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The diverse functions and therapeutic implications of cancer-associated fibroblasts in colorectal cancer

Zeyin LAI[1]; Hangyuan ZHAO[1]; Hong DENG[1,2,*]

[1] Department of Pathology, Key Laboratory of Disease Proteomics of Zhejiang Province, School of Medicine, Zhejiang University, Hangzhou, 310058, China
[2] Department of Pathology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, 310018, China

Abstract: In the development of colorectal cancer (CRC), cancer-associated fibroblasts (CAFs) play a pivotal role in establishing tumor-permissive extracellular matrix structures, angiogenesis, and modulating the immune status of the tumor microenvironment (TME), thereby influencing tumor metastasis and resistance to radiotherapy and chemotherapy. The pleiotropic effects of CAFs in the TME may be attributed to the heterogeneous origin and high plasticity of their population. Given the specificity of CAFs, they provide a variety of potential target molecules for future CRC treatment, which may play an indispensable role in CRC therapeutic strategies. This review summarizes the origin of CAFs and their roles in the CRC tumor microenvironment, including the interaction between exosomes and CAFs in CRC. Additionally, we discuss potential therapeutic strategies targeting CAFs.

Abbreviations

5-FU	5-Fluorouracil
ACTA2	Actin alpha 2
AOM	Azoxymethane
BMP4	Bone morphogenetic protein 4
BMP5	Bone morphogenetic protein 5
C1QC	Complement C1q C chain
CAC	Colitis-associated cancer
CAF	Cancer-associated fibroblast
CAFs-exo	Cancer-associated fibroblast-derived exosome
CCL2	C-C motif chemokine ligand 2
CELF2	CUGBP elav-like family member 2
CRKL	CRK like proto-oncogene: adaptor protein
CXCL1	C-X-C motif chemokine ligand 1
CRC	Colorectal cancer
CTSH	Cathepsin H
DSS	Dextran sodium sulfate
ECM	Extracellular matrix
EMT	Epithelial-to-mesenchymal transition
FAP	Fibroblast activation protein
FBXW7	F-box and WD repeat domain-containing 7
FXR	Farnesoid X receptor
HGF	Hepatocyte growth factor
IAF	Inflammatory associated fibroblasts
ICB	Immune checkpoint blockade
ICRG	Immune- and CAF-related gene
IL-1	Interleukin-1
KLF5	Krüppel like factor 5
KRAS	Kirsten rats arcamaviral oncogene homolog
L-OHP	Oxaliplatin
Lepr	Leptin receptor
lncRNA	Long non-coding ribonucleic acid
lnc-FAL1	Focally amplified lncRNA on chromosome 1
LOX	Lysyl oxidases
MCAM	Melanoma cell adhesion molecule
MDSC	Myeloid-derived suppressor cell
MERFISH	Multiplexed error-robust fluorescence in situ hybridization
MFAP	Microfibrillar-associated protein
MOAP1	Modulator of apoptosis 1
MMP	Metalloproteinase
MSC	Mesenchymal stem cell
MYL9	Myosin light chain 9
NF-κB	Nuclear factor kappa B
NK cell	Natural killer cell
OXA	Oxaliplatin
PDGFA	Platelet derived growth factor subunit A
PDGFRA	Platelet derived growth factor receptor A

POSTN	Periostin
PTEN	Phosphatase and tensin homolog
RNA	Ribonucleic acid
ROS	Reactive oxygen species
TAGLN	Transgelin
TAZ	Transcriptional co-activator with PDZ-binding motif
TFCP2	Transcription factor CP2
TGF-β	Transforming growth factor-β
TLR	Toll-like receptor
TME	Tumor microenvironment
TNF	Tumour necrosis factor
Treg	Regulatory T cell
TRIM3	Tripartite motif containing 3
VEGF	Vascular endothelial growth factor
WNT5B	Wnt family member 5B
WWOX	WW domain-containing oxidoreductase
YAP	Yes-associated protein
yCRC	Young-onset colorectal cancer

Introduction

Colorectal cancer (CRC) is one of the most common cancers globally [1], often accompanied by desmoplasia during its advancement. This pathological process is marked by the proliferation and accumulation of fibrous tissue, often predictive of unfavorable disease outcomes and therapeutic response [2–4]. The desmoplastic reaction consists mainly of activated fibroblasts, also called cancer-associated fibroblasts (CAFs). In the complex and dynamic milieu of tumor microenvironment (TME), CAFs occupy a pivotal position [5]. These specialized stromal cells, originating from a heterogeneous population with high plasticity, play a multifaceted role in tumor progression. Since Rudolf L.K. Virchow's initial observations of CAF, the function and role of fibroblasts have been extensively investigated, particularly in the context of cancer. In CRC, CAFs are not merely passive bystanders, rather, they actively contribute to the establishment of tumor-permissive extracellular matrix structures, angiogenesis, and modulation of the immune status within the TME. The significance of CAFs in CRC is underscored by their involvement in key processes such as tumor metastasis and resistance to radiotherapy and chemotherapy. This intricate interplay between CAFs and cancer cells within the TME represents a novel and promising target for therapeutic intervention. The pleiotropic effects of CAFs are attributed to their diverse origins, including the activation of quiescent fibroblasts and other stromal cell populations [6]. The resulting heterogeneity in CAFs is reflected in their ability to secrete a wide range of factors that influence tumor behavior. In this review, we delve into the origins of CAFs and their diverse functions in the CRC TME. We examine the complex interactions between CAFs and tumor cells, including the role of exosomes in mediating these interactions. Furthermore, we discuss the therapeutic implications of targeting CAFs in CRC, highlighting their potential as novel therapeutic targets. Here we specifically propose the mechanisms underlying the role of diet and microbiota in promoting CRC progression through their interactions with CAFs. Understanding the complex roles of CAFs in CRC progression holds the key to developing more effective therapeutic strategies against this deadly disease.

The Origin of CAF in CRC

Fibroblasts occupy a fundamental position among the cellular constituents of connective tissue, essential for maintaining the structural scaffold and physiological functions of these tissues. In 1858, the German pathologist Rudolf L.K. Virchow first reported spindle cells in connective tissue. These cells are embedded in the fibrous matrix and are responsible for the synthesis and secretion of extracellular matrix (ECM). In rectal juvenile polyps, Römer captured the morphology of fibroblastic cells, which are spindle-shaped or flat star-shaped with protrusions, considering that these mesenchymal components have great proliferation potential [7]. Fibroblasts in tumor stroma are collectively known as CAFs. Current researchers have identified certain sources of CAF, as depicted in Fig. 1. These originate from the activation of quiescent fibroblasts and stellate cells, the recruitment and differentiation of bone marrow-derived mesenchymal stem cells (MSCs), and furthermore, the transdifferentiation process of epithelial cells, endothelial cells, pericytes, and adipocytes [6,8]. Different opinions have been expressed about the origins of CAFs. The origin of CAF is still controversial since there are no specific markers to them. The consensus among experts suggests that the principal source of CAFs lies in their indigenous precursors, though it is noteworthy that a minor fraction of CAFs traces their origins to alternative ancestral lineages [9]. Among all the origins, fibroblasts are the primary source of CAF in CRC. Within the context of gastrointestinal cancer, native fibroblasts that inhabit the vicinity of tumor cells have been identified as undergoing activation mediated by signaling cues emanating from the tumor cells. This activation process contributes significantly to the emergence of a specific subset of CAFs [10]. Some special sources have been found in CRC. In the colitis-associated cancer (CAC) mouse model, intestinal smooth muscle cells undergo transformation into fibroblasts through the activation of YAP/TAZ, initiating the CAC process, and this transformation process is age-dependent [11]. Furthermore, using lineage-tracing techniques, studies have found that leptin receptor (Lepr)-lineage intestinal stromal cells proliferate and differentiate into melanoma cell adhesion molecule (MCAM)+ CAFs during the development of CRC. These CAFs form a tumor-promoting immune microenvironment by interacting with the nuclear-factor-κB-interleukin 34/C-C Motif Chemokine Ligand 8 (NF-κB-IL34/CCL8) signaling pathway that facilitates the chemotactic migration of macrophages [10].

Different sources of CAF have different effects on tumors because they retain some of the function of the tissue of origin. On the other side, CAFs originating from diverse tissues exhibit a series of unique molecular signatures, which significantly differentiate their molecular expression profiles from those of CAFs of other origins. These distinctive
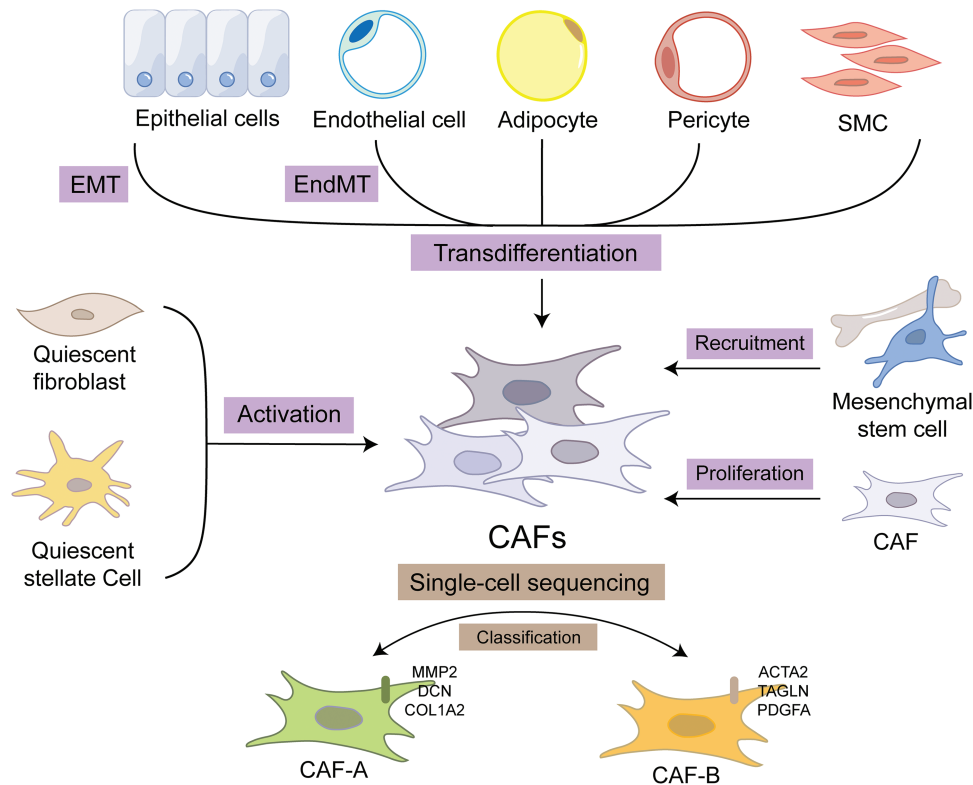
FIGURE 1. The diverse origins of CAF and the classification. The sources of CAF include the activation of quiescent fibroblasts and stellate cells, the recruitment and differentiation of bone marrow-derived mesenchymal stem cells as well as the transdifferentiation of epithelial cells, endothelial cells, pericytes, and adipocytes. CAF itself also proliferates, which promotes the aggregation of CAF. These different sources of CAFs can be classified by single-cell sequencing methods. CAF-A is linked to extracellular matrix (ECM) remodeling, expressing MMP2, DCN, and COL1A2. While CAF-B expresses markers that are characteristic of activated myofibroblasts, including ACTA2, TAGLN, and PDGFA. CAF, cancer-associated fibroblast; EMT, epithelial-to-mesenchymal transition; EndMT, endothelial-to-mesenchymal transition; SMC, smooth muscle cell; MMP, matrix metalloproteinase; DCN, decorin; COL1A2, collagen type I alpha 2; ACTA2, actin alpha 2; TAGLN, transgelin; PDGFA, platelet-derived growth factor subunit A.

molecular expression patterns are crucial for elucidating their functional roles and underlying mechanisms of CAFs in tumor progression, metastasis, and other pathological processes. In addition, the different molecular expressions of CAFs also suggest their diverse functions. Utilizing single-cell RNA sequencing, Li et al. classified CAFs in CRC into two distinct types: CAF-A and CAF-B. CAF-B expresses markers of activated myofibroblasts, such as actin alpha 2 (ACTA2), transgelin (TAGLN), and platelet-derived growth factor subunit A (PDGFA), affecting TME and cell invasion. CAF-A is linked to ECM remodeling, which expressed metalloproteinase 2 (MMP2), decorin (DCN), and Collagen Type I Alpha 2 (COL1A2), potentially as an intermediate or independent CAF subtype, enabling tumor invasion and metastasis [12]. The functional heterogeneity of CAF is related to the difference in its molecular expression, and its origin is an important factor determining the molecular expression of CAF. Therefore, the functional heterogeneity of CAF may be related to the diversity of its sources.

The Function of CAF in CRC

CAF occupies a pivotal position in many key aspects of tumorigenesis (Fig. 2). The diverse effects of CAFs on cancer may stem from their heterogeneity and plasticity, manifesting in the contextual impact of carcinogenesis. The

progression of CRC is a complex and progressive process, stemming from the synergistic effect of multiple carcinogenic factors [13]. It is crucial to obtain more comprehension of its underlying biological mechanisms. In the pathogenetic process of CRC, there exists a complex and multidirectional interactive pattern between CAFs and tumor cells. This relationship is not one-sided but rather a dynamic process involving mutual influences between the two parties. CAFs possess the ability to release a diverse array of bioactive molecules, including growth factors, chemokines, and extracellular matrix proteins, which can directly or indirectly stimulate tumor cell proliferation and survival, thereby promoting the malignant progression of tumors [14]. Furthermore, CAFs possess a remarkable ability to modify the tumor microenvironment. Serving as the "breeding ground" for tumor proliferation and dissemination, those environment exerts a decisive influence on the biological behavior of tumor cells. By virtue of their ability to secrete various enzymes and cytokines, CAFs are able to reshape the structure of the TME, promote the formation of blood vessels and lymphatic vessels, and simultaneously suppress the activity of immune cells, thus creating a more favorable environment for tumor cell growth and dissemination [15].

In recent years, the scientific community has gained a deeper understanding of the role played by fibroblasts in
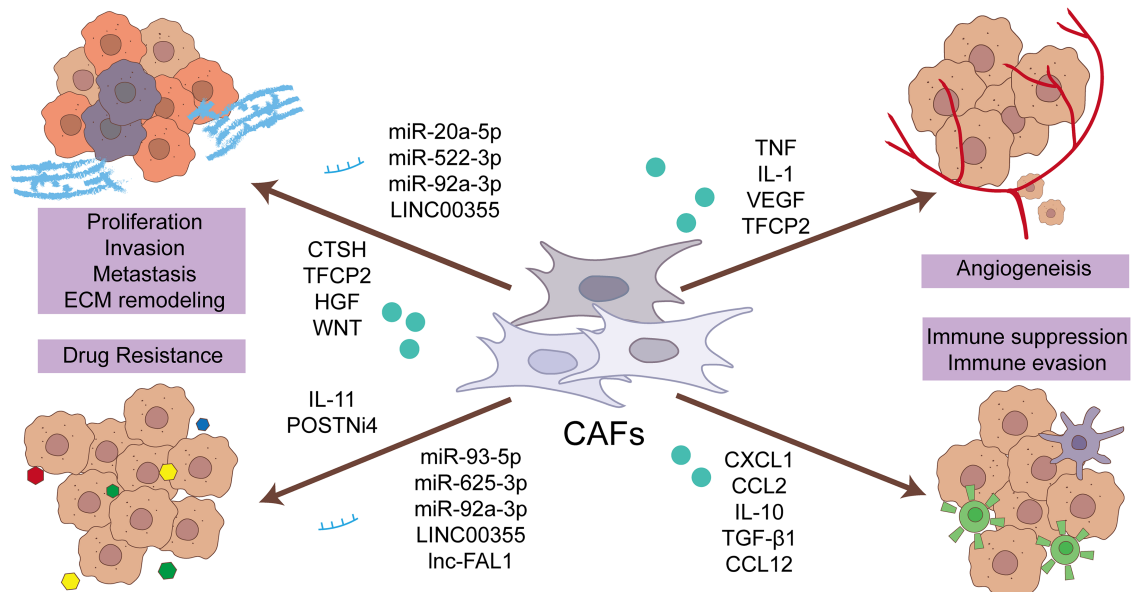
FIGURE 2. The function of CAF in driving the progression of CRC resides in its ability to influence the biological activities of CRC cells, blood vessels, immune cells, and the ECM. Specifically, CAFs promote tumor proliferation, angiogenesis, immune suppression, and ECM remodeling, thereby fostering the growth, invasion, and immune evasion of CRC. Furthermore, CAFs are a contributing factor to drug resistance, posing a significant challenge in the clinical management of CRC. This multifaceted role of CAFs underscores their significance in the complex TME. CRC, colorectal cancer cell; CAF, cancer-associated fibroblast; ECM, extracellular matrix; CCL2, C-C motif chemokine ligand 2; CXCL1, C-X-C motif chemokine ligand 1; CTSH, cathepsin H; HGF, hepatocyte growth factor; lnc, long non-coding RNA; miR, microRNA; POSTNi4, periostin isoform 4; TFCP2, transcription factor CP2; TGF-β, transforming growth factor-β; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor; WNT, Wnt family member.

tumor formation and development. Specifically, people are beginning to recognize that the protumorigenic state of fibroblasts can emerge even prior to the malignant alteration of tumor cells [16]. CAFs may form due to damage to the colonic mucosa, oxidative stress, or chronic inflammation [17–19], these changes may precede mutations in epithelial cells. When mutations eventually occur in epithelial cells, these pre-existing CAFs may already be poised to participate in the tumor transformation process, significantly influencing the occurrence and progression of CRC. In the azoxymethane/dextran sodium sulfate (AOM/DSS)-induced colitis-associated cancer model, collagen type VI alpha 1 (Col6a1)+ CAFs can promote tumor-associated angiogenesis and exert oncogenic functions through their innate immune activation by tumour necrosis factor receptor 1 (TNFR1) or IL (interleukin)-1 receptor signaling pathways [20]. Cadinu et al. used multiplexed error-robust fluorescence in situ hybridization (MERFISH) technology to delineate four different subtypes of inflammatory-associated fibroblasts (IAF) in colitis, which are closely related to the spatial organization of the intestinal tract. Among them, IAF1 is associated with early changes in normal lamina propria fibroblasts, while IAF4 located in the top crypt is closely related to extracellular matrix (ECM) remodeling and various immune activation processes [21,22]. These activated fibroblasts in inflammatory bowel disease can promote tumorigenesis [22]. The function of CAF is heterogeneous. Just as the function of CAF in different regions of the same tumor is different, the function of CAF in different development stages of the same tumor is also different. CAFs exhibit stage-specific differential function. For example, in the early stage of CRC (T1CRC), CAFs can

upregulate the level of CD44 in tumor cells through direct intercellular communication, thereby promoting matrix remodeling. On the other hand, Cathepsin H is significantly upregulated in CAFs, and directly induces matrix remodeling. While the sustained upregulation of Cathepsin H (CTSH) is specifically observed in T1CRC [23].

CAFs serve as a pivotal perpetrators in the malignant progression. CAFs can secrete related proteins to reshape the extracellular matrix by the balance of metalloproteinases (MMPs) and their inhibitors, alongside other enzymes such as lysyl oxidases (LOX) and play its function by interacting with tumor cells and other stromal cells [24,25]. During the progression of tumorigenesis, CAFs emerge as the key regulators in the unbalanced collagen turnover, ultimately contributing to desmoplasia—a condition characterized by excessive deposition of collagen in the TME [13,24,26]. In CRC, tumors exhibiting a high stromal content have been associated with a dismal prognosis for patients, suggesting a poor clinical outcome [4]. The pattern of desmoplastic reaction (DR) correlates with CRC recurrence [2,27] and liver metastasis [3]. In the context of TME, high expressions of angiogenic factors and inflammatory cytokines, as well as hypoxia, are all contributory factors that significantly enhance tumor angiogenesis [28,29]. In CRC, the absence of p53 significantly triggers the generation of reactive oxygen species (ROS), thereby potently inducing vascular endothelial growth factor (VEGF) production in fibroblasts, ultimately contributing to tumor progression [30]. Kirsten rats arcomaviral oncogene homolog (KRAS) activates the transcription factor CP2 (TFCP2) which upregulates the expression of pro adipogenic factors bone morphogenetic protein 4 (BMP4) and Wnt family member 5B (WNT5B),

triggering the transformation of CAFs into lipid-rich CAFs. These lipid-rich CAFs are capable of further producing VEGFR, thereby promoting angiogenesis and tumor progression [31]. KRAS is capable of modulating cellular response to hepatocyte growth factor (HGF) through the HGF-C-MET axis, thereby affecting invasive capabilities [32]. However, one research indicates that despite the crucial role of KRAS mutation in CRC, CRC cells maintain the ability to regulate tumor-promoting characteristics of fibroblasts even in the absence of KRAS expression, suggesting a potential mechanism for resistance to KRAS inhibition [33].

It is noteworthy that CAFs engage in interactions with a majority of cells within TME, encompassing diverse types of immune cells. CAFs can regulate the immune system of the TME by secreting a variety of proteins, cytokines, chemokines, etc., thus promoting the progression of CRC [34–36]. CAFs with different phenotypes have different mechanisms in regulating the immune microenvironment. For example, CAFs expressing myosin light chain 9 (MYL9) exhibit regulatory functions in modulating the release of cytokines and chemokines, including C-X-C motif chemokine ligand 1 (CXCL1), C-C Motif Chemokine Ligand 2 (CCL2), IL-10, and transforming growth factor-β1 (TGF-β1). This modulation triggers the polarization from macrophages M0 to macrophages M2, enhancing the recruitment of macrophages M2 and hindering the activation of dendritic cells [37]. While microfibrillar-associated protein (MFAP5)+ fibroblasts release complement C3, which interacts with myeloid cells, specifically complement C1q C chain (C1QC)+ macrophages, activating the complement system. In turn, myeloid cells can enhance the invasive phenotype of MFAP5+ fibroblasts [38]. In the context of cancer biology, the interaction between CAFs and immune cells generates a positive feedback loop that intensifies, thus fostering the malignant transformation and progression of tumors. Furthermore, research has established that algorithmic models, which capitalize on immune- and CAF-related genes (ICRGs), exhibit remarkable predictive value in forecasting both the prognosis and the efficacy of immunotherapy for patients diagnosed with colorectal cancer [39,40]. Under physiological conditions, the immune system possesses the capability to identify and eliminate abnormal tumor cells. In scenarios where the immune system is impaired or weakened, malignant cells gain the capacity to circumvent the immune system's surveillance and clearance mechanisms, culminating in tumor genesis. Extensive research has revealed that CAFs play a pivotal role in fostering immunosuppression within the TME and enabling immune evasion in CRC. Specifically, CAFs hinder the infiltration and functional activity of critical immune cells, including CD8+ T-cells, CD4+ T-cells, and natural killer (NK) cells. Furthermore, they can concomitantly promote the activation and recruitment of immunosuppressive cells, exemplified by M2 macrophages, myeloid-derived suppressor cells (MDSCs), and regulatory T-cells (Tregs), thereby augmenting the immune evasion capabilities of tumor cells [41].

One significant pathway tumors employ to achieve immune evasion is through the overexpression of immune checkpoint (IC) molecules. This overexpression attenuates the killing effect of T cells against tumor cells. The essence of immunotherapy targeting immune checkpoints lies in the liberation of T cells, restoring their normal activation level, and enhancing their capability to attack tumor cells [42]. CAF can promote immunotherapy resistance in CRC by mediating T cells. CAFs may suppress CD8+ T cell infiltration through TGFβ signaling, thereby executing immune checkpoint blockade (ICB) [43]. CAFs also play a role in mediating the development of resistance to traditional chemotherapeutic drugs. The production of ECM proteins and matrix remodeling by CAFs, through MMPs, leads to an increase in matrix stiffness, and intertumoral pressure, thereby hindering the penetration of chemotherapeutics and targeted therapies [44]. CAF can also establish intercellular communication with CRC cells via exosomes, leading to tumor drug resistance (as will be further discussed later).

Additionally, one research focusing on young-onset CRC (yCRC) revealed that *Actinomyces* residing in CAFs promote inflammation and suppress anti-tumor responses by inducing the activation of Toll-like receptor 2/nuclear factor kB (TLR2/NF-kB) and Toll-like receptor 4/nuclear factor kB (TLR4/NF-kB) pathways, while reduces the infiltration of CD8+ T lymphocytes in the TME [45]. This suggests that the progression of CRC can occur via modulation of the gut microbiota existing in CAF, yet these mechanisms require further investigation.

CAF-Derived Exosomes in CRC Progression

In 1981, Trams and his colleagues named the small vesicles with specific membrane structures discovered in the supernatant of cultured sheep red blood cells as "exosomes" [46]. These exosomes are round or elliptical membranous vesicles with an average diameter of 100 nanometers [47]. They are rich in various components such as lipids, proteins or peptides, mRNA, microRNA (miRNA), and long non-coding RNA (lncRNA) [47–49]. Extant investigations have revealed the pivotal significance of exosomes in intercellular communication and disease progression [50]. The exosomes secreted by CAF harbor numerous factors that possess the ability to regulate signaling pathways, pivotal in the advancement of cancer. For example, CAF-derived exosomes (CAFs-exo) miR-20a-5p enhances the proliferation and migration capabilities by targeting phosphatase and tensin homolog (PTEN) to induce the expression of EMT markers, which is closely associated with the occurrence of lymph node metastasis in advanced stages of the tumor [51]. CAFs-exo miR-522-3p promotes the growth and metastasis of CRC by downregulating bone morphogenetic protein 5 (BMP5) [52]. The exosomal miR-625-3p derived from CAFs-xxo may promote the development of chemotherapy resistance in CRC by inhibiting the CUGBP elav-like family member 2/WW domain-containing oxidoreductase (CELF2/WWOX) pathway [53]. CAFs elevate the level of miR-92a-3p in CRC

cells via exosomes, thereby activating the Wnt/β-catenin pathway and inhibiting mitochondrial apoptosis by directly suppressing F-box and WD repeat domain-containing 7 (FBXW7) and modulator of apoptosis 1 (MOAP1). This process contributes significantly to the enhancement of cellular stemness, EMT, metastasis, and 5-fluorouracil/oxaliplatin (5-FU/L-OHP) resistance in CRC [54].

In a similar fashion to miRNA, lncRNA secreted by CAF via exosomes has exhibited properties that contribute to tumor progression and promotion. By modulating the miR-34b-5p/CRK Like proto-oncogene (miR-34b-5p/CRKL) axis, LINC00355 derived from CAFs-exo promotes epithelial-to-mesenchymal transition (EMT) and chemotherapy resistance in CRC [55]. CAFs-exo LINC00355 facilitates EMT and resistance to chemotherapy with 5-FU, Oxaliplatin (OXA), and cisplatin via modulation of the miR-34b-5p/CRKL axis [55]. The combination of platinum-based drugs with other chemotherapy drugs (such as 5-FU and leucovorin calcium) is one of the standard basic chemotherapy regimens for colorectal cancer [56]. Studies have found that CAF upregulates the expression of IL11 and periostin isoform 4 (POSTNi4) through direct activation of the TGF-β pathway, leading to the development of resistance to platinum-based drugs in CRC [57]. CAFs-exo also has the ability to induce resistance to platinum-based drugs in CRC, indicating that they may have an emerging role in drug resistance during the treatment of CRC. CAFs-exo lnc-FAL1 promotes the development of oxaliplatin resistance in CRC by facilitating tripartite motif containing 3 (TRIM3)-dependent Beclin1 polyubiquitination and degradation, which consequently inhibits oxaliplatin-induced autophagic cell death [58]. Besides, CAFs-exo miR-93-5p induces the proliferation of SW480 cells, thus resisting the apoptosis induced by radiotherapy [59]. These findings not only reveal the significant role of CAFs-exo in the progression of CRC but also provide new potential targets for the treatment.

Tackling Strategies for CAFs

During the progression of CRC, CAFs play a pivotal role by virtue of their unique abilities to regulate tumor cell proliferation, invasion, and metastasis, while also influencing cellular immune responses and chemotherapy resistance. Given the complexity of the TME and the multifaceted support provided by CAFs for tumor growth, they emerge as highly promising targets for cancer therapy [60]. Therapeutic strategies targeting CAFs are anticipated to offer novel perspectives and approaches for cancer intervention and treatment. The potential therapeutic approaches based on CAFs have been extensively investigated, and their core concepts can be summarized in two major directions (Fig. 3). Firstly, the therapeutic strategy targeting CAFs themselves primarily focuses on achieving therapeutic goals by eliminating specific CAF subpopulations. FAP+ CAF is currently the most commonly used target [61]. Other targets include platelet-derived growth factor receptor alpha (PDGFRA), and CD142 [62,63]. Secondly, researchers have also concentrated on regulating the interaction between tumor cells and CAFs,
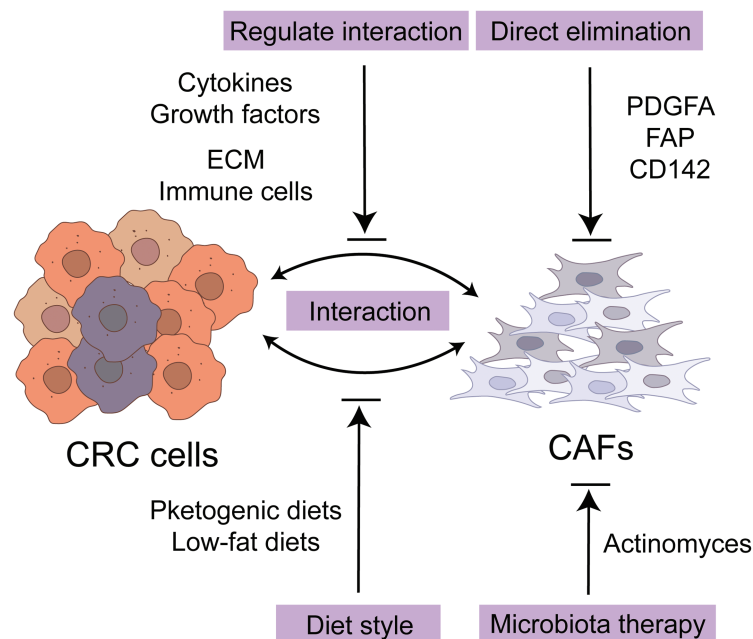

FIGURE 3. Potential therapeutic strategies for CRC with CAF. The potential therapeutic approaches based on CAFs can be summarized in two major directions. Firstly, the therapeutic strategy targeting CAFs themselves focuses on eliminating specific CAF subpopulations including FAP+, PDGFRA+, and CD142+. Secondly, researchers have also concentrated on regulating the interaction between tumor cells and CAFs, mediated by cytokines and growth factors. Additionally, some other strategy indicates modulating immune cells within the ECM or the physical properties of the ECM. Furthermore, ketogenic diets and low-fat diets have the potential to extend the survival duration of patients with CRC. Targeting microbiota also presents a potential approach for achieving therapeutic efficacy in CRC. CRC, colorectal cancer cell; CAF, cancer-associated fibroblast; ECM, extracellular matrix; FAP, fibroblast activation protein; PDGFA, platelet-derived growth factor subunit A.

aiming to attenuate their synergistic effects on cancer development, particularly targeting the positive feedback mechanisms that promote cancer progression [64]. This interaction involves the activation of various tumor-related pathways mediated by cytokines and growth factors. By intervening in the intercellular communication between tumor cells and CAFs, CAFs can be deactivated, inducing their transition to non-tumor-promoting subtypes, or directly inhibiting the tumor-promoting effects of CAFs on tumor cells [65,66]. Additionally, some other strategy involves modulating immune cells within the ECM or the physical properties of the ECM to influence the function of CAFs, thereby providing new perspectives and methods for treatment [43,44,67,68]. These CAF-based treatments are primarily carried out through pharmacological interventions, and the progress of these drugs and their clinical studies has been comprehensively outlined in previous reviews [16,69].

Furthermore, several metabolic-based studies have indicated the potential of ketogenic diets and low-fat diets to extend the survival duration of patients with CRC [70,71]. A ketogenic diet can increase ketone body production in the TME of MC38 CRC mice, thereby inhibiting Krüppel factor 5 (KLF5)-dependent CXCL12 expression in CAFs. By reducing the level of CXCL12, NK cells and CD4+ T cells are enriched in the TME, while immunosuppressive Treg cells and MDSCs are depleted. This reconstruction of the immune tumor microenvironment and reactivation of immune surveillance can enhance the anti-cancer effect of PD-1 blockade in murine CRC [70]. Following the intake of a high-fat diet, the metabolic production of conjugated bile acids (BAs) prompts an increase in the number of bacteria with bile salt hydrolase activity in the colon, thereby disrupting the normal metabolic process of BAs. This alteration results in a significant rise in the levels of deconjugated and secondary BA within the colon. These elevated BA, via the farnesoid X receptor (FXR), excessively activate the WNT signaling pathway in colonic MSC, inducing CAF-like properties of MSC, ultimately exerting tumorigenesis [71]. Additionally, given the association between the occurrence of CRC and the intestinal microbiota residing in CAFs, targeting these microbiotas through therapeutic interventions presents a potential approach for achieving therapeutic efficacy in CRC [45]. In yCRC, a reduced tumor microbial diversity was observed, with *Actinomyces* serving as a key microbiota that primarily resides in CAFs. Notably, *Actinomyces* coexists with other tumor-promoting microbiota, including Bacteroidia, Gammaproteobacteria, and *Pseudomonas*. On the other hand, *Actinomyces* has been found to facilitate intestinal inflammation and suppress antitumor immunity, thereby contributing to tumor progression. Consequently, microbial therapy emerges as a promising non-invasive therapeutic target.

Conclusion and Perspective

In the intricate landscape of CRC progression, CAFs have emerged as crucial players in tumor development, metastasis, and resistance to therapeutic interventions. The pleiotropic effects of CAFs, stemming from their heterogeneous origin and high plasticity, are now being recognized as potential targets for novel therapeutic strategies [35,72]. This review has provided a comprehensive overview of the origin of CAFs, their multifaceted roles in the CRC tumor microenvironment (TME), and the interplay between CAFs and exosomes.

The understanding of CAFs' role in CRC has evolved from mere stromal components to active modulators of tumor growth and metastasis. CAFs not only contribute to the establishment of tumor-permissive extracellular matrix structures and angiogenesis but also modulate the immune status of the TME. These activities facilitate tumor cell invasion, migration, and evasion from immune surveillance, ultimately influencing tumor progression and therapeutic resistance. Exosomes, as intercellular communication vehicles, have been shown to play a significant role in the crosstalk between CAFs and tumor cells. These nano-sized vesicles carry a cargo of proteins, lipids, and nucleic acids, which can be transferred to recipient cells, modulating their behavior. The role of exosomes in CAF-mediated tumor progression and metastasis remains an area of active investigation. Given the specificity and complexity of CAFs in CRC, targeting CAFs represents a promising therapeutic approach [73]. Potential strategies include the inhibition of CAF activation, disruption of CAF-tumor cell crosstalk, and modulation of CAF-derived signaling pathways. However, the translation of these preclinical findings into clinical practice faces several challenges, including the identification of specific CAF markers, the development of target-specific therapeutics, and the assessment of their safety and efficacy in clinical trials [74]. Future research should focus on elucidating the molecular mechanisms underlying CAF heterogeneity and plasticity, as well as their role in tumor progression and therapeutic resistance. This will not only provide insights into the biology of CAFs but also identify potential therapeutic targets. Furthermore, the development of novel CAF-specific biomarkers will enable the selection of appropriate therapeutic strategies.

In conclusion, CAFs represent a promising therapeutic target in CRC. The understanding of their role in tumor progression and the development of CAF-specific therapeutics could significantly impact the management of CRC patients. However, further research is needed to address the challenges faced in translating these findings into clinical practice.

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