant organs, including the brain, lungs, liver and bone (133). Previous studies have revealed that NFs undergo metabolic changes after differentiating into CAFs, which promotes tumor metastasis (134) (Table IV). For example, in ovarian cancer cell lines, CAFs stimulate glycogen mobilization, which supports glycolysis in tumor cells and is involved in tumor metastasis (135). CRC liver metastasis is achieved by TGF-β1-induced conversion of

Table IV. Specific mechanisms by which metabolic reprogramming of CAFs promotes tumor metastasis.

First author/s, year	Type of tumor	Metabolic mode	Activating factors	Mechanism	(Refs.)
Curtis *et al*, 2019	Ovarian cancer	Glycolysis	CAFs	p38α MAPK pathway	(135)
Wang *et al*, 2024	Colorectal cancer liver metastases	Glycolysis	TGFβ1	Src-SH3BP5-Rab11 Axis	(136)
Zhang *et al*, 2022	Colorectal cancer liver metastases	Lipid metabolism	HSPC111-containing exosomes	CXCL5-CXCR2 Axis	(137)
Li *et al*, 2019	Gastric cancer liver metastases	Aerobic glycolysis	TGF-β1	A Positive Feedback Loop involving the TGF-β1-LOX Axis and Aerobic Glycolysis	(138)

CAF, cancer-associated fibroblast; CXCL, C-X-C motif chemokine receptor; LOX, lysyl oxidase; MAPK, mitogen-activated protein kinase; Rab11, Ras related proteins in brain type 11; SH3BP5, SH3 domain-binding protein 5; TGFβ1, transforming growth factor β 1.

Table V. Specific mechanisms by which metabolic reprogramming of CAFs promotes tumor drug resistance.

First author/s, year	Type of tumor	Metabolic mode	Activating factors	Mechanism	(Refs.)
Wu *et al*, 2020	Nasopharyngeal carcinoma	Aerobic glycolysis	LMP1-containing EBV exosomes	NF-κB p65 pathway	(116)
Gong *et al*, 2020	Breast cancer	Amino acid metabolism	PDAC-CAF Interaction	Mitochondrial Oxidative Metabolism	(117)
Mishra *et al*, 2018	Prostate cancer	Amino acid metabolism	androgen signaling deprivation therapy	The Ras-Macropinocytosis-Glutamine Metabolic Axis	(109)

CAF, cancer-associated fibroblast; EBV, Epstein-Barr virus; LMP1, latent membrane protein 1; NF-κB, nuclear factor-κB; PDAC pancreatic ductal adenocarcinoma.

hematopoietic stem cells into pro-metastatic CAFs, resulting in increased glucose uptake and glycolysis. The specific mechanism involves the combination of steroid receptor coactivator SH3 domain and SH3 domain-binding protein that forms the steroid receptor coactivator/SH3 domain-binding protein/Rab11/GLUT1 complex, which activates Rab11-dependent plasma membrane GLUT1 transport under TGF-β1 stimulation (136). Additionally, the CRC cell-derived exosome HSPC111 reprograms the lipid metabolism of CAFs, promoting the formation of a premetastatic microenvironment and CRC liver metastasis (137). Li *et al* (138) screened for lysyl oxidase, a CAF-derived oxidase that promotes the formation of a microenvironment in liver-metastatic gastric cancer by enhancing the Warburg effect.

Metabolic reprogramming of CAFs promotes tumor drug resistance. Tumor drug resistance is a challenge for patients with cancer receiving anti-tumor therapy (139). Tumor cells do not respond to anti-tumor therapy when they are insensitive to anti-tumor drugs (primary resistance) and when they initially respond well to anti-tumor drugs, but the latter cannot achieve long-term benefits (secondary drug resistance) (140). Additionally, various tumor resistance mechanisms have been identified (141), including overexpression of ATP-binding cassette transporter excretion of drugs, EMT, cancer stem cells, cytoprotective autophagy, apoptosis and gene mutations. Tumor drug resistance is caused by the tumor cells and other cells in the TME, including CAFs. Zaal and Berkers (142) summarized the metabolic alterations associated with resistance to different antineoplastic drugs and found that the metabolic state of cells largely influences their therapeutic efficacy. Tumor cells adjust their metabolism to antineoplastic drugs through different mechanisms, such as maintaining a high glycolysis rate, switching glycolytic metabolites to the biosynthetic pathway and rewiring glutamine metabolism in mitochondria. A previous study found that metabolic alterations were associated with resistance to treatment. Broekgaarden *et al* (143) used a 3D culture model of PDAC and CAFs and found that metabolic alterations in tumor-matrix interactions caused statistically significant resistance of CAFs to anti-tumor drugs shown using high-throughput imaging or image analysis tools. Studies have proposed that specific metabolic pathway changes, such as in aerobic glycolysis and amino acid metabolism, are related to treatment resistance

(Table V). For example, aerobic glycolysis of activated CAFs promotes the development of radiotherapy resistance in nasopharyngeal carcinoma cells (116). Ko *et al* (144) found that autophagic fibroblasts in breast cancer may be a significant source of glutamine and stromal fibroblasts and that glutamine exerts a synergistic effect that renders breast cancer cells resistant to tamoxifen. Additionally, Mishra *et al* (109) found that antagonizing Gln uptake (which involves CAF-driven micropinocytosis) in prostate cancer, restores the sensitivity to androgen deprivation therapy.

5. Clinical trials targeting metabolic reprogramming in CAFs

CAFs possess intrinsic characteristics that make them more amenable to therapeutic targeting than tumor cells. Their unique metabolic programs supply essential nutrients to tumor cells and support multiple stages of tumorigenesis. Metabolic reprogramming is central to meeting tumor energetic demands and adapting to the malignant microenvironment, making it a key vulnerability. Disrupting core CAF metabolic pathways thus represents a promising strategy to prevent cancer dissemination and recurrence and several clinical trials are underway. In CAFs exhibiting hyperactive glycolysis, the inhibitor 2-deoxy-D-glucose competitively blocks GLUTs and hexokinase, suppressing glycolysis and lactate secretion and depriving tumor cells of a critical energy source. This approach has been validated in patients with glioma and advanced solid tumors, where it also delayed repair of radiation- and chemotherapy-induced damage (145,146). The sensitizing effect of lonidamine, a direct hexokinase inhibitor, has also been demonstrated in solid tumors, including advanced breast, ovarian and lung cancers (147). Furthermore, clinical trials targeting lipid metabolic reprogramming in CAFs have focused primarily on fatty acid synthesis and oxidation. Since recurrent high-grade astrocytomas overexpress fatty acid synthase to fuel lipid biosynthesis and proliferation, combining the fatty acid synthase inhibitor TVB-2640 with bevacizumab nearly doubled the 6-month progression-free survival rate vs. bevacizumab alone (31.4 vs. 16%) (148). Similar clinical trials are ongoing for other types of cancer, including non-small cell lung cancer, breast, ovarian, prostate, colon and pancreatic cancers (148). Preclinical studies have confirmed that inhibiting acetyl-CoA carboxylase, a key rate-limiting enzyme in *de novo* fatty acid synthesis, with ND-646 can also control non-small cell lung cancer growth (149). Additionally, fatty acid β-oxidation is a crucial energy source for numerous tumor cells. It has been discovered that carnitine palmitoyltransferase 1 (CPT1) is not only the rate-limiting enzyme of fatty acid oxidation (150) but also essential for maintaining mitochondrial structure and function (151). Gugiatti *et al* (152) reported that microenvironment-activated chronic lymphocytic leukemia cells rely on carnitine palmitoyltransferase1A-mediated fatty acid oxidation to fuel proliferation and that combining the carnitine palmitoyltransferase1A inhibitor ST1326 with venetoclax produces a synergistic antitumor effect. Therapeutic targeting also has a focus on Gln metabolism: Gln is converted to glutamate by glutaminase and glutamate then fuels the TCA cycle. A Phase I study demonstrated that the glutaminase inhibitor telaglenastat (CB-839) has a favorable safety profile, pharmacokinetics/pharmacodynamics and antitumor activity in patients with solid tumors (153). Subsequent studies confirmed the efficacy of CB-839 in melanoma, renal cell carcinoma and non-small cell lung cancer, where it sensitizes tumors to other therapies and reverses drug resistance (154,155).

6. Conclusions and outlook

The occurrence and development of tumors are inseparable from the energy supply (156). A previous study found that most of the energy requirements of tumor tissues are due to changes in metabolic pathways (157). In the TME, metabolic reprogramming occurs as a single metabolic pathway and interactions within the entire metabolic network (158). Based on the source heterogeneity and phenotypic plasticity of CAFs, the present review described the metabolic reprogramming of CAFs and its role in tumorigenesis and development, including tumor proliferation, migration and invasion, angiogenesis, metastasis and drug resistance. It aimed to clarify future research directions by understanding the relevant research on CAF metabolic reprogramming in oncology. CAFs are the primary regulators of the TME, which directly interact with tumor cells and regulate immune cells to affect the occurrence and development of tumors (159). Additionally, metabolic reprogramming can act on immune cells to assist tumor cells in immune escape (160). Therefore, future studies should explore whether metabolic reprogramming of CAFs may act on immune cells to affect the occurrence and development of tumors.

CAFs are genetically stable and have a low possibility of drug resistance (161). Therefore, CAFs may be a potentially effective therapeutic target. Previous studies have investigated the use of CAFs as therapeutic options, including determining biomarkers targeting CAFs (18), activating CAFs to reverse their resting state (162), targeting CAF-related signaling pathways (162), reducing interstitial pressure and improving drug delivery (163) and coating drugs targeting CAFs by nano-counting to improve drug delivery (164). However, none of these studies achieved good treatment results, which may be because of the different CAF subtypes in the different types of cancer. Dysregulation of energy metabolism has become a research hotspot, including the development of inhibitors that inhibit key metabolic enzymes such as mutant isocitrate dehydrogenase. Glutathione peroxidase 4 and nicotinamide phosphoribosyl transferase have exhibited sound anti-tumor effects. Different CAF subtypes can affect tumorigenesis and development through metabolic mode changes; therefore, it was concluded that tumor progression can be inhibited by interfering with CAF metabolic reprogramming.

Analysis of multiple studies reveals that the differences in the metabolic profiles of CAFs across various types of cancer are likely attributable to the heterogeneity of CAF subtypes. For instance, breast cancer-associated CAFs predominantly rely on a glycolytic metabolism, characterized by enhanced glycolysis and increased lactate secretion (73). The hypoxic microenvironment can induce epigenetic reprogramming of HIF-1α and glycolytic enzymes, which sustains a hyper-glycolytic phenotype in CAFs. This results in the production of excess lactate and pyruvate that are subsequently transported

to and utilized by cancer cells (103). Similarly, CAFs in melanoma (165) and head and neck squamous cell carcinoma (166) also primarily exhibit a high-glycolysis phenotype. PDAC is characterized by an abundant deposition of ECM by CAFs, with the ECM being primarily composed of collagen (167), which is rich in glycine, proline and their derivatives. Netrin G1 has been identified as a promoter of PDAC development; specifically, Netrin G1-positive CAFs support PDAC survival through Netrin G1-mediated glutamate/Gln metabolism (167). This suggests that PDAC-associated CAFs are mainly dependent on an amino acid-based metabolic program. By contrast, prostate cancer cells display a metabolic signature dominated by *de novo* fatty acid synthesis. Balaban *et al* (168) discovered that one subpopulation of prostate cancer cells (such as C4-2B) enhances fatty acid oxidation, while another (such as PC-3) increases triglyceride synthesis via DGAT1. Together, these distinct metabolic strategies cooperatively support the overall survival of the cancer cell population. Therefore, for clinical applications, scRNA sequencing can be employed to characterize the specific CAF subtypes present in individual patients across different cancers. This information can then guide the selection of the most appropriate inhibitors targeting the dominant CAF metabolic pathways.

Preclinical studies and early-phase clinical trials targeting CAF metabolic reprogramming have yielded encouraging preliminary results. However, translating these findings into effective clinical strategies remains a formidable challenge. First, the tumor microenvironment operates as an integrated metabolic network, which may activate compensatory pathways that lead to therapeutic resistance. Second, given the functional heterogeneity among CAF subtypes, the efficacy of monotherapeutic and non-selective targeting of CAF metabolism is unpredictable. Finally, therapeutic strategies targeting CAF metabolic reprogramming currently lack validation from large-scale, prospective studies to confirm their safety and efficacy profiles. Therefore, it was hypothesized that combining interventions against CAF metabolism with other anti-tumor therapies may be a viable therapeutic strategy. Research has found that metabolites from CAFs create an immunosuppressive TME, leading to resistance to immune checkpoint inhibitors in cancer patients (169). Targeting CAF metabolism to reduce the production of immunosuppressive metabolites can restore T-cell activity and have a sensitizing effect. Specifically, in soft tissue sarcoma, glycolytic CAFs not only form a physical barrier to block T-cell infiltration but also highly express GLUT1 to secrete CXCL16, which binds to CXCR6 on T-cells and impedes their migration into the tumor parenchyma. Targeting this immune barrier could potentially increase the efficacy of immune checkpoint inhibitors (170).

While molecularly targeted therapies are advancing towards the goal of precision medicine, the metabolic reprogramming of CAFs can help tumor cells survive the cytotoxic effects of these drugs by providing energy or metabolites. Co-targeting both CAF metabolic reprogramming and key gene mutations may reverse or delay the onset of resistance. For example, in renal cell carcinoma, monotherapy with signaling inhibitors such as cabozantinib or everolimus can easily lead to compensatory metabolic resistance. Emberley *et al* (171) attempted to add telaglenstat (CB-839) to inhibit glutaminase, thereby blocking glutaminolysis to cut off the tumor's energy supply and delay resistance. Targeting CAF metabolism can also reduce tumor cell self-repair and combining it with conventional anti-tumor therapies such as chemotherapy (172) or radiotherapy (173) may have a sensitizing effect. Currently, this combination strategy is still in the early stages of investigation and requires further research.

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RL and YL designed the review and wrote the manuscript. RL prepared the figures and tables. Data authentication is not applicable. Both authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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