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REVIEW

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Cancer associated fibroblasts and metabolic reprogramming: unraveling the intricate crosstalk in tumor evolution

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Abstract

Metabolic reprogramming provides tumors with an energy source and biofuel to support their survival in the malignant microenvironment. Extensive research into the intrinsic oncogenic mechanisms of the tumor microenvironment (TME) has established that cancer-associated fibroblast (CAFs) and metabolic reprogramming regulates tumor progression through numerous biological activities, including tumor immunosuppression, chronic inflammation, and ecological niche remodeling. Specifically, immunosuppressive TME formation is promoted and mediators released via CAFs and multiple immune cells that collectively support chronic inflammation, thereby inducing pre-metastatic ecological niche formation, and ultimately driving a vicious cycle of tumor proliferation and metastasis. This review comprehensively explores the process of CAFs and metabolic regulation of the dynamic evolution of tumor-adapted TME, with particular focus on the mechanisms by which CAFs promote the formation of an immunosuppressive microenvironment and support metastasis. Existing findings confirm that multiple components of the TME act cooperatively to accelerate the progression of tumor events. The potential applications and challenges of targeted therapies based on CAFs in the clinical setting are further discussed in the context of advancing research related to CAFs.

Keywords Cancer-associated fibroblasts, Metabolic reprogramming, Immune suppression, Inflammatory microenvironment, Tumor metastasis, Tumor therapy

Introduction

Tumor cell survival and proliferation require substantial energy consumption, to adapt to the malignant environment of hypoxia and nutrient deprivation, tumor cells must reprogramme metabolic pathways (that is, tumor pathological metabolic pathways encompass enhanced glucose uptake, augmented glycolysis, elevated lipid metabolism, and the activation of the pentose phosphate pathway, alongside mitochondrial alterations and the reconfiguration of the tricarboxylic acid cycle within tumor cells) via oncogenic signals, to generate sufficient energy and biosynthetic precursors that support tumor cell proliferation and metastasis [1, 2]. The energy metabolism is not only essential for the survival of tumor

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cell but also indispensable for non-tumor cells, including immune and stromal cells [3]. The competitive and immunosuppressive tumor microenvironment (TME) may be generated by the shared needs and nutrient competition between tumor/non-tumor cells resulting from metabolic reprogramming-mediated changes in immune cell phenotypes and release of inflammatory factors [4].

The TME is a highly complex and heterogeneous ecosystem comprising the tumor cells themselves, immune and stromal cells, and the cellular environment surrounding the tumor (including microvasculature, biomolecules, cytokines, and signaling molecules) [4, 5]. The metabolic program of individual regions within the TME has a strong influence on tumor development, which may be attributed to spatial heterogeneity of the constituent cell populations shaped by variations in the oxygen and nutrient supply across these regions [6, 7]. Considering the heterogeneity of tumor growth and nutritional differences among various tumor tissues, the availability of nutrients in the TME is suggested to be closely related to tumor type, tumor location, and nutritional status of the host [8]. To meet the cellular requirements for survival, cells in the TME adaptively utilize different nutrients and fuel proliferation and metastasis through metabolic heterogeneity, as reprogramming of cellular metabolism affects multiple steps in the metastatic cascade response (for instance, an acidic environment created due to accumulation of metabolic waste favors tumor progression) [9, 10]. Various biological behaviors including tumor immune escape, tumor proliferation and metastasis are closely related to the metabolism of matter and energy. Understanding the mechanism of metabolic reprogramming to promote tumor development and selectively controlling certain metabolic pathways in tumor cells may block the corresponding malignant phenotypes.

Cancer-associated fibroblasts (CAFs) are a crucial component of the TME that contribute significantly to tumor proliferation and dissemination. CAFs originate from multiple cell types and are characterized by elevated expression of specific markers, such as α-smooth muscle actin (α-SMA), fibroblast activation protein (FAP), fibroblast specific protein 1 (FSP1), and platelet-derived growth factor receptor (PDGFR)-α/β [11]. Compelling evidence indicates that CAFs regulate cancer progression in multiple ways through influencing tumor cell invasion and metastasis, stimulating angiogenesis, and inducing chemoresistance [12, 13]. Moreover, CAFs can remodel the tumor immune microenvironment (TIME), leading to tumor immune escape [14]. The tumor immune microenvironment is composed of several immune cell populations, including innate and adaptive immune cells, and cytokines secreted by immune cells [15]. CAFs achieve immunosuppressive effects through interactions with TIME, in particular, via intercellular communication with immune cells and inflammatory factors released by multiple cell types [16]. The immunosuppressive TME clearly limits the effectiveness of immunotherapy due to the production of cytokines that weaken the immune response of anti-tumor cells, such as T cells and macrophages [17], an effect attributed to metabolic dysfunction. CAFs and metabolic reprogramming may promote the phenotypic/functional changes in immune cells and chronic inflammation, eventually leading to tumor immune escape and unlimited proliferation [18]. In turn, proliferation of tumor cells further stimulates the development of CAFs and metabolic dysfunction, as well as the continued generation of an immunosuppressive TME, providing favorable conditions for the vicious cycle of tumor growth and metastasis [19]. To address this challenge and develop effective therapeutic interventions, systematic, in-depth evaluation of the mechanisms by which CAFs and metabolic reprogramming contribute to the establishment of immunosuppressive TME is essential. The current review focuses on the pathways by which CAFs promote tumor proliferation and metastasis (including metabolic reprogramming, immune-phenotypic shifts, and chronic inflammation) and tumor-targeted therapeutic strategies developed based on exploitation of CAFs.

Heterogeneity and plasticity of CAFs

Cellular phenotype heterogeneity of CAFs

CAFs are derived from a variety of cell types, among which tissue-resident fibroblasts or fibroblast-like cells, including hepatic and pancreatic stellate cells [20, 21]. Other sources of CAFs are epithelial or endothelial cells undergoing epithelial/endothelial-mesenchymal transformation, and circulating bone marrow-derived mesenchymal stem cells can also acquire a CAFs-like phenotype [22, 23]. CAFs obtained from different cellular precursors exhibit distinct cellular phenotypes and tumor functions. Single-cell sequencing technology has greatly advanced our understanding of the heterogeneity of CAFs in TME. Several CAFs subtypes have been identified to date, including myofibroblast CAFs (myCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs) (Fig. 1) [24, 25]. myCAFs are typically located near tumor cells, express high levels of αSMA, and release fewer inflammatory cytokines [26], while iCAFs are positioned further away from tumor cells and express lower levels of α-SMA but more inflammatory factors (including IL-6, IL-8, and IL-11) [20]. Both myCAFs and iCAFs are proposed to promote pancreatic and breast cancer immune escape and progression of malignant events through activation of STAT3 signaling [27, 28]. Earlier scRNA-seq and immunohistochemical analyses identified apCAFs expressing MHC II and CD74 but not classical

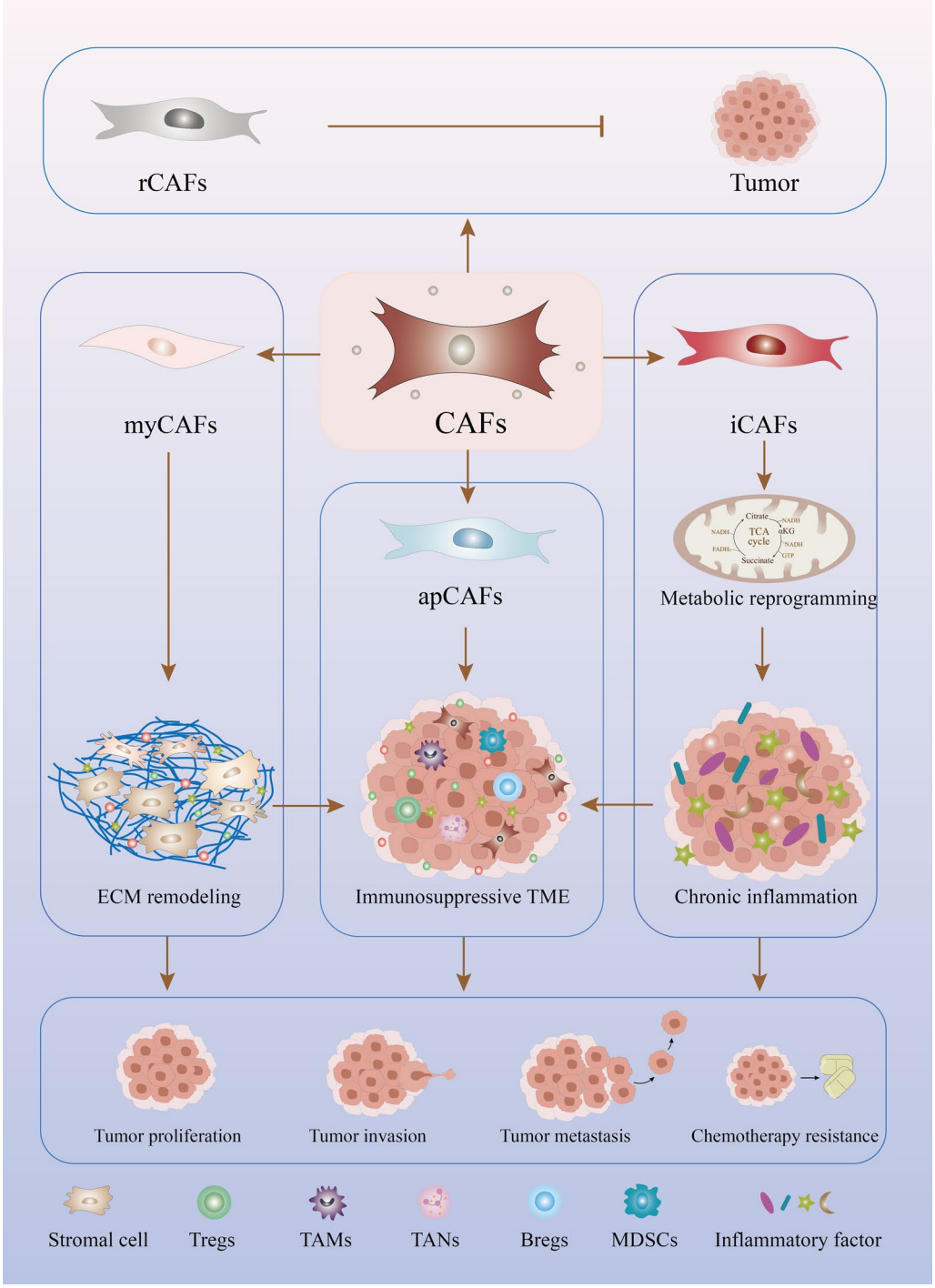

Fig. 1 CAFs are classified into a range of subgroups (iCAFs, apCAFs, myCAFs, and rCAFs). iCAFs, apCAFs, and myCAFs contribute to tumor proliferation, metastasis, invasion, and chemo-resistance in multiple ways. For example, myCAFs remodel through the ECM and iCAFs induce chronic inflammation through metabolic reprogramming, ultimately supporting an immunosuppressive TME and tumor progression

co-stimulatory molecules (e.g., CD80, CD86, CD40) [25]. The apCAFs subtype could present antigens and contribute to the suppression of T cell-mediated anti-tumor responses.

Biomarkers, such as FAP, CD29, α-SMA, FSP1, and PDGFRβ, may be effectively utilized to resolve CAFs subgroups with different characteristics in cancer (Table 1). In a single-cell sequencing study, based on biomarker

Table 1 Identification of CAFs via markers and elucidation of their role in tumor progression

Cancer type	CAFs marker	In vivo model	Findings	Ref.
BC	Cav-1	Human breast cancer tamoxifen resistance models: Co-injection of human breast cancer cells (MDA-MB-231) and stromal fibroblasts (wild-type vs. Cav-1-deficient)	Cav-1-deficient stromal fibroblasts release metabolites in a paracrine manner via glycolysis to support angiogenesis and proliferation in breast cancer	[266]
OSCC	α-SMA	Subcutaneous tumor mouse model: different groups of cells were injected into the abdomen of mice, including HSC3-Ctrl & CAFs-Ctrl, HSC3-Ctrl & CAFs-ITGB2	ITGB2 regulates the PI3K/AKT/mTOR pathway, enhancing glycolytic activity in CAFs and releasing lactate to promote OSCC proliferation	[58]
NPC	α-SMA, FAP	Subcutaneous tumor mouse model: NPC cells were injected subcutaneously into mice along with fibroblasts	The NF-κB p65 pathway activates CAFs and promotes aerobic glycolysis and autophagy, thereby increasing cancer cell proliferation and migration	[196]
PCa	FSP-1	NG	p62 deficiency in stromal fibroblasts leads to asparagine production through regulating the pyruvate carboxylase-asparagine synthase cascade reaction, which provides the raw material for stromal cell and tumor epithelial cell proliferation	[267]
CRC	α-SMA	Subcutaneous tumor mouse model: CRC cells were injected subcutaneously into the spleen of nude mice with CAFs or fibroblasts	Reprogramming of lipid metabolism in CAFs enhances colorectal cancer cell migration	[47]
PCa	Tenascin C, FAP	Tissue recombination mouse models: epithelial cells were mixed with CAFs or stromal cells to prepare cellular recombinants and collagen plugs placed in the anterior prostate and under the renal capsule of C57BL/6 male mice to establish tumor models	CAFs drive glutamine synthesis through oncogenic Ras activity and serve as an energy source to promote neuroendocrine prostate cancer reprogramming	[252]
BC	α-SMA; FAP	Subcutaneous tumor mouse model (animals were subcutaneously injected with BC cells and different subgroups of CAFs)	Enhanced oxidative ATM-mediated glycolysis in breast cancer-associated fibroblasts promotes tumor invasion via lactate as metabolic coupling	[55]
PCa	α-SMA	Subcutaneous tumor mouse model (animals were injected subcutaneously with wild-type or MCT1-silenced PCa together with CAFs)	CAFs undergoing Warburg metabolism and mitochondrial oxidative stress can program prostate cancer cells to follow aerobic metabolism, thereby driving tumor cell growth	[60]
OVCA	NG	Orthotopic OVCA mouse model: subcutaneous injection of tumor cells into mice	High expression of glutaminase in CAFs favors glutamine metabolism and supports proliferation and metastasis of ovarian cancer	[69]
PDAC	α-SMA	Subcutaneous tumor mouse model: PDAC cells and pancreatic stellate cells were injected into mice	Differentiation of pancreatic stellate cells into CAFs occurs during lipid metabolism, promoting progression of PDAC	[66]

expression, CAFs subpopulations were classified into S1-S4 groups, among which CAFs-S1 and CAFs-S4 subpopulations exhibited pro-tumorigenic properties [29]. The CAFs-S1 subpopulation enhanced Treg cell differentiation, recruitment, and activation, thereby promoting breast cancer immunosuppression, similar to the CAFs-S1 subpopulation detected in ovarian cancer [29, 30]. In a study of axillary lymph node metastasis, the CAFs-S1 subpopulation promoted breast cancer cell migration and the onset of epithelial mesenchymal transition (EMT), mainly through secretion of CXCL12 and TGF-β, whereas the CAFs-S4 subpopulation facilitated migration and invasion through the NOTCH pathway [31]. The use of single-cell sequencing and spatial transcriptome analyses could aid in clarification of the mechanisms underlying the cellular phenotypic heterogeneity of CAFs. ScRNA-seq has been effectively employed to identify different subpopulations of CAFs in breast cancer. Two of these subpopulations, ECM-myCAFs and TGFβ-myCAFs, were shown to promote breast cancer progression through acceleration of immunosuppression and resistance to immunotherapy [32], which is due to the expression of EMILIN1 in TGFβ-myCAFs and ECM-myCAFs-enriched regions correlates with TGF-β activity and CD8 T cell infiltration in breast cancer. Multiple types of CAFs have additionally been identified in mouse models of breast cancer, including vascular CAFs (vCAFs), stromal CAFs (sCAFs), circulating CAFs (cCAFs), and developmental CAFs (dCAFs) [33]. Among these subpopulations, vCAFs and mCAFs with distinct clinical significance are derived from the perivascular region and resident fibroblasts, respectively.

The identification of different subpopulations of CAFs based on cell surface biomarkers remains a significant challenge. Since CAFs originate from multiple cell types, their heterogeneity makes it almost impossible to obtain universally applicable markers across different tumor types. A combination of scRNA-seq, spatial transcriptome sequencing, and in vivo models may aid in understanding the diversity of CAFs in terms of cellular origin, surface markers, RNA profiles, and spatial distribution.

Functional heterogeneity of CAFs

The heterogeneity of CAFs encompasses variations in both function and cellular phenotype. Two main subpopulations of CAFs with opposing functions have been identified: cancer-promoting CAFs (pCAFs) and cancer-restraining CAFs (rCAFs) [34]. Studies have confirmed that rCAFs could inhibit tumor progression. For example, myCAF-expressed type I collagen in pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer (CRC) could impede tumor growth through mechanical signaling pathways [35]. In contrast, as important constituents of the TME, pCAFs have been shown to induce tumor cell proliferation, promote angiogenesis, shape the immunosuppressive microenvironment, and accelerate tumor escape from immune surveillance [36]. Therefore, during tumor progression, the majority of the CAFs population contributes to development of the TME in the form of pCAFs rather than rCAFs (to reflect this, Chapter 3 initially focuses on the mechanisms by which CAFs promote tumor progression). Reliable evidence suggests that pCAFs, which predominantly express FAP-α or α-SMA, suppress anti-tumor immunity and accelerate tumor proliferation. For example, the cytokines TGF-β, IL-6, IL-10, and VEGF secreted by pCAFs support tumor immunosuppression and favor skin cancer cell proliferation [37]. Noteworthy, pCAFs promote tumor-associated vascular growth by recruiting myeloid cells through secretion of angiogenic regulators, such as VEGF, PDGFC, HGF, and CCL12, and ultimately support tumor proliferation through attracting vascular endothelial cells and recruiting monocytes [38, 39]. Notably, the tumor-suppressive effect of rCAFs and tumor-promoting effect of pCAFs have been reported in different cancer types. The collective findings indicate that the functional heterogeneity of CAFs subpopulations is complex and may be closely related to tumor location, nutrition, and environment [40]. However, further exploration of the heterogeneity of CAFs in different cancer types is extremely challenging, given the paucity of detailed information on their phenotypic and functional characteristics.

Plasticity of CAFs

Different heterogeneous subpopulations of CAFs can be indirectly interconverted, indicative of high plasticity of this cell population. Earlier studies have demonstrated that transformation of iCAFs into myCAFs is facilitated by activation of TGF-β signaling or IL-1-mediated inhibition of JAK/STAT signaling in pancreatic cancer, providing evidence of the potential plasticity of different CAFs subtypes [41]. Furthermore, single-cell sequencing results suggest that downregulation of MEK and STAT3 contributes to the suppression of IL-6/CXCL1-expressing iCAFs and myCAFs phenotypes, while simultaneously enriching for CAFs with MSC-like features expressing LY6A/CD34 [42]. Importantly, elucidation of the mechanisms underlying CAFs plasticity is important to comprehend the dynamic evolution of CAFs in tumor progression and provide guidance for developing potential targets for tumor therapy [43]. Future research needs to focus on the key pathways (e.g., epidermal growth factor receptor (EGFR), Wnt, and Hippo signaling pathways) and transcription factors (RUNX1, TCF4, ZEB2 and TBX2) [44].

CAFs and metabolic reprogramming in TME

Accumulating research has revealed that metabolic reprogramming and immune escape are typical hallmarks of tumor progression. Metabolic reprogramming not only provides energy for the survival and functional maintenance of tumor cells but also contributes to the remodeling of the immune microenvironment to generate hypoxic, hypoglycemic, and acidic conditions suitable for tumor proliferation and metastasis [45]. However, tumor progression can further lead to metabolic disorders and exacerbate the formation of malignant TME, culminating in a recurrent cycle of tumor-promoting events [46]. Notably, metabolic programs associated with CAFs are hypothesized to actively participate in the complex metabolism of tumors and remodel the immunosuppressive TME to achieve the adaptive modifications required for tumor proliferation [47].

Glucose metabolism

Tumor proliferation and the necessary maintenance of function cannot be achieved without the support of nutrients and bioenergetics. The energy required for these processes is potentially provided by glycolysis in CAFs. Even under aerobic conditions, tumor cells are capable of glucose uptake and lactate secretion via glycolysis, a phenomenon known as the "Warburg effect" [48]. Oxygen depletion that accompanies tumor proliferation poses a barrier to the nutritional requirements of tumors. Under these conditions, the TME undergo adaptive changes to meet increased biosynthetic demands of tumor proliferation through multiple metabolic pathways [49]. In response to these complex microenvironmental changes, metabolic reprogramming in CAFs induces a shift in energy production from mitochondrial to glycolytic sources, which contributes to the formation of a hypoxic and acidic TME that supports tumor growth in several dimensions [19, 50].

The significant shift from oxidative phosphorylation to aerobic glycolysis in CAFs is associated with proliferation events, including oncogenic signaling, mutation/loss of tumor suppressors (e.g., VHL or p53), altered glycolytic enzyme activity, and activation of hypoxic signaling [51, 52]. These oncogenic factors drive cell-intrinsic aerobic glycolytic growth signals, primarily by modulating the expression of glycolytic enzymes, such as IDH3α, LDHA, and PKM2, to influence tumor progression [53, 54]. Sun et al. [55] demonstrated that hypoxia-induced oxidative ataxia-telangiectasia mutated protein kinase (ATM) promotes glycolytic activity in breast cancer-associated fibroblasts via phosphorylation of glucose transport protein 1 (GLUT1) at S490 and upregulation of PKM2. Additionally, breast cancer cell-derived exosomal miR-105 activates MYC signaling in CAFs that induces an increase in glucose and glutamine metabolism to fuel tumor proliferation [56].

Interestingly, significant expression of MCT1, fumarate hydratase, and succinate dehydrogenase has been reported in pancreatic cancer cells, indicative of metabolic coupling between CAFs and tumor cells [57]. High expression of ITGB2 in CAFs of oral squamous carcinoma (OSCC) origin is associated with poor clinical characteristics and outcomes in patients [58]. Mechanistically, ITGB2 enhances glycolytic activity and lactate release in CAFs through regulation of the PI3K/AKT/mTOR pathway. Lactate released from CAFs is taken up by tumor cells and metabolizedto produce NADH, which is oxidized within the mitochondrial oxidative phosphorylation system (OXPHOS) to produce ATP, providing energy for tumor growth. In view of these findings, it is proposed that the onset of glycolysis in CAFs contributes to lactate release, tumor cells take up lactate to sustain their own development, and unlimited tumor proliferation further exacerbates hypoxia and lactate release in the TME, thus creating a vicious cycle of tumor proliferation [59]. Notably, owing to metabolic heterogeneity in TME, not all CAFs in tumor tissues provide nutrients for cell proliferation via glycolysis. High expression of GLUT1 and MCT4 in CAFs of prostate cancer cells is associated with increased glucose uptake and lactate output of CAFs [60]. However, upon interaction of prostate cancer cells with CAFs, glycolysis is reprogrammed to aerobic metabolism, resulting in decreased GLUT1 expression and increased lactate uptake via the lactate transporter protein MCT1 [60]. The overall findings suggest that glycolysis of CAFs during tumor cell proliferation provides the energy and acidic TME required for sustained proliferation. However, the metabolic heterogeneity of CAFs from diverse cancer types and spatial locations require further consideration.

Lipid metabolism

Multiple enzymes are involved in catabolism, digestion, and absorption of fat to maintain homeostasis in the intracellular environment. The high nutritional demands of tumor cells require them to provide material and energy sources for their own proliferation and metastasis through regulating lipid metabolism (fatty acid oxidation) in CAFs [61]. In malignant TME, the ability of CAFs to secrete lipids is significantly increased. Fatty acids, phospholipids, and glycerides secreted by CAFs are taken up by tumor cells and used as nutrients for proliferation and migration [47]. This process is associated with reprogramming of lipid metabolism driven by various enzymes, such as fatty acid synthase (FASN), acetyl coenzyme acetyltransferase 1 (ACAT1), and arachidonate

lipoxygenase-5 (ALOX5) [47, 62]. However, the mechanisms by which dysregulated lipid metabolism in CAFs regulate tumor progression require further in-depth exploration. Definitive studies have shown that CAFs enhance liver metastases in pancreatic and colorectal cancers through modulation of lipid metabolism-induced processes, including ferroptosis, chemotherapy resistance, epigenetic alterations, and TME remodeling [63, 64]. For example, CAFs secrete macrophage migration inhibitory factor through the lipid metabolic pathway to generate an immunosuppressive microenvironment in hepatocellular carcinoma (HCC) [65] and tumor-derived exosomal HSPC111 promotes colorectal cancer liver metastasis in vivo by reprogramming lipid metabolism in CAFs [63]. Mechanistically, HSPC111 alters the lipid metabolism of CAFs by phosphorylating ATP-citrate lyase (ACLY) to promote accumulation of acetyl-coenzyme A, which enhances secretion of CXCL5 by CAFs to remodel the pre-metastatic ecological niche of colorectal cancer in mice. Furthermore, during the activation of pancreatic stellate cells into CAFs, increased intracellular levels of lysophospholipids and lysophosphatidic acid activate the AKT2 pathway, which promotes the development of pancreatic cancer [66]. Given this signaling affects tumor growth and proliferation through lipid metabolic reprogramming, molecules of this pathway may serve as potential targets for tumor therapy. Ovarian cancer cell-derived lysophosphatidic acid is proposed to regulate hypoxia-inducible factor-1 (HIF-1α) through interactions with the receptor to induce a glycolytic phenotype in CAFs, which could be attributable to complex crosstalk within the TME [67]. These findings support the existence of reciprocal crosstalk between CAFs and tumor cells and cooperation between glycolysis and lipid metabolism to support tumor progression. Notably, tumor proliferation-mediated microenvironmental hypoxia alters lipid metabolism in CAFs, which enhances metastasis by modulating matrix degradation and programmed cell death ligand 1 (PD-L1) expression, inducing an immunosuppressive tumor microenvironment. Dysregulation of lipid metabolism in CAFs thus appears to be a key event in the malignant cycle of tumor progression.

Amino acid metabolism

The rapid proliferation of tumors leads to an increased demand for amino acids. CAFs provide a nitrogen source for amino acid metabolism by regulating the uptake and synthesis of glutamine and glutamate to support the TCA cycle that generates ATP for promoting growth [68]. Therefore, amino acid metabolism is considered another critical factor closely related to tumor progression. CAFs-metabolized glutamine is reported to be taken up by ovarian cancer cells and converted to glutamate by glutaminase, supporting ovarian cancer cell growth via the TCA cycle (a replenishment process of metabolic pathway intermediates) [69]. These findings provide further evidence of the metabolic heterogeneity of CAFs and the importance of tumor nutrient uptake. Similarly, exosome-loaded LINC01614 in CAFs interacts directly with ANXA2 and p65 to promote NF-κB activation, leading to upregulation of the glutamine transporter proteins (SLC38A2 and SLC7A5) and ultimately, glutamine uptake by lung cancer cells [70]. Under conditions of tumor proliferation, pro-inflammatory cytokines are released that upregulate LINC01614 in CAFs-derived exosomes, constituting a feedback loop between CAFs and cancer cells. Accordingly, glutamine metabolism in CAFs promotes a recurrent cycle of tumor proliferation (CAFs glutamine metabolism—tumor proliferation—cytokine release—enhanced glutamine metabolism). Furthermore, this process may influence immune cell functions, leading to remodeling of TIME to support renal cancer metastasis [71]. Metabolomic analyses of renal cancers have revealed that encoded secreted proteins SPARC in CAFs may regulate the expression levels of 4-hydroxyproline, cysteine, lactate, and glutamine, in turn, affecting tumor immunity [72]. Similarly, glutamine fructose-6-phosphate aminotransferase 2 (GFPT2) has been identified as a key regulator of cancer-associated fibroblasts that affects TIME and promotes gastric cancer progression [73]. The metabolism of a number of other amino acids, including arginine, tryptophan, glycine, and serine, is also significantly associated with CAFs metabolism and TME remodeling, highlighting the diversity and complexity of mechanisms involved in cancer progression [74–76]. However, it is important to elucidate whether there is relevant crosstalk exists between multiple metabolic programs (such as glycolysis, lipid and amino acid metabolism) in CAFs that cooperate to provide energy for tumor growth and raw materials required for metabolism.

Metabolic reprogramming and nutrient availability

CAFs-related metabolites

Accumulating studies have shown that metabolic reprogramming of CAFs can generate metabolites that function in promoting an immunosuppressive TME that favors tumor cell proliferation and metastasis [47]. Lactic acid accumulation and acidic TME resulting from CAFs metabolism have a significant impact on anti-tumor immunity. Lactate released by metabolic reprogramming in CAFs is taken up by neighboring cells and inhibits effector T cells [77]. For example, lactate released from glycolysis in CAFs feeds the TCA cycle in breast cancer cells [78]. Definitive evidence suggests that lactate released from the metabolism of CAFs promotes the

production of T regulatory cells (Tregs), but the role of lactate secreted by CAFs on the other tumor-immunosuppressive cells, such as tumor-associated macrophages (TAMs), needs to be more explored [77, 79]. Since tumor tissue hypoxia induces mitochondrial stress as well as anti-T cell and macrophage depletion and supports lactate-mediated immunosuppression, a feasible theory is that recruitment of these immunosuppressive cells accelerates the secretion of immunosuppressive or pro-tumor cytokines to promote the formation of an immunosuppressive TME [80, 81]. Interestingly, lactic acid may conversely exert anti-tumor effects under specific conditions [82], suggesting that its flexible effects on immune cells are potentially related to the heterogeneity of metabolic reprogramming. In normoxia, lactate promotes the TCA and maintains effector function. Nevertheless, constrained by existing literature, a more profound investigation into the dynamic impacts of lactate released from the metabolism of CAFs on the tumor immune microenvironment is warranted.

Importantly, other metabolites, such as succinate and α-ketoglutarate (α-KG), also modulate TME to promote tumor progression [53, 83]. Mechanistically, miR-424 regulates the effective level of α-KG with succinate during the melanoma CAFs formation by affecting IDH3α expression [53].

Since multiple metabolites exist, exhaustive analysis of their impacts on the immune microenvironment is not feasible. Several of these metabolites are equally deserving of research attention. For instance, glutamine released from the metabolism of CAFs drives tumor nutrient acquisition and immunosuppression, thereby promoting pancreatic cancer growth [84, 85]. In summary, the metabolites released by CAFs via reprogramming act in concert to support tumor progression by modulating TME. In response, the proliferating tumor further exacerbates metabolic dysregulation and sustains the malignant cycle, ultimately leading to systemic nutritional depletion.

Metabolic reprogramming and positional dependence in TME

The type and location of tumor affect nutritional access of cells in the TME. Compared to normoxic tissues, hypoxic tumor regions display increased lactate secretion, along with recruitment and polarization of tumor-associated macrophages (TAMs), thereby blocking immune surveillance of tumors [86]. In hypoxic ecological niches, TAMs adapt to the environment through metabolic alterations, thereby acquiring a tumor migratory phenotype through angiogenesis [87]. Tumor energy acquisition and nutrient uptake are dependent on mTOR-regulated metabolic programs, such as glycolysis, lipid synthesis, protein synthesis, and transcription. Hypoxia in tumors leads to inhibition of mTOR complex 1 (mTORC1) function, triggering a shift from glycolysis to other pathways, such as lipid metabolism and glutaminolysis [88, 89].

Tumor proliferation usually induces redistribution of angiogenesis and low and irregular distribution of blood vessels in the core tumor region leads to inefficient delivery of nutrients and metabolites [90]. Hypoxic necrotic tumor regions experience severe long-term nutrient deficiencies due to insufficient angiogenesis and reduced blood supply [91]. In fact, tumor cores usually contain lower levels of amino acids, such as glutamine, asparagine, and serine, compared to tumor margin tissues [92]. These events mediate the onset of metabolic heterogeneity and location-dependent nutrient uptake, thereby inducing extreme stress in parts of the TME. Interestingly, renal cancer cells in necrotic regions show higher clonal diversity relative to those in marginal tumor tissues, suggesting that the malignant TME creates selective pressures for tumor cell survival arising from nutrient deprivation and adaptive metabolic changes, which may further favor metastasis and invasion by surviving tumor cells [93].

Consequently, the spatial distribution of metabolites and metabolic programs within the tumor microenvironment is undoubtedly crucial for tumor development. However, contemporary research predominantly addresses the metabolic heterogeneity of tumor cells and immune cells. Given the spatial distribution and subtype variability of CAFs, along with the influence of their metabolites on tumor progression, we emphasize the importance of exploring the spatial heterogeneity of CAFs metabolism. The metabolic programs exhibited by CAFs may vary according to their proximity to the core regions of the tumor, which could enhance our understanding of the metabolic pathways in CAFs that govern tumor progression.

CAFs and metabolic reprogramming in the immunosuppressive TME

Metabolic reprogramming in CAFs is proposed to be closely associated with tumor progression. Recent studies have focused on tumor immunomodulation to address persistent immunosuppression in the TME (Fig. 2).

CAFs and innate immune cells in the TME

CAFs and natural killer (NK) cells

Natural killer (NK) cells are important members of the innate immune system involved in anti-tumor, anti-viral, and immunomodulation activities [94]. The activity of NK cells predominantly depends on the expression and stimulation of activating or inhibitory receptors on the surface. In solid tumors, CAFs impair NK cell function

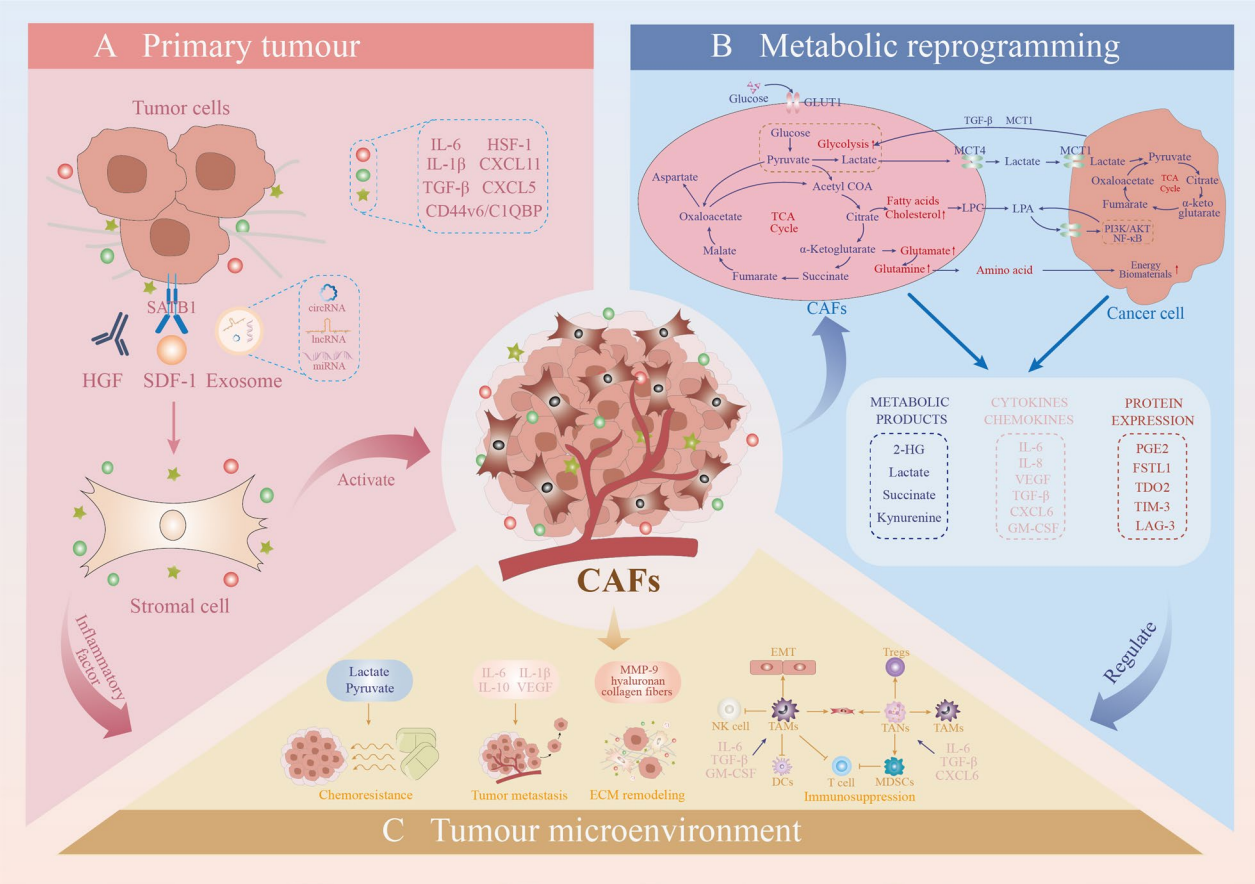

Fig. 2 The primary tumor promotes activation of CAFs through multiple modalities, including exosomes, cytokines, chemokines, and receptor activation. Activated CAFs achieve crosstalk with tumor metabolism through metabolic reprogramming, which stimulates the release of metabolites and inflammatory mediators and regulates the expression of related proteins, ultimately leading to tumor chemoresistance, ECM remodeling, metastasis, and the generation of an immunosuppressive TME

through multiple pathways (including NK cell receptor activation, cytotoxic activity, and cytokine release) to remodel tumor microenvironments with immunosuppressive properties. For example, CAFs-derived follicle suppressor-like protein 1 (FSTL1) upregulates NCOA4 expression in NK cells through the DIP2A-P38 pathway, leading to impairment of the cytotoxic function of NK cells in gastric cancer [95]. Notably, disruption of NK function in TME appears closely associated with tryptophan metabolic pathway in CAFs, since immunosuppressive factors, such as indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase 2 (TDO2) could be released by CAFs though metabolic pathways, inhibit NK cytotoxicity and induce resistance to trastuzumab in breast cancer [75]. Similarly, glutamate/glutamine metabolism regulated by CAFs via NetG1 inhibits NK cell-mediated tumor cytotoxicity via a mechanism related to a signaling axis comprising AKT/4E-BP1, p38/FRA1, vesicular glutamate transporter protein 1, and glutamine synthetase [85].

Compelling evidence supports the involvement of multiple cytokines in the complex crosstalk between CAFs and NK cells. For instance, TGF-β secreted by CAFs significantly inhibits the activation and cytotoxic activity of NK cells [96]. CAFs and metabolism may be extensively involved in the regulation of NK cell function through cytokines. According to a study by Wei et al. [97], attenuation of ketogenesis in CAFs promotes the release of CXCL12, which inhibits the activation of both NK cells and T lymphocytes and, consequently, the colonic rectal cancer killing impact of these immune cells. Furthermore, it has been reported that NK cells are markedly diminished in areas abundant with iCAFs and that iCAFs in these regions are linked with various metabolic pathways, including lipid metabolism and bile acid metabolism [98]. However, the precise mechanisms by which CAFs influence NK cell function through metabolic processes to bolster tumor immunosuppression necessitate more comprehensive studies.

CAFs and dendritic cells (DCs)

Dendritic cells (DCs) are antigen-presenting cells in the body, which can efficiently take up, process, and present antigens. Mature DCs effectively activate the initial T-cells and play a pivotal role in the initiation, regulation, and maintenance of the immune response [99]. Definitive studies have demonstrated that CAFs drive tumor escape from immune surveillance by impeding DCs maturation, antigen presentation, and associated adaptive immune responses [100]. Indeed, distinct subpopulations of DCs and metabolic reprogramming may be involved in the mechanisms by which CAFs weaken anti-tumor immunity. Under conditions of IL-6-mediated activation of the STAT3 pathway, CAFs in HCC stimulate the generation of regulatory DCs, which are characterized by low expression of co-stimulatory molecules and high release of inhibitory cytokines [101]. Further studies have demonstrated that regulatory DCs may be metabolically released IDO, the inflammatory cytokine rate-limiting enzyme of tryptophan catabolism, which induce proliferative damage of T cells, limiting T cell-mediated anti-tumor immunity [101]. On the other hand, CAFs activated by lung cancer cells facilitate metabolism of tryptophan through TDO2, releasing the metabolic by-product kynurenine that influences the differentiation and function of DCs, thereby inducing proliferation and migration of tumor cells [102]. Therefore, literature evidence indicates that metabolic may connect CAFs and DCs and promote tumor immunosuppression and further focus on the effects of metabolic reprogramming on differentiation of DCs subpopulations, recruitment of immunosuppressive cells, such as TAMs/Tregs. Noteworthy, cytokines released from the CAFs, influence the differentiation and antigen-presenting functions of DCs, ultimately promoting tumor progression [103]. This may be related to immune surveillance and response to immune checkpoint blockade. For instance, the COL13A1-expressing population of CAFs releases chemokines to recruit TAMs and Tregs while limiting the recruitment and function of DCs and effector T cells [104]. However, whether CAFs can release cytokines via metabolic pathways to regulate DCs in TME is not known.

CAFs and macrophages

Macrophages, essential immune cellular components of the TME, are mainly classified into M1 and M2 types. M1-type macrophages exert anti-tumor effects in TIME primarily by mediating antibody-induced cytotoxicity while M2-type macrophages exhibit tumor-promoting activity through fostering immunosuppression, proliferation, and invasion [105, 106].

Earlier studies have revealed the presence of macrophages around fibroblasts, which may account for the finding that fibroblasts achieve mutual crosstalk with macrophages through autocrine and paracrine signaling that supports normal physiological functions of tissues and organs [107]. For example, CSF1 secreted by fibroblasts functions to maintain macrophage activity and facilitates the provision of ligands expressing the PDGF receptor by macrophages to fibroblasts to maintain their survival [108]. In the TME, macrophages can be educated to transform into TAMs and, together with CAFs, drive multiple aspects of tumor progression, including proliferation, metastasis, immunosuppression, and treatment resistance [109]. High expression of markers of CAFs and TAMs (such as α-SMA, FAP, CD163, and CD209) may be indicative of poor prognosis in patients with multiple cancers [110, 111]. This finding may be attributed to the fact that CAFs secrete multiple cytokines to promote monocyte recruitment and convert them into tumor-promoting macrophage subpopulations (M2-type TAMs), ultimately inducing tumor immune evasion via damaging NK cell function [112]. In addition, a tendency of CAFs to recruit monocytes for polarization into TAMs has been observed in breast and prostate cancers [113, 114].

While the collective studies suggest close crosstalk between CAFs and TAMs, the underlying signals require in-depth investigation. Currently, cytokines, chemokines, and growth factors secreted by CAFs and TAMs are proposed to mediate CAFs-TAM interactions in tumors [79]. In multiple tumor types, including skin and breast cancers, CAFs secrete regulatory factors, such as IL-6, IL-10, IL-8, TGF-β, GM-CSF, CCL2, and CXCL12, that recruit monocytes and macrophages to the tumor area and polarize them into TAMs to promote tumor progression [38, 79, 113, 115]. For instance, in colorectal cancer, increased GM-CSF and IL-6 release by CAFs has been shown to enhance infiltration of M2-like TAMs [79]. Chitinase-3-like-1 secreted by CAFs in breast cancer recruits and polarizes macrophages into TAMs, ultimately contributing to reduced $CD8^+$ T cell infiltration and tumor immunosuppression [114]. Interestingly, the crosstalk between CAFs and TAMs in TME is reciprocal and TAMs with a M2 phenotype also regulate the activation and progression of CAFs. For example, TAMs enhance EMT progression through secreting factors, such as IL-6 and SDF-1, that activate CAFs [113]. Similarly, macrophages in precancerous lesions induce MSCs to acquire CAFs-like properties and a pro-inflammatory phenotype to modify the inflammatory microenvironment, thereby enhancing oncogenic transformation of gastric epithelial cells [22]. Subsequently, TAM-induced activation of CAFs promotes further recruitment and polarization

of TAMs, ultimately forming a feedback loop of tumor immunosuppression.

Indeed, metabolic reprogramming is intimately associated with CAF-mediated immunosuppression via TAMs, whereby CAFs accelerate the release of cytokines to remodel the TME [79]. For example, an earlier study reported that the abundance of CAFs within the TME showed a positive correlation with TAMs, and FGF5-mediated glycerophospholipid metabolism in CAFs may be involved in recruiting TAMs and promoting lung cancer cell proliferation [116]. Similarly, the expression of MCT1 in head and neck cancer and CPT1C in gastric cancer is believed to promote glycolysis and lipid oxidation in CAFs, thereby inducing macrophage migration and M2-type polarization, respectively, which ultimately results in the increased release of IL-6 and CCL2 within the TME [117, 118]. Thus, owing to the significant heterogeneity of CAFs, a range of metabolic reprogramming mechanisms are implicated in the creation of an immunosuppressive TME by CAFs. However, the precise mechanisms by which CAFs recruit immunosuppressive cells and promote tumor progression remain to be established. The associations and crosstalk between immune cells in construction of the immunosuppressive TME cannot be overlooked. For example, TAMs recruited by CAFs are reported to suppress the anti-tumor effects of $CD8^+$ T and NK cells [112, 114].

CAFs and neutrophils

Neutrophils, one of the circulating leukocyte types in the body, play a key role in the innate immune response, acute infections, and tumor progression [119]. Tumor-associated neutrophils (TANs) display significant phenotypic plasticity attributable to TME crosstalk and are capable of exerting either anti-tumor (N1) or pro-tumor (N2) functions dependent on specific microenvironmental signals [120].

In recent years, numerous studies have confirmed the existence of crosstalk between CAFs and neutrophils that supports the formation of an immunosuppressive TME and drives tumor progression. HCC-CAFs-derived IL-6 activates STAT3 in neutrophils, which supports neutrophil survival and function, ultimately impairing T-cell function via the PD1/PDL1 signaling pathway [121]. With the education of HCC cells, CLCF1 secreted by CAFs promotes TGF-β secretion, ultimately polarizing neutrophils into TANs and driving HCC progression [122]. CAFs-TAN crosstalk may be bidirectional, which further confirms their mutual crosstalk in TME. TANs isolated from mouse pancreatic cancer have been shown to induce polarization of CAFs towards an inflammatory phenotype through secretion of IL-1β and promote CAF-tumor cell crosstalk through the IL6/STAT3 pathway [123]. CAFs can connect neutrophils and other immune cells, these immune cells work together in multiple ways to construct immunosuppressive TME. For example, TANs in the microenvironment promote the accumulation of polymorphonuclear-myeloid-derived suppressor cells (PMN-MDSCs) that infiltrate breast and lung cancers [124, 125]. However, there is no evidence that metabolism in CAFs can construct a TIME via neutrophils, and more reports have focused on CAFs-mediated paracrine effects promoting tumor immunosuppression.

CAFs and myeloid-derived suppressor cells (MDSCs)

Myeloid-derived suppressor cells (MDSCs) originate from the bone marrow and are known for their ability to significantly suppress immune cell responses [126]. Activation of MDSCs in TME releases anti-inflammatory cytokines, ROS, and nitric oxide (NO), in turn, accelerating tumor invasion and metastasis [127, 128]. Recent studies have demonstrated that CAFs enhance immunosuppression by promoting production of MDSCs through secretion of a range of cytokines and chemokines [128]. CAFs derived CCL2 plays an important role in the recruitment of MDSCs and regulation of the anti-tumor immune response, potentially through the activation of the STAT3 signaling pathway [129]. Subsequent accumulation of immunosuppressive subpopulations, such as MDSCs, in the TME restricts $CD8^+$ T cell proliferation and IFN-γ release, ultimately leading to widespread suppression of T cell function [130]. Interestingly, recruitment of MDSCs by CAFs may also be achieved through lipid metabolism. Zhu et al. [65] demonstrated that high levels of lipid metabolism and macrophage migration inhibitory factor (MIF) expression in $CD36^+$ CAFs facilitated the recruitment of $CD33^+$ MDSCs and suppression of the T cell anti-tumor immune response. In addition, cytokines released by CAFs may regulate lipid metabolism in MDSCs and promote tumor immunosuppression. For instance, IL-6 and IL-33 derived from CAFs mediate lipid metabolism in MDSCs via 5-lipoxygenase to promote stemness in intrahepatic cholangiocarcinoma [131]. Moreover, specific subpopulations of MDSCs (e.g., circulating fibroblasts) exhibit phenotypic and functional similarities with CAFs, further validating the association between MDSCs and CAFs [132]. Therefore, elucidating the metabolism of specific CAFs and MDSCs subpopulations is essential to elucidate the mechanism of TME interaction with the immune system.

CAFs and adaptive immune cells in the TME

CAFs and T lymphocytes

As a major component of the human immune system, T cells are important immune mediators against infection and tumor development and function by directly killing

target cells, assisting B cells to produce antibodies, triggering responses to specific antigens and mitogens, and producing cytokines [133]. T lymphocytes consist of different subpopulations, such as Treg cells, T helper (Th) cells and cytotoxic T lymphocytes (CTL) [134]. CAFs metabolism-mediated TME remodeling can affect T cell phenotype/function to accelerate tumor evasion of immune surveillance. Ge et al. [135] defined a metabolic cancer-associated fibroblast (meCAFs) subpopulation. Expression of PLA2G2A in meCAFs is proposed to promote pancreatic cancer proliferation by impairing the anti-tumor capacity of $CD8^+$ T cells through regulation of MAPK/Erk and NF-κB signaling pathways. Similarly, the lipid metabolism-related gene CYP19A1 was shown to be positively correlated with CAFs and negatively correlated with $CD8^+$ T cells, which could be attributed to lipid metabolism in colon cancer through GPR30-AKT signaling, resulting in the inhibition of $CD8^+$ T cells [136]. The collective results demonstrate that CAFs and metabolism is critical for functional changes in T cells. Paracrine and autocrine secretion by CAFs promotes cytokine release, thereby regulating T cell proliferation and differentiation within the TME. For example, the release of CXCL12, CCL5, VEGF, IL-6, and TGF-β from CAFs can lead to a reduction in $CD8^+$ T-cell infiltration or inhibit $CD8^+$ T-cell recruitment to the tumor site [37, 137–139]. Consistently, CAFs have been shown to promote Th1 and Th17 polarization releasing a variety of cytokines (such as TGF-β1 and IL-6), thereby converting Th cells into an immunosuppressive subpopulation, and ultimately leading to tumor immunosuppression and creation of a cancer-adaptive TME [139]. Importantly, Marina et al. [140] identified a subpopulation of glycolytic CAFs using scRNA-seq in a mouse sarcoma model and showed that this subpopulation prevents cytotoxic T-cells from infiltrating into the tumor region via CXCL16. Thus, metabolic reprogramming and CAFs may release chemokines/cytokines to modulate tumor immunity, but this speculation needs to be confirmed by more research.

The TME is a dynamically evolving ecosystem in which the components crosstalk with each other. Suppression of cytotoxic T lymphocytes favors not only the recruitment of Tregs and Th cells but also infiltration of TAMs. In CAFs, upregulation of COL13A1 expression contributes to the production of chemokines that limit the recruitment of dendritic cells and cytotoxic T cells while enhancing the recruitment of TAMs and Tregs [104]. In addition, CAFs also interfere with the normal differentiation of DCs or NK cells, thereby impeding antigen presentation, leading to impaired cytokine production and impairing cytotoxicity against tumor cells [141]. Tumor progression is a recurrent cycle where CAFs releases cytokines to shape an immunosuppressive tumor microenvironment and accelerates tumor proliferation. Under these conditions, CAFs differentiation is further enhanced [142]. Differentiation of CAFs further induces immunosuppressive cell infiltration that supports tumor immune escape. Therefore, comprehensive understanding of the impact of CAFs on immunosuppressive TME and tumor progression is necessary.

CAFs and B cells

B cells are a major component of humoral immunity and participate in the immune response and inflammatory regulation by releasing large amounts of cytokines. Earlier reports have shown that CAFs inhibit activation of B lymphocytes in cholangiocarcinoma by secreting cytokines, such as IL-10 and TGF-β [143] and IL-8 secreted by CAFs affects B cell recruitment [144]. However, limited research to date has focused on CAFs-B cell interactions. Considering the heterogeneity and plasticity of CAFs, it may be of interest to analyze the activation of B cells by different subpopulations. For instance, bone marrow mesenchymal stem cells in the microenvironment contribute to B-cell acute lymphoblastic leukemia via transformation into CAFs [145]. Since different CAFs subpopulations secrete cytokines with distinct functions that may alter the anti-tumor immune response and tumor progression [146], research attention additionally needs to be paid to the effects of these subpopulations on immune cells, such as B cells.

CAFs and metabolic reprogramming contribute to chronic inflammation

In the tumor context, crosstalk between adaptive and innate immune cells is disrupted and an inflammatory response is induced. Under the influence of tumor proliferation-mediated inflammatory signals, hypoxia, acidic TME, and altered metabolite levels, the inflammatory response is sustained and becomes a risk factor for malignant progression [147, 148].

CAFs are proposed to remodel the inflammatory microenvironment in the TME, with tumor proliferation leading to dysregulated metabolism of CAFs and the release of metabolites, which, in conjunction with cytokines and chemokines secreted by CAFs, contribute to the inflammatory microenvironment (Table 2) [149, 150]. Meanwhile, cytokines/chemokines can recruit or polarize immune cells to exacerbate the secretion of inflammation molecules, ultimately promoting tumor immunosuppression and chronic inflammation in the surrounding microenvironment [151]. For example, CAFs trigger chronic inflammation in breast cancer by activating the NLRP3 inflammasome pathway through damage-associated molecular

Table 2 CAFs secrete factors that regulate tumor biological behavior

Factor	Cancer type	Recipient cell	Signaling pathway	Biological function	Ref.
Growth factors					
VCAM-1	LC	Tumor cell	AKT/MAPK pathway	Promoting tumor growth and invasion	[268]
TGF-β1	BC	Tumor cell	TGF-β/Smad pathway	Promoting tumor growth and migration	[269]
IGF-1	CRC	Tumor cell	IGF-1/IGF1R pathway	Promoting tumor growth	[270]
IGF-2	LC	Tumor cell	IGF-2/IGF-1R	Inducing treatment resistance in tumors	[271]
HGF	HCC	Tumor cell	MEK-ERK1/2 pathway	Inducing treatment resistance in tumors	[272]
GDF15	PCa	Tumor cell	TGF-β/GDF15 pathway	Supporting tumor progression	[273]
GPER	BC	Tumor cell	GPER/EGFR/ERK pathway	Promoting tumor cell growth	[274]
FGF1	OVAC	Tumor cell	FGF/FGFR pathway	Supporting tumor proliferation and invasion	[275]
FGF2	LC	Tumor cell	FGF/FGFR pathway	Supporting tumor proliferation	[276]
FGF9	GC	Tumor cell	ERK and AKT pathway	Promoting tumor invasion	[277]
Cytokines					
IL-1β	BC	Tumor cell	IL-1β/ IL-1R pathway	Promoting tumor invasion	[278]
IL-6	HNSC	Tumor cell	Integrin αvβ3/NF-κB pathway	Supporting tumor progression	[279]
IL-6	HCC	Neutrophils	STAT3/PD-L1 pathway	Promoting HCC immune escape	[121]
IL-8	GC	Tumor cell	NF-κB pathway	Inducing cisplatin resistance	[280]
IL-11	GC	Tumor cell	JAK/STAT3 pathway	Inducing chemotherapy resistance	[281]
IL-22	GC	Tumor cell	STAT3 and ERK pathway	Promoting tumor invasion	[282]
IL-25	BC	Tumor cell	NG	Inhibiting tumor metastasis	[283]
IL-33	HNSC	Tumor cell	NG	Promoting tumor progression	[284]
Chemokines					
CXCL2	LC	Tumor cell	NG	Promoting tumor immunosuppression	[285]
CXCL5	CRC	Tumor cell	PI3K/AKT pathway	Promoting tumor immunosuppression	[286]
CXCL9	OSCC	Tumor cell	CXCR3 pathway	Promoting tumor survival	[287]
CXCL12	CRC	Tumor cell	PI3K/AKT pathway	Promoting tumor metastasis	[288]
CXCL12	OVCA	Tumor cell	CXCL12/CXCR4	Inducing chemotherapy resistance	[289]
CXCL16	BC	monocyte	NG	Promoting monocyte recruitment	[290]
CCL3	PCa	Tumor cell	JAK/STAT3 pathway	Promoting tumor progression	[291]
CCL5	GC	Tumor cell	CCL5/CCR5 pathway	Promoting tumor progression	[292]
SDF-1	PDAC	Tumor cell	SDF-1/CXCR4 pathway	Promoting chemotherapy resistance	[293]
Others					
TGF-α	BC	Tumor cell	EGFR/AKT/ERK pathway	Promoting tumor proliferation	[294]
Asporin	GC	Tumor cell	CD44-Rac1 pathway	Promoting tumor invasion	[295]
Activin A	CRC	Tumor cell	NG	Promoting EMT and migration of CRC	[296]

patterns (DAMP), leading to pro-inflammatory signaling and IL-1β secretion [125]. Interestingly, tumor-associated inflammation induced by CAFs appears to be associated with inflammatory mediators, such as TGF-β, IL-10, IL-4, IFN-γ, IL-6, COX-2, CXCL1, and IL-2, which enhance tumor immunosuppression and inflammatory TME [152–155]. In addition, tumor proliferation induces significant changes in the microenvironment, resulting in increased numbers of dysfunctional $CD8^+$ T cells, Tregs, and regulatory B cells, with $CD4^+$ T cells tending to have a pro-inflammatory Th2 phenotype and DCs exhibiting changes in response to local inflammatory signals [101, 156, 157]. Cytokines and chemokines derived from CAFs can induce the release of inflammatory mediators from immunosuppressive cells (Tregs, TAMs, TANs, and MDSCs) to remodel the TIME [115]. For example, CAFs release IL-8, IL-6, and CCL2 to recruit and polarize TAMs, stimulating TAM-mediated release of IL-10 that exacerbates chronic inflammation in the TME [158–160]. Metabolic reprogramming is involved to some extent in formation of the inflammatory microenvironment. A study by Peng et al. [98] demonstrated that iCAFs-mediated lipid metabolism promotes chronic inflammation in colorectal cancer. In addition, vitamin A metabolism of CAFs promotes the release of IL-6,

which contributes to elevated tumor inflammation in colorectal cancer [161]. TGF-β1-activated aerobic glycolysis in CAFs is also associated with chronic inflammation [53, 162]. Multiple factors released by tumor proliferation (e.g. TGF-β, IL-1β, HSF-1) can induce the activation of CAFs, thereby contributing to an inflammatory microenvironment (Table 3). CAFs support the release of IL-6, IL-10, GM-CSF from MDSCs and TAMs to promote tumor immunosuppression and chronic inflammation [79, 131, 160]. However, the processes of glycolysis and lipid metabolism in tumor cells during proliferation stimulate the secretion of VEGF-A, CCL2, MCP-1, CXCL, CXCL8, IL-8, and COX-2 to further induce chronic inflammation [163–165]. Overall, metabolic reprogramming connects CAFs to tumors and co-promotes the inflammatory microenvironment.

Thus, complex crosstalk within the TME leads to the secretion of cytokines and chemokines by CAFs, which mediate chronic inflammation. This inflammatory microenvironment promotes tumor immune escape by recruiting and polarizing immunosuppressive cells to release inflammatory mediators. Proliferating tumors continue to release regulatory factors to activate CAFs, TAMs, and MDSCs, forming a vicious feedback loop.

CAFs and metabolic reprogramming provides favorable conditions for tumor invasion and metastasis

Angiogenesis

Angiogenesis is the process of development of new capillaries required for oxygen and nutrient supply when tumors grow beyond 1–2 mm in size [166]. This complex process involves extensive crosstalk between pericytes, tumor cells, immune cells, and CAFs, resulting in a haphazard, leaky and complex vascular system that ultimately affects the tumor oxygen supply, alters the immune cell status, and induces drug resistance of the tumor [167, 168].

Metabolic reprogramming in CAFs serves as a key factor in tumor angiogenesis. CAFs promote tumor angiogenesis through reprogramming of glutamine and lipid metabolism generation. Specifically, miRNA-21 activates hepatic stellate cells as CAFs and induces aberrant lipid metabolism in CAFs, resulting in the release of pro-angiogenic mediators such as VEGF, MMP2, MMP9, bFGF, and TGF-β, thereby supporting tumor progression [21]. Furthermore, altered levels of glycine, proline, and lipids in CAFs may also induce stromal stress or the release of VEGF-A, promoting tumor angiogenesis [169, 170].

Table 3 Multiple stimulatory factors are involved in CAFs activation and regulation of tumor progression

Cancer type	Factors	Activating mechanisms	Findings	Ref.
CRC	TGF-β	Activation of TGF-β/Smad signaling causes fibroblasts to transdifferentiate into α-SMA-positive CAFs	Promotes accumulation of TGF-β and proteases in TME, thereby creating a feedback loop that enhances cancer progression	[297]
Skin cancer	IL-1β	NF-κB signaling induces activation of CAFs	CAFs induce sustained inflammation to promote neovascularization and tumor growth	[298]
BC, CRC	HSF-1	Wnt and YAP/TAZ signaling-mediated activation of CAFs	DKK3 in CAFs promotes ECM remodeling and cancer cell proliferation through Wnt signaling	[299]
BC	ROS	ROS production and oxidative stress	Ethanol treatment induces ketone body production in CAFs and ketone body reuse in epithelial cancer cells, stimulating tumor cell growth via oxidative mitochondrial metabolism (OXPHOS)	[300]
PDAC	CD44v6/C1QBP	Exosomes secreted by PDAC induce activation of stem stellate cells (HSCs) into CAFs	Exosomal CD44v6/C1QBP complexes are delivered to the plasma membrane of HSCs, leading to phosphorylation of insulin-like growth factor 1 signaling molecules, which, in turn, triggers HSC activation and liver fibrosis	[301]
BC	SDF-1	TGF-β and SDF-1 promote differentiation of CAFs	TGF-β and SDF-1 autocrine signaling promotes the generation of CAFs in breast cancer to support tumor progression	[302]
OVCA	CXCL11	Cancer cell-derived lymphotoxin induces stromal fibroblasts via LTBR-NF-κB signaling	CXCL11 secreted by CAFs promotes ovarian cancer cell proliferation and migration via the chemokine receptor CXCR3	[303]
CRC	CXCL5	CAFs positively correlate with PD-L1 expression	CAFs-derived CXCL5 upregulates PD-L1 expression and tumor progression in mouse tumor cells through activation of PI3K/AKT signaling	[286]
HCC	IL-6	HCC-CAFs-derived IL-6 promotes STAT3 activation in neutrophils	CAFs promote immunosuppression in hepatocellular carcinoma by inducing PD-L1$^+$ neutrophils via the IL6-STAT3 pathway	[121]

As suggested in the above discussion, CAFs promote the release of cytokines and chemokines that recruit immunosuppressive cells to support immunosuppressive TME. These immune cells also support angiogenesis and increase vascular permeability through releasing pro-angiogenic mediators (VEGF-A, FGF2, PIGF, TNF, and BV8) in a direct or indirect manner [171, 172]. For example, mediators released from CAFs recruit and polarize TAMs that promote tumor vascular growth [160]. TANs in the TME generate MMP-9 and BV8 to drive angiogenesis in pancreatic cancer models [173]. Thus, CAFs and immunosuppressive cells such as TAMs support tumor angiogenesis. Although elevated levels of lipids and amino acids in CAFs favor tumor angiogenesis, there is no evidence to suggest that metabolism in CAFs is directly linked to immunosuppressive cell-mediated tumor angiogenesis.

Interestingly, angiogenesis favors tumor proliferation, which can lead to hypoxia. Several molecules responsive to hypoxia promote angiogenesis, the main drivers being vascular endothelial growth factor (VEGF) and its downstream signaling pathways [174]. Moreover, hypoxia enhances the plasticity of CAFs to increase the production of iCAFs, ultimately stimulating the release of inflammatory factors (including TNF, BV8 and G-CSF) to enhance chronic inflammation in the TME [175]. Moreover, hypoxia may induce metabolic dysregulation in CAFs to promote tumor proliferation. For instance, CRMP2 derived from CAFs drives ovarian cancer progression via the hypoxia-inducible factor-1α-glycolysis signaling pathway [176], hypoxia regulates glycolysis in CAFs and promotes breast cancer proliferation by inducing epigenetic reprogramming [51]. The collective results indicate that CAFs promote tumor angiogenesis by releasing mediators that support tumor proliferation. Tumor proliferation-induced hypoxia-driven metabolic dysregulation in CAFs, ultimately creating a CAFs-tumor angiogenesis-hypoxia feedback loop that facilitates malignant progression.

Remodeling of the extracellular matrix

The extracellular matrix (ECM) is a complex network of collagen, enzymes, and glycoproteins [177]. Fibroblasts, a major component of the tumor stroma, are activated and converted into CAFs by primary tumor or immunosuppressive cells for participation in ECM remodeling and immunosuppression and supporting circulating tumor cell colonization and metastasis [178, 179].

In animal models, fibroblasts can release collagen to remodel the ECM and attract colonization by melanoma and lung cancer cells [180, 181]. In primary tumors, such as breast and colorectal cancers, CAFs release large amounts of collagen to enhance EMT and/or invasiveness of tumor cells, which creates gaps in the stroma or basement membrane and alters the ECM stiffness of the stroma to direct long-distance colonization of tumor cells [182, 183]. Mechanistically, activation of YAP in CAFs induces an increase in ECM stiffness and promotes tumor angiogenesis and invasion [184]. Similarly, active heterophilic adhesion between N-calmodulin on CAFs and E-calmodulin on tumor cells mediates intercellular physical dynamics and drives tumor cell colonization in the TME [185].

Recently, considerable research attention has focused on metabolic plasticity in the TME. Earlier studies have reported that pyruvate metabolic plasticity is critical for ECM remodeling and colonization of circulating tumor cells (CTCs) in lung cancer metastasis [186]. Higher levels of pyruvate in TME of lung cancer facilitate transamination between glutamate and pyruvate, leading to ECM remodeling and metastasis through the synthesis of alanine and α-ketoglutarate for activation of collagen prolyl-4-hydroxylase [187]. Furthermore, in the crosstalk between tumor cells and CAFs, increased ECM stiffness and activation of mechanistic signaling promotes glycolysis and glutamine metabolism, which orchestrates non-essential amino acid fluxes within the tumor ecotone [68]. Specifically, aspartic acid released from CAFs metabolism facilitates tumor proliferation, whereas glutamate released from proliferating tumor cells modulates the redox state of CAFs to promote ECM remodeling, which ultimately supports invasion and metastasis [68]. Additionally, CAFs secrete lactate and pyruvate (energy metabolites produced by aerobic glycolysis) through metabolic reprogramming. Tumor cells can then take up and utilize these energy-rich metabolites to remodel the ECM, providing the necessary microenvironment to promote angiogenesis, invasion, and metastasis [188]. However, few studies have investigated the involvement of CAFs metabolism in ECM remodeling, with most limited to glycolysis and amino acid metabolism. Further research is required to ascertain whether other metabolic pathways are involved in remodeling of the tumor ecosystem through the ECM and clarify the mechanisms by which CAFs contribute to metabolic plasticity of the pre-metastatic ecological niche.

Pre-metastatic niche

Tumor development not only affects the local TME but also remodels the microenvironment in distant organs through paracrine effects, providing a favorable setting for the metastatic spread of the primary tumor (known as the pre-metastatic niche—PMN) [189]. PMN has been reported in salivary adenoid cystic carcinoma model, extracellular vesicles of CAFs can form pre-metastatic ecological niches in the lung tissue [190]. In addition,

lipid metabolic reprogramming in CAFs through the uptake of HSPC111 in colorectal cancer cell-derived exosomes promotes liver metastasis in colorectal cancer [63]. These seminal results have informed substantial advances in understanding of the molecular and cellular mechanisms of pre-metastatic ecological niches that provide fertile soil for disseminated cancer cells (Fig. 3).

Activation of CAFs in the TME is critical for tumor metastasis, as this process induces differentiation of myofibroblasts and alters the extracellular matrix composition. CAFs activation by TGF-β1 secreted by tumor cells stimulates the release of ECM proteins (fibronectin and collagen) and proteases, which alter extracellular matrix stiffness and provide favorable conditions for metastasis [191]. In addition, CAFs release bioactive molecules (IL-6, proteins, and miRNAs) into the ECM, thereby altering the ecological environment of breast, gastric, and bladder cancer tissue [192–194]. On the other hand, CAFs can remodel TIME to support PMN formation. As discussed in Chapter 5, IL-6, IL-10, IL-8, TGF-β, GM-CSF, and CCL2 secreted by CAFs contribute to the formation of an immunosuppressive TME by affecting the phenotype and function of macrophages, neutrophils, and effector T cells. In this respect, CAFs-induced remodeling of the TIME should also generate conditions conducive to tumor metastasis.

Notably, CAFs facilitate the remodeling of the PMN through multiple pathways. CAFs can secrete cytokines and chemokines, thereby creating an environment conducive to breast cancer metastasis [195]. Additionally, the activation of CAFs may influence tumor metabolism and promote the release of tumor metabolites, which combined with the products of CAF metabolism, remodel the PMN [71, 196]. This process ultimately supports the malignant crosstalk between tumor proliferation and CAFs activation. Therefore, both CAFs and metabolic reprogramming in tumors are pivotal for tumor metastasis.

CAFs and metabolic reprogramming promote tumor metastasis

Tumor metastasis is a major cause of poor prognosis. The role of CAFs in metastasis, particularly that of liver, lung, and bone, is of significant research interest.

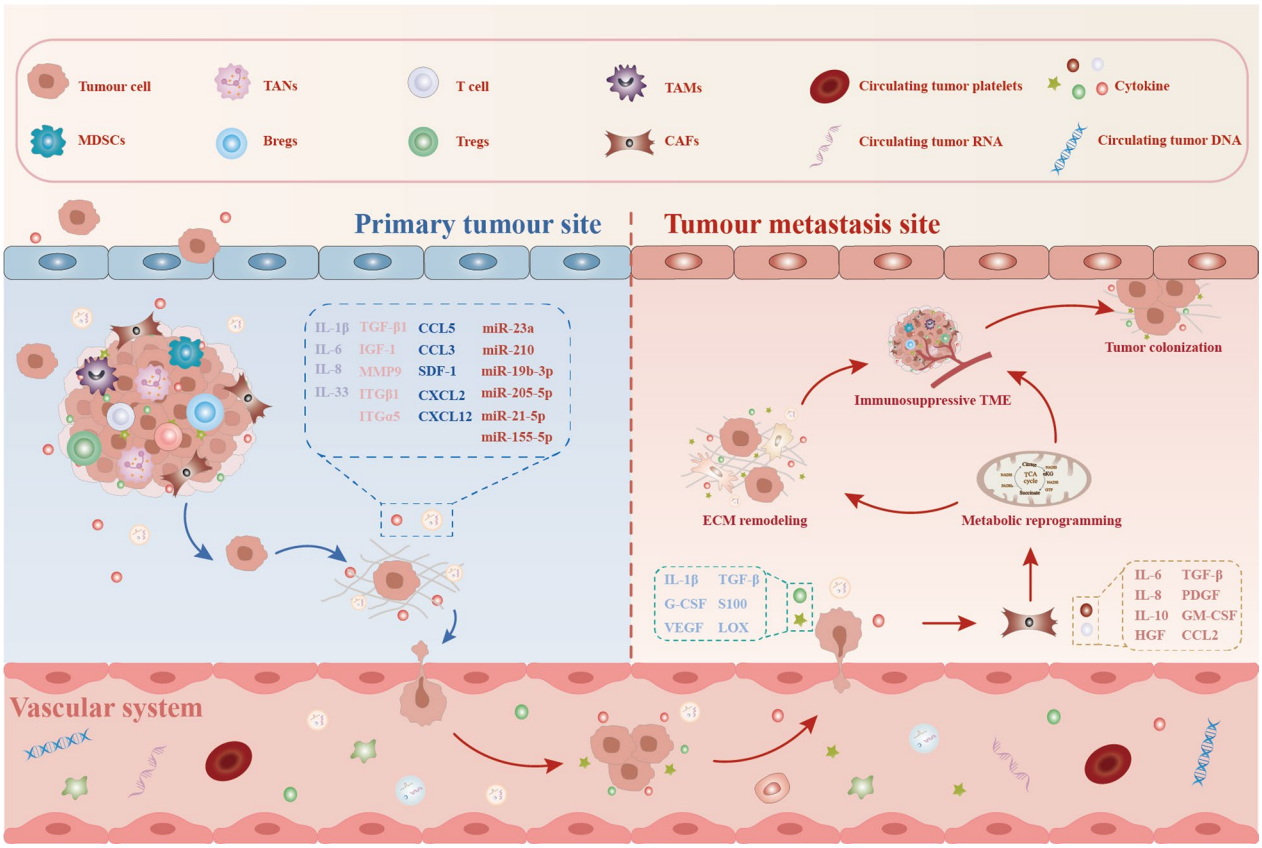

Fig. 3 The primary tumor sheds and releases inflammatory mediators and exosome-loaded miRNAs into the vascular system to reach distant tissues, which regulates the onset of metabolic reprogramming through activation of CAFs and release of cytokines, in turn, promoting ECM remodeling and immunosuppressive TME formation, and eventually achieving distant colonization of tumor cells

Liver metastasis

Owing to the provision of dual blood supply from the hepatic portal vein and hepatic artery, the liver is a common organ for distant metastasis, and the infiltration and colonization of CTCs is accelerated due to the susceptibility of the hepatic vascular system to damage. CAFs are extensively involved in metastatic growth regulation in the liver. For example, CXCL3 in the tumor inflammatory microenvironment promotes the differentiation of myCAFs and facilitates metastasis of pancreatic cancer cells to the liver through recruitment of TAMs [197]. Moreover, tumor cells can induce the production of iCAFs and remodel the PMN by altering the expression of DNA methylation and metabolism-related genes, ultimately promoting metastasis and colonization of pancreatic cancer cells to the liver [64]. Available evidence suggests that PMN formation and the emergence of tumor metastasis are associated with metabolic reprogramming of CAFs. A study by Zhang and co-workers [63] demonstrated that the CRC-derived exosomal HSPC111 supports PMN formation and liver metastasis by reprogramming lipid metabolism in CAFs to increase CXCL5 expression and secretion. Moreover, CAFs-derived lysyl oxidase (LOX) in the liver metastasis ecotope remodels the extracellular matrix and induces tumor cells to secrete TGF-β1 to nourish CAFs, consequently accelerating LOX production, which further supports migration of gastric cancer cells to the liver via the Warburg effect [198]. In view of the above findings, tumor progression may be effectively alleviated by drugs that inhibit the function of CAFs and ECM deposition [199]. For instance, bevacizumab exerts enhanced anti-angiogenic effects through targeted inhibition of metastasis-associated fibroblast function and extracellular matrix deposition, ultimately alleviating symptoms in patients with liver metastatic colorectal cancer [200].

Lung metastasis

The spread, colonization, and growth of tumor cells has been extensively studied in lung tissue. Indeed, given the high vascularity and large surface area of lung, this organ is clear target for metastatic dissemination [201]. Crosstalk between the tumor and ECM coordinates tumor growth and metastasis, which is dependent on ECM deposition and activation of cellular metabolism-mediated signals to promote tumor metastasis [202]. Specifically, CAFs-derived aspartate sustains cancer cell proliferation, while cancer cell-derived glutamate balances the redox state of CAFs to promote ECM remodeling [68]. Furthermore, CAFs can exert physical force on tumor cells through heterophilic adhesion of *N*-calmodulin and *E*-calmodulin to cell membranes, which further triggers enhanced β-collagen recruitment and adhesion to accelerate metastasis and invasion [203]. In addition to metabolically mediated physical signals, inflammatory factors released by CAFs favor tumor metastasis. For example, CRC-derived miR-146a-5p and miR-155-5p can activate CAFs via JAK2-STAT3/NF-κB signaling, which, in turn, induces release IL-6, TGF-β, TGF-α, and CXCL12 from CAFs, and ultimately promotes CRC lung metastasis via remodeling the ECM [204]. Moreover, different signaling-activated CAFs secrete CCL5, IL-6, IL-8, and TGF-β to further induce ECM deposition, thereby stimulating metastasis of HCC and osteosarcoma to lung tissues [138, 205, 206]. Signaling plays an important role in CAFs-mediated tumor metastasis. For instance, activation of β1-integrin-NF-κB signaling facilitates CAFs-induced lung metastasis in hepatocellular carcinoma cells [205], whereas Notch 1-WISP-1 signaling potentially inhibits this process [207]. Consequently, there is a metabolic coupling between CAFs and tumor lung metastasis. Metabolism in CAFs may release lactate and aspartate to provide nutrients for tumor proliferation, tumor proliferation via signaling or metabolic pathways to promote CAFs activation, and activated CAFs release mediators to support lung metastasis ecotope formation.

Bone metastasis

In recent years, significant research attention has focused on the link between bone and tumor biology, in view of the finding that a large proportion of cancer patients, in particular, those with breast and prostate cancer, develop bone metastases [208]. The bone microenvironment includes tissue-resident osteoblasts, osteoclasts, adipocytes, a rich vascular system, immune cells, and an abundance of bone marrow and ECM [209]. The dynamic evolution of tumor progression may lead to osteolytic metastases and increased risk of fracture.

The development of disseminated tumor cells into metastatic lesions depends on the establishment of a favorable microenvironment in the target organ stroma. Tumor-secreted IL-1β activates CAFs to modulate the surrounding bone microenvironment, ultimately triggering increased secretion of pro-inflammatory cytokines, altered functional activity, and attraction to tumor cells [210]. An earlier study by Zhang et al. [211] focused on the role of breast tumor stroma in identifying cancer cells primed for bone metastasis. The group suggested that CAFs in breast tumors stimulate cancer cell populations to secrete CXCL12 and IGF1 and select cancer cells with high Src activity, preparing a CXCL12-rich microenvironment through the PI3K-Akt pathway, and ultimately promoting bone metastasis of breast cancer.

The bone metastatic ecological niche also promotes communication between CAFs and bone-resident cells that trigger metastasis. Osteoblasts and osteoclasts are

subsequently induced by tumor cells to secrete factors, including IL-6, IGF, and matrix-degrading enzymes, which act in concert to promote metastatic growth, osteolysis, and skeletal changes underlying many of the clinical manifestations of advanced bone metastasis [212, 213]. Tumor-stroma interactions can be achieved via cytokines and CAFs that ultimately mediate metastasis. Therefore, inhibition of CAFs and reduction of cytokine release may serve as an effective strategy to inhibit tumor bone metastasis. For example, Rictor deficiency reduces the shift of BMSCs to CAFs, along with inhibiting the secretion of cytokines (IL-6, RANKL, and TGF-β) and TM40D-induced osteolytic bone destruction, which ultimately reduces breast cancer bone metastasis [214]. Furthermore, expression of Axin2 in oral cancer is reported to facilitate the activation of CAFs and release of CCL5 and IL-8 to promote tumor bone metastasis, whereas its knockdown significantly reduces the connective proliferative response and osteolytic lesions in the cranium [215]. However, reports in the literature are limited and further research is required to ascertain whether metabolic reprogramming of CAFs is involved in tumor bone metastasis. Elucidation of the mechanisms by which CAFs stimulate development of tumor metastasis to the liver, lung, and bone requires attention to the ways that different subpopulations of CAFs interact with the immune system in the TME as well as metabolic heterogeneity among tumor types, since different CAFs subgroups and tumor metabolism pathways differentially affect the immune microenvironment.

Potential clinical applications of CAFs

An intrinsic correlation between CAFs and the tumor immune microenvironment has been established, supporting the utility of CAFs as a potential therapeutic target for tumor intervention (Table 4). The current CAFs-based targeted therapeutic strategies primarily involve depletion of CAFs, preventing activation of CAFs,

Table 4 Potential of CAFs-based tumor-targeted therapies for clinical applications

Cancer type	Drugs	Classification	Combination therapy	Findings	Preclinical/Clinical	Ref.
LC, BC, CRC	RG7386	FAP targeting antibody	Adriamycin/irinotecan	Induces apoptosis in tumor cells and causes tumor regression	Preclinical	[304]
CRC	ValboroPro	FAP enzyme inhibitors	Cisplatin	Inhibits tumor progression	Phase II	[305]
Melanoma	α-FAP-PE38	Immunotoxins targeting CAFs	Paclitaxel, anti-CAFs vaccine	Delays tumor proliferation by activating cytotoxic $CD8^+$ T cells	Preclinical	[306]
Melanoma	DC-shA20-FAP-TRP2	FAP-targeted DC vaccine	Combined therapy with anti-CAFs	CAFs-targeted therapy in combination with dendritic cell-based vaccines enhances anti-tumor immune responses	Preclinical	[307]
PDAC	Galunisertib	TGF-β inhibitor	Gemcitabine	Prolongs the survival of tumor patients	Phase II	[231]
OVCA	Tolizumab	Blockage of IL-6/STAT3 signaling	Carboplatin/doxorubicin	Enhances anti-tumor immunity	Phase I	[308]
OVCA	AMD3100	CCR2 inhibitor	Anti-PD-1 therapy	Enhances anti-tumor immunity	Preclinical	[309]
BC	Cellax	Nanoparticles targeting α-SMA	Paclitaxel	Inhibits tumor stroma and angiogenesis	Preclinical	[227]
BC	Balixafotide	CXCL12/CXCR4 signaling inhibitor	Eribulin	Enhances anti-tumor immunity	Phase I	[310]
PDAC	Galunisertib	TGF-β inhibitor	Durvalumab	Combination therapy improves tolerance	Phase I	[311]
PDAC	ATRA	FAP targeting antibody	Gemcitabine/paclitaxel	Repurposing ATRA as a matrix-targeting agent for gemcitabine-albumin-bound paclitaxel is safe and tolerable	Phase I	[312]
PDAC	Simtuzumab	IgG4 monoclonal antibody to LOXL2	Gemcitabine	Addition of cetuximab to gemcitabine-based therapy did not improve the clinical outcomes of patients with metastatic PDAC	Phase II	[313]

restriction of CAFs-induced ECM remodeling, and metabolic therapies.

Depletion of CAFs

The expression of surface markers of CAFs (FAP, α-SMA, and PDGFR) provides a viable strategy for inhibitor-mediated depletion of CAFs. The FAP marker is of significant interest in the context of CAFs-targeted tumor therapy [216]. Depletion of CAFs through targeting of FAP alters the tumor immune response by specific inflammatory mediators in the TME and enhances the toxic effects of $CD8^+$ T cells through reducing ECM remodeling [217].

FAP-based DNA vaccines showing good anti-tumor potential are currently under development. Researchers have developed DNA vaccines against the tumor stromal antigen FAP in primary tumors of colon and breast cancers in multidrug-resistant mice, which can effectively delay tumor proliferation and metastasis by killing and eliminating CAFs via $CD8^+$ T cells [218]. Similarly, the novel SynCon FAP DNA vaccine developed by Duperret et al. [219] is capable of disrupting tumor immune tolerance and inducing anti-tumor immune responses in $CD8^+$ and $CD4^+$ T cells, ultimately leading to inhibition of tumor progression. However, the anti-tumor efficiency of single vaccines targeting FAP is limited due to the complex crosstalk of TME. Combination of specific anti-tumor agents, such as cyclophosphamide, with FAP vaccines is a potential therapeutic strategy that may help to further deplete CAFs and block the tumor extracellular matrix, in addition to enhancing toxic effects of anti-tumor agents on cancer cells [220].

Notably, FAP serves as a potential target for adoptive T cell therapy, including chimeric antigen receptor (CAR) therapy. Previous studies have shown that FAP-specific CAR-T cells destroy most FAP-expressing, including CAFs, and thereby inhibit remodeling of the tumor stroma, in turn, enhancing the penetration and uptake of chemotherapeutic agents and, consequently, anti-tumor efficacy [217]. For example, FAP-CAR T therapy can inhibit the growth of pancreatic cancer by reducing extracellular matrix proteins and glycosaminoglycans to deplete FAP (+) stromal cells [221]. Interestingly, FAP-CAR T therapy has also demonstrated promising applicability against malignant pleural mesothelioma [222], metastatic lung tumors [223], and glioblastoma [224]. Moreover, radiolabeled FAP inhibitors applied to PET imaging could potentially be used to monitor the therapeutic response to FAP-targeted CAR T cell therapy, thereby reducing the limitations of therapy [225]. However, the use of FAP-CAR T therapy to treat subcutaneous tumors in mice has been linked with severe myelotoxicity and malignancy [226]. Therefore, further rigorous validation of the efficacy and safety of FAP-CAR T therapy is essential before application in the clinical setting.

Other markers of CAFs have also shown therapeutic promise. However, the significant challenges posed by the heterogeneity and plasticity of CAFs have led to slow progress in α-SMA-based therapies. In breast cancer and pancreatic cancer models, depletion of α-SMA (+) CAFs was shown to inhibit metastasis as well as angiogenesis [227]. Furthermore, expression of α-SMA induced disease invasion and progression through enhancing infiltration of $CD3^+$ $Foxp3^+$ Treg cells in the TME [228]. Further clinical trials are required to validate the utility of the remaining CAFs markers.

Blockage of CAFs activation

Given the tumor immunosuppressive effects mediated by CAFs in TME, another feasible strategy is targeting key effector molecules and signaling pathways to block the activation of CAFs. Since TGF-β is critical for CAFs activation, its inhibition may enhance anti-tumor immunity [229]. Galunisertib (LY21577299) is a small-molecule inhibitor of TGF-β currently under investigation. Results from phase II clinical trials on pancreatic and hepatocellular carcinomas have demonstrated anti-tumor effects of galunisertib, both as monotherapy and in combination with gemcitabine [230, 231]. Furthermore, CAFs can be activated to support CRC invasion and metastasis via the TGF-β/SMAD4 signaling pathway. The TGF-β inhibitor LY2109761 affects CAFs-induced tumor immunosuppression by suppressing Treg levels in the TME and altering CAFs [232]. Similarly, resveratrol-loaded liposomes (L-RES) have been shown to block the activation of CAFs and suppress the expression of α-SMA and IL-6, thereby delaying colorectal cancer progression by inhibiting the function of CAFs [233]. Recent studies suggest that p62 promotes lung cancer progression and hydroxychloroquine (HCQ) inhibits autophagy to block activation of CAFs and reduce release of TGF-β, both of which restrict tumor proliferation [234]. Specifically, p62-induced autophagy favors the expression of NRF2 and ATF6 and promotes activation of CAFs. Conversely, pharmacological blockade of the NRF2-ATF6 pathway prevents CAFs activation [234]. Moreover, activation of CAFs and tumor immunosuppression are associated with the chemokine SDF-1. Blockage of the interactions of SDF-1 and its receptor, CXCR4, by AMD3100 (a CXCR4 inhibitor) prevents activation of CAFs and promotes accumulation of T-cells, which effectively kill tumor cells [235].

Inhibition of the exchange of information between CAFs and tumor cells can also inhibit tumor progression. Recent studies have highlighted the potential of the IGF2-IGF1R-YAP1 axis as a therapeutic target for CRC,

with IGF2 expressed predominantly by CAFs and IGF1R (the receptor for IGF2) by cancer cells. IGF2 interacts with IGF1R to induce nuclear accumulation of YAP1 and upregulation of YAP1 target signatures, thereby supporting tumor cell proliferation [236]. Notably, IGF1R depletion and treatment with the IGF1R inhibitor picropodophyllin (AXL1717) could abrogate the IGF2-mediated cascade activation and suppress progression of CRC. Furthermore, CAFs-derived SDF-1 induces EMT in lung cancer via CXCR4/β-catenin/PPARδ signaling. Targeting of this cascade using XAV-939, a β-catenin inhibitor, and GSK3787, a PPARδ inhibitor, significantly suppressed CAFs-mediated lung cancer metastasis [237]. The collective results confirm the potential application of CAFs signaling blockade in tumor therapy.

Suppression of CAFs-induced ECM remodeling

Given the crucial involvement of the ECM (including deposition of ECM proteins and CAFs-induced ECM remodeling) in tumor proliferation and metastasis, alteration of ECM stiffness through targeting CAFs presents another potential therapeutic option [238]. Changes in ECM stiffness could inhibit the recruitment of immunosuppressive cells in the TME, thereby enhancing anti-tumor immunity.

A promising strategy to limit ECM remodeling is targeting of CAFs-derived ECM proteins, such as tenascin C (TNC), hyaluronan (HA), and matrix metalloproteinases (MMP). High expression of TNC is associated with poor prognosis in specific tumors, such as breast cancer, in line with the finding that TNC modulates angiogenesis and tumor immunity, promoting tumor cell adhesion, migration and invasion [239, 240]. Researchers have recently developed specific antibodies against TNC to ameliorate ECM-mediated tumor progression. For instance, a TNC-specific antibody, F16, developed as a complex with IL-2 by Brack et al. [241] exerted better tumor suppressive effects than chemotherapeutic agents alone in breast cancer models [242]. Furthermore, in studies on autophagy-deficient triple-negative breast cancer, inhibition of TNC expression promoted T-cell-mediated cytotoxicity and improved the anti-tumor effects of single anti-PD1/PDL1 therapies, indicating that combination of TNC blockers and immune checkpoint inhibitors presents an effective approach for treatment of triple-negative breast cancer [239]. The glycosaminoglycan HA is abundantly expressed in several solid tumors and, together with collagen, promotes tumor vascular compression, thereby preventing the transport of immune cells and anti-tumor drugs to the tumor vasculature [243, 244]. Earlier studies have demonstrated a role of chlorosartan in limiting the activation of CAFs through inhibiting TGF-β, thereby reducing CAFs-mediated secretion of ECM components, such as hyaluronic acid and collagen, to enhance drug delivery and immunotherapy efficacy [245]. Notably, the polyethylene glycolated recombinant human hyaluronidase (PEGPH20) enzyme has been shown to induce depletion of HA and improve the efficiency of chemotherapeutic drug transport in the vasculature [246]. A phase Ib clinical trial (NCT01453153) demonstrated that PEGPH20 in combination with gemcitabine inhibited pancreatic cancer progression and provided a therapeutic benefit, with a PR rate of 35.7%, which was higher than the ORR rate for gemcitabine alone (7–13%), and 96.4% of the adverse events occurring during treatment [247]. While a number of novel drugs based on MMP therapy are currently under investigation in clinical trials, the anti-tumor effects of MMP inhibitors are not as promising as anticipated and require further exploration.

Additionally, considering that the FAK signaling pathway is involved in CAFs-induced alterations in ECM stiffness and tumor progression, improvement of CAFs-induced stromal stiffness and recruitment of immunosuppressive cells (TAMs, MDSCs, and Tregs) by FAK inhibitors could also provide therapeutic benefits [248]. However, additional clinical studies are required to validate their safety.

CAFs and tumor metabolic therapy

Tumor cells can hijack the metabolism of CAFs to access the energy sources provided by glutamine, lipids, and glucose [69]. Metabolic coupling between tumor cells and CAFs has been suggested as an adaptive modification to overcome low nutrient availability in the TME, which could present potential novel targets for tumor therapy. Lactate generated from the metabolic reprogramming modulates the expression of genes that regulate lipid metabolism in prostate cancer cells to promote lipid accumulation in tumor cells, thereby maintaining mitochondrial metabolism and tumor function through histone acetylation [249]. In a mouse model, targeted inhibition of bromodomain and extraterminal (BET) protein has been shown to interfere with lactate-dependent lipid metabolism and hinder the proliferation and migration of prostate cancer cells [249]. In prostate cancer, lactate released from the CAFs alters the NAD/NADH ratio of cancer cells, establishing a metabolic symbiosis between CAFs and prostate cancer cells by affecting mitochondrial mass and inducing dysregulation of the tricarboxylic acid cycle as well as accumulation of new metabolites (cholesterol and steroids) [250, 251]. Interestingly, in this study, dual inhibition of cholesterol and steroid synthesis via simvastatin and AKR1C3 inhibitors led to significant inhibition of tumor cell progression. Acquired resistance is a significant factor limiting the efficacy of tumor therapy. A number of studies have confirmed that CAFs can

induce specific programmed differentiation or metabolic initiation and complete signal exchanges with metabolites to trigger tumor resistance. For example, in prostate cancer, silencing of RASAL3 in CAFs induces oncogenic Ras activity and enhances glutamine synthesis mediated by megacytosis. In response, glutamine secreted by CAFs promotes the mitochondrial metabolism of cancer cells and orchestrates an adaptive response to androgen signaling deprivation therapy (ADT) [252]. However, in models of denuded resistance xenografts, inhibition of glutamine uptake restores sensitivity to ADT.

Tumor metabolism mediated by multiple fatty acid synthases, such as acetyl coenzyme A synthase (ACSS), ACLY, ACC, and FASN, is another key factor in the progression of malignancy. Inhibitors of these enzymes have demonstrated varying degrees of suppressive effects on tumor proliferation [253–256]. Notably, these inhibitors not only affect tumor cells but also interfere with their metabolism, and tumor cells can adapt to changes in metabolism via activating alternative pathways or obtaining nutrients from the environment (a phenomenon known as metabolic plasticity). These factors pose significant challenges in targeting metabolic pathways for therapeutic purposes [257, 258].

Conclusions and future perspectives

To survive in a nutrient-poor tumor microenvironment, tumor cells adapt to the dynamic evolution of the TME with the aid of various strategies. Due to the intricate interplay among multiple factors in the microenvironment, comprehensive elucidation of the complex association of CAFs with multiple constituents in the TME remains a significant challenge. Based on the available data, a number of conclusions can be drawn. (1) CAFs generate several metabolites through metabolic reprogramming processes (including aerobic glycolysis, lipid metabolism, and amino acid metabolism) of the TME, which provide nutrients and energy sources to maintain the biosynthetic materials required for tumor progression. (2) CAFs alter the immune cell phenotype by releasing cytokines and chemokines, while promoting the recruitment of immunosuppressive cells and remodeling TIME, enabling tumor immune evasion. (3) In the immunosuppressive TME, CAFs and immunosuppressive cells, such as TAMs, TANs and Tregs, release inflammatory mediators that collectively support chronic inflammation and modify the pre-metastatic ecological niche of the tumor by promoting angiogenesis and ECM remodeling, ultimately supporting metastasis and invasion. However, tumor progression exacerbates the generation of an acidic and hypoxic TME and further mediates the recurrent cycle of tumor events by inducing dysregulated metabolism and immunosuppressive characteristics of TME. (4) Elucidation of the mechanisms by which CAFs regulate tumor progression should provide insights that guide the development of therapeutic regimens and provide clinically useful information for patient prognosis. Combinations of CAFs-based targeted-tumor therapy with immunotherapy or metabolism-based targeted treatments may lead to innovative strategies with enhanced efficacy.

Tumor cells are driven from a primitive to highly invasive and metastatic state involving changes in cellular secretion factors, TME biophysical structures, and tumor macroscopic features by metabolic reprogramming of CAFs, in conjunction with immune cell phenotypic alterations [43, 115]. However, the issue of CAFs-mediated promotion of tumor progression remains to be addressed.

1. The subpopulation of CAFs is widely heterogeneous within and between tumors and among different patient groups. One effective way to address the heterogeneity of CAFs subpopulations is to trace their origins, which poses new technical requirements for the study of CAFs. Owing to rapid advances in single-cell sequencing and spatial transcriptomic technologies, genes expressed by different clusters of CAFs have been identified. Commonly used markers of CAFs include α-SMA, FAP, FSP 1, PDGFRα/β, waveform proteins, and Tenascin C [259]. However, these markers are not specific and can be detected in other cell types. For example, CAFs have the potential to co-aggregate with tumor cells that have undergone EMT and share mesenchymal markers. Further investigation of CAFs-specific markers is therefore essential to clarify the dynamic evolution of CAFs in TME.
2. The characteristics of CAFs may overlap with certain other cell types. Therefore, it is crucial to standardize the nomenclature and scientific annotation of CAFs subpopulations. Currently, CAFs are mainly classified into three subpopulations, designated iCAFs, myCAFs, and apCAFs, based on their functions in pro-myofibroblastogenesis, inflammation/immunomodulation, and antigen presentation, respectively. However, different subtypes of CAFs in tumors have unique features, including marker expression patterns and secretion capacity, which may vary according to tumor type, organ, and species [260, 261]. Therefore, annotation of the function of each CAFs subgroup by specific markers can be performed, ultimately leading to the characterization of the properties of different CAFs subgroups as well as standardized nomenclature.

3. The majority of current studies have employed in vitro assays to explore the molecular mechanisms by which CAFs promote tumor progression. However, isolation of CAFs in tumor tissues may results in alterations in their phenotype as well as intracellular signaling due to the lack of TME encapsulation and stimulation by the surrounding components. In addition, primary cells have a limited lifespan, and during the process of senescence in CAFs, cytokines are released that affect the accuracy of the experiments. Unidentified components in the culture medium may also affect a number of metabolic programs in CAFs. Furthermore, models constructed using gene-edited animals are preferable to validate that CAFs regulate tumor progression in vivo, although this remains a significant challenge for most laboratories.
4. Owing to the high heterogeneity and metabolic plasticity of CAFs and lack of specific markers, it is difficult to establish clinically relevant experimental models for monitoring CAFs in real time. Several novel cell lineage tracing model systems may be beneficial for functional studies on CAFs, but are restricted by the limited availability of CAFs-specific markers. Novel CAFs markers identified via single-cell sequencing and spatial transcriptome technologies should contribute to the generation of new lineage-tracking models in the future, and given the rapid advances in proteomics and metabolomics, combined use of these technologies should also be beneficial for monitoring the evolution of CAFs. Moreover, in vivo imaging techniques may be useful for dynamic surveillance of CAFs in tumors.
5. CAFs can enhance glycolysis levels in tumor cells by releasing chemokines to activate protein kinase A. Tumor cell metabolism releases lactate to stimulate IL-6 expression in CAFs, culminating in a vicious cycle of CAFs and tumor metabolism [19, 262, 263]. Therefore, exploring the intrinsic mechanism of this malignant crosstalk using multi-omics techniques may be beneficial for the development of tumor-targeted therapeutic strategies.
6. Immunotherapy for cancer has received significant attention in recent years. It should be noted that immunotherapy may be highly effective in some tumor types while virtually ineffective in others. The primary reason for the lack of response to PD-1/PD-L immune checkpoint therapy is the inability of $CD8^+$ T-cells to infiltrate the TME of the 'cold tumor', which is mainly attributed to the physical barrier formed by CAFs-induced remodeling of the ECM, which prevents the infiltration of anti-tumor immune cells and effective drug delivery [264, 265]. Therefore, a potential strategy for optimization would be to initially target CAFs-induced ECM to disrupt the physical barrier, followed by tumor immunotherapy. Considering that CAFs can recruit immunosuppressive cells, such as TANs and TAMs, to promote tumor progression and resistance to therapy, attenuation and obstruction of the recruitment and infiltration of immunosuppressive cells in a specific manner is another potential therapeutic option. In conclusion, the objectives of CAFs-based tumor immunotherapy are to normalize the ECM, impede the interference of immunosuppressive cells, and complement tumor immunotherapy with other anti-tumor strategies, all of which may help improve the efficacy of immunotherapy.

Overall, comprehensive exploration of the complex associations of CAFs in TME, including metabolic reprogramming-mediated immunosuppressive TME and chronic inflammation, should aid in elucidating the impact of CAFs on tumor invasion and metastasis and contribute to the development of effective therapeutic strategies. Given the intricate interplay and dynamic evolution of TME, future studies should focus on multifaceted combination strategies targeting CAFs, metabolism, and immunotherapy.

List of symbols

2-HG	2-Hydroxyglutarate
ACAT1	Acetyl coenzyme acetyltransferase 1
ACLY	ATP-citrate lyase
ALOX5	Arachidonate lipoxygenase-5
apCAFs	Antigen-presenting CAFs
BC	Breast cancer
Bregs	B regulatory cells
CAFs	Cancer-associated fibroblasts
CAR	Chimeric antigen receptor
cCAFs	Circulating CAFs
CCL-	C–C motif chemokine ligand
CRC	Colorectal cancer
CTCs	Circulating tumor cells
CTL	Cytotoxic T lymphocytes
CXCL-	C–X–C motif chemokine ligand
DAMP	Damage-associated molecular patterns
dCAFs	Developmental CAFs
DCs	Dendritic cells
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
EMT	Epithelial mesenchymal transition
EPCs	Endothelial progenitor cells
FAP	Fibroblast activation protein
FASN	Fatty acid synthase
FSP1	Fibroblast specific protein 1
FSTL1	Follistatin like protein 1
GC	Gastric cancer
GFPT2	Glutamine fructose-6-phosphate aminotransferase 2
GLUT1	Glucose transport protein 1
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HA	Hyaluronan
HCC	Hepatocellular carcinoma
HCQ	Hydroxychloroquine
HGF	Hepatocyte growth factor
HIF-1α	Hypoxia-inducible factor

HNSC	Head and neck squamous carcinoma
iCAFs	Inflammatory CAFs
IDO	Indoleamine 2,3-dioxygenase
IFN-γ	Interferon-γ
IGF1	Insulin-like growth factor 1
IL-	Interleukin-
LAG-3	Lymphocyte-activation gene3
LC	Lung cancer
LOX	Lysyl oxidase
LPC	Lysophosphatidylcholine
MCT1	Monocarboxylate transporter 1
MCT4	Monocarboxylate transporter 4
MDSCs	Myeloid-derived suppressor cells
meCAFs	Metabolic cancer-associated fibroblast
MIF	Macrophage migration inhibitory factor
MMP	Matrix metalloproteinases
mTORC1	MTOR complex 1
myCAFs	Myofibroblast CAFs
NG	Not given
NK	Natural killer
NO	Nitric oxide
NPC	Nasopharyngeal carcinoma
OSCC	Oral squamous cell carcinoma
OVCA	Ovarian cancer
OXPHOS	Oxidative phosphorylation system
PCa	Prostate cancer
pCAFs	Cancer-promoting CAFs
PDAC	Pancreatic ductal adenocarcinoma
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PD-L1	Programmed cell death ligand 1
PGE2	Prostaglandin E2
rCAFs	Cancer-restraint CAFs
sCAFs	Stromal CAFs
SDF1	Stromal cell derived factor 1
TAMs	Tumor-associated macrophages
TANs	Tumor-associated neutrophils
TCA	Tricarboxylic acid
TDO2	Tryptophan 2,3-dioxygenase 2
TGF-β	Transforming growth factor-β
TIM-3	T cell immunoglobulin domain and mucin domain-3
TME	Tumor microenvironment
TNC	Tenascin C
Tregs	T regulatory cells
vCAFs	Vascular CAFs
VEGF	Vascular endothelial growth factor
α-SMA	α-Smooth muscle actin

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Declarations

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