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Contents

Monthly Volume 16 Number 12 December 15, 2024

EDITORIAL

REVIEW

ORIGINAL ARTICLE

Case Control Study

Retrospective Cohort Study

World Journal of Gastrointestinal Oncology

Monthly Volume 16 Number 12 December 15, 2024

Contents

World Journal of Gastrointestinal Oncology

Monthly Volume 16 Number 12 December 15, 2024

Contents

LETTER TO THE EDITOR

World Journal of Gastrointestinal Oncology

Monthly Volume 16 Number 12 December 15, 2024

Contents

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REVIEW

Unraveling the role of cancer-associated fibroblasts in colorectal cancer

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Abstract

Within the intricate milieu of colorectal cancer (CRC) tissues, cancer-associated fibroblasts (CAFs) act as pivotal orchestrators, wielding considerable influence over tumor progression. This review endeavors to dissect the multifaceted functions of CAFs within the realm of CRC, thereby highlighting their indispensability in fostering CRC malignant microenvironment and indicating the development of CAFs-targeted therapeutic interventions. Through a comprehensive synthesis of current knowledge, this review delineates insights into CAFs-mediated modulation of cancer cell proliferation, invasiveness, immune evasion, and neovascularization, elucidating the intricate web of interactions that sustain the pro-tumor metabolism and secretion of multiple factors. Additionally, recognizing the high level of heterogeneity within CAFs is crucial, as they encompass a range of subtypes, including myofibroblastic CAFs, inflammatory CAFs, antigen-presenting CAFs, and vessel-associated CAFs. Innovatively, the symbiotic relationship between CAFs and the intestinal microbiota is explored, shedding light on a novel dimension of CRC pathogenesis. Despite remarkable progress, the orchestrated dynamic functions of CAFs remain incompletely deciphered, underscoring the need for continued research endeavors for therapeutic advancements in CRC management.

Key Words: Colorectal cancer; Cancer-associated fibroblasts; Therapeutic strategies; Microbiota; Neovascularization

Core Tip: Within the intricate milieu of colorectal cancer (CRC) tissues, cancer-associated fibroblasts (CAFs) act as pivotal orchestrators, wielding considerable influence over tumor progression. This review endeavors to dissect the multifaceted functions of CAFs within the realm of CRC, thereby highlighting their indispensability in fostering CRC malignant microenvironment and indicating the development of CAFs-targeted therapeutic interventions. Through a comprehensive synthesis of current knowledge, this review delineates insights into CAFs-mediated modulation of cancer cell proliferation, invasiveness, immune evasion, and neovascularization, elucidating the intricate web of interactions that sustain the pro-tumor metabolism and secretion of multiple factors. Additionally, recognizing the high level of heterogeneity within CAFs is crucial, as they encompass a range of subtypes, including myofibroblastic CAFs, inflammatory CAFs, antigen-presenting CAFs, and vessel-associated CAFs. Innovatively, the symbiotic relationship between CAFs and the intestinal microbiota is explored, shedding light on a novel dimension of CRC pathogenesis. Despite remarkable progress, the orchestrated dynamic functions of CAFs remain incompletely deciphered, underscoring the need for continued research endeavors for therapeutic advancements in CRC management.

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INTRODUCTION

Malignant tumors have become a significant factor affecting the mortality worldwide, with colorectal cancer (CRC) being among the crucial types of malignancies. CRC is the third most common cancer and the second leading cause of cancer-related death worldwide[1]. It is well known that the development of tumors is not solely due to changes of genes within tumor cells, and the alterations in the surrounding microenvironment also play a significant role in tumor progression.

Over 100 years ago, Paget and others elucidated the importance of the tumor microenvironment (TME) with the "seed and soil" hypothesis which implied a synergistic interaction between tumors and their microenvironment[2]. Numerous studies have confirmed that the stromal components of the TME have crucial impacts on the occurrence and evolution of tumors. As the most abundant non-cancerous stromal cell type, cancer-associated fibroblasts (CAFs) play vital roles in the development of CRC by influencing the proliferation, invasion, and metastasis of cancer cells as well as angiogenesis and immune response through reshaping the extracellular matrix (ECM), secreting soluble factors (chemokines and growth factors), and modulating the microbial community[3,4].

In this review, we aim to delve into the crucial role of CAFs in the progression and treatment of CRC. Additionally, we provide a comprehensive overview of the diverse functions of CAFs, including their impact on cancer cell proliferation, invasiveness, immune evasion, and neovascularization, as well as their role in shaping the TME and influencing tumor growth and metastasis. This exploration highlights the intricate network between CRC and CAFs and clarifies how these interactions affect the disease's prognosis and treatment efficacy. Moreover, we introduce a novel perspective on the symbiotic relationship between CAFs and the intestinal microbiota, potentially opening new avenues for targeting CAFs.

ORIGIN OF CAFS

Function of fibroblasts

Normal fibroblasts (NFs) are spindle-shaped mesenchymal cells possessing non-epithelial, non-endothelial, and non-immunological characteristics[5,6] which commonly locate in the connective tissue and help to maintain tissue homeostasis[7]. Functionally, fibroblasts synthesize and secrete laminin, type IV collagen, and other basement membrane-related proteins under normal physiological conditions. Particularly, fibroblasts in intestinal tissue exhibit specialized functions that are crucial for supporting epithelial cells and maintaining barrier integrity[8]. Their roles in ECM production, tissue remodeling, cell communication, immunoregulation, and wound healing collectively contribute to the maintenance of the intestinal epithelial function. In addition, fibroblasts exhibit inhibitory effects on the occurrence, development, invasion, and metastasis of tumor cells through various mechanisms including direct cell-to-cell contact, secretion of soluble factors, and preservation of an intact ECM environment[9]. However, in the context of malignant tumors, changes in the structure and function of the TME lead fibroblasts to transition from their initial anti-tumor characteristics to pro-tumor preference[10].

Origins of CAFs

CAFs are generally considered to be all fibroblasts embedded within and around cancerous tissues, representing a crucial component of TME[11]. Progenitor cells of CAFs are recruited from several sources and developed by distinct pathways [12], and most of the available evidence supports that the majority of CAFs may originate from the activation of locally resident fibroblasts[13]. Tissue-resident quiescent fibroblasts can be activated by various factors including inflammatory cytokines, constipation, microorganisms, and chemokines [interleukin (IL)-6], as well as growth factors such as transforming growth factor-β (TGF-β)[14] (Figure 1). Persisted activation tends to cause morphological and functional transformations of NFs into CAFs which are involved in cancer initiation, progression, and chemoresistance[15]. It should be noted that CAFs and NFs are interconvertible, although the underlying mechanism is still poorly understood. Fibrocytes represent a quiescent fibroblast state, which are also considered as one of the sources of CAFs[16,17]. For example, fibrocytes derived from hepatic stellate cells (HSCs) expressing fibroblast growth factor receptor 2 were identified as the origin of CAFs in esophageal squamous cell carcinoma[18].

Mesenchymal stem cells (MSCs) are proposed as potential precursors for CAFs, and Notch and Akt signaling pathways have been reported to be involved in the differentiation of bone marrow MSCs into CAFs[19,20] (Figure 1). In addition, MSCs could acquire CAF-like characteristics while stimulated by TGF-β, tumor necrosis factor-α, and IL-1β[21]. Intriguingly, macrophages can assist MSCs in developing CAF-like features[22]. Stellate cells are also an alternative origin of CAFs in certain tumors[23,24] (Figure 1). Insufficient vitamin A can trigger the transformation of pancreatic stellate cells into CAFs[25], and insulin-like growth factor-1 (IGF-1) signaling is crucial for activating HSCs into CAFs[26]. Adipocytes are recognized as another category of CAFs precursors[17,27] (Figure 1). Adipocytes may play a role in tumorigenesis through a mechanism of adipocyte-fibroblast transition[28]. Tumor cells could induce morphological changes and, meanwhile, decrease lipid content and marker expression of adipocytes. Bochet *et al*[29] found that adipocytes may dedifferentiate into cancer-associated adipocytes, and cancer-associated adipocytes become less adipocyte-like and phenotypically mirror fibroblasts with increased expression of ECM components. Moreover, epithelial and endothelial cells can differentiate into CAFs through epithelial-to-mesenchymal transition (EMT) and endothelial-to-mesenchymal transition[30-33]. Through the TGF-β-mediated EMT, epithelial cells are able to differentiate into functional CAFs expressing ferroptosis suppressor protein 1 and α-fibroblast activation protein (FAP)[34], whereas during the endothelial-to-mesenchymal transition, endothelial cells acquire a mesenchymal-like phenotype as well as invasive and migratory properties[35]. Cell types, including pericytes[36], monocytes[37], mesothelial cells[38], hematopoietic stem cells[39], circulating bone marrow cells[40], and smooth muscle cells[41], are also identified as potential precursors for CAFs. Understanding the origins of CAFs can provide new targets for cancer stromal remodeling process.

HETEROGENEITY OF CAFS

Heterogeneity transcends not only between individuals with the same tumor but also manifests as striking variations within a single tumor[42]. This dynamic variability evolves continuously over time and across spatial dimensions, interacting intricately with the surrounding microenvironment, making it a perpetually shifting and complex process. Distinct subtypes of CAFs are characterized by unique biological markers. In CRC, commonly identified CAF biomarkers include α-smooth muscle actin (α-SMA), FAP, vimentin, fibroblast specific protein 1, podoplanin, and platelet-derived growth factor receptors α/β (PDGFRα/β)[43]. With the advent of sequencing technologies, researchers have begun to analyze CAF populations at the single-cell level and revealed substantial heterogeneity among CAFs[44]. Single-cell sequencing has identified two principal CAF subsets named CAF-A and CAF-B in human CRC: CAF-A expresses high levels of FAP, matrix metalloproteinase-2 (MMP-2), and collagen type I alpha 2 while CAF-B is characterized by the expression of myofibroblastic markers such as α-SMA, transgelin, and PDGFα[45].

Additionally, recent studies have revealed two distinct subpopulations of CAFs in CRC: Myofibroblastic CAFs (myCAFs), characterized by high α-SMA and IL-6 expression, and inflammatory CAFs (iCAFs), which exhibit low α-SMA and high IL-6 expression[23,46-51]. myCAFs are primarily involved in regulating the ECM, collagen deposition, cellular contraction, and adhesion, whereas iCAFs are distinguished by their secretion of cytokines and chemokines and their interactions with immune cells[50,51]. Interestingly, we discovered that iCAFs were particularly concentrated around dilated blood vessels at the colonic luminal margin and demonstrated greater activity than myCAFs in mismatch repair-deficient tumors[46].

As research continues to deepen, the classification of CAF subtypes has become increasingly nuanced. Khaliq *et al*[51] utilized large-scale single-cell sequencing across diverse ethnic groups to achieve a more detailed categorization of myCAF and iCAF subtypes in CRC tissue, drawing on classification methods previously used in breast cancer[49]. The myCAF group was further subdivided into ecm-myCAFs, associated with ECM proteins; wound-myCAFs, linked to wound healing signaling; and TGFβ-myCAFs, dependent on the TGFβ pathway[51]. Similarly, the iCAF group was refined to include IL-iCAFs, related to IL signaling, and detox-iCAFs, associated with detoxification pathways. In addition to myCAFs and iCAFs, a type of vascular-associated CAFs expressing pericyte markers and hypoxia-inducible factor 2 has also been identified in CRC, participating in angiogenesis and vascular development and potentially contributing to tumor invasion and metastasis[51-53].

CAFs are frequently linked to the promotion of CRC, but recent studies have also uncovered their potential role in inhibiting CRC growth[54,55]. Kobayashi *et al*[56] discovered that CAFs can polarize into GREM1$^+$ CAFs, which promote tumor progression, and ISLR$^+$ CAFs, which inhibit tumor progression, under the regulation of the TGFβ-FOXL1-GREM1/ISLR axis. Although the specific mediators secreted by ISLR$^+$ CAFs that inhibit CRC progression remain unidentified, it is clear that these mediators contribute to activating bone morphogenetic protein signaling in CRC cells.

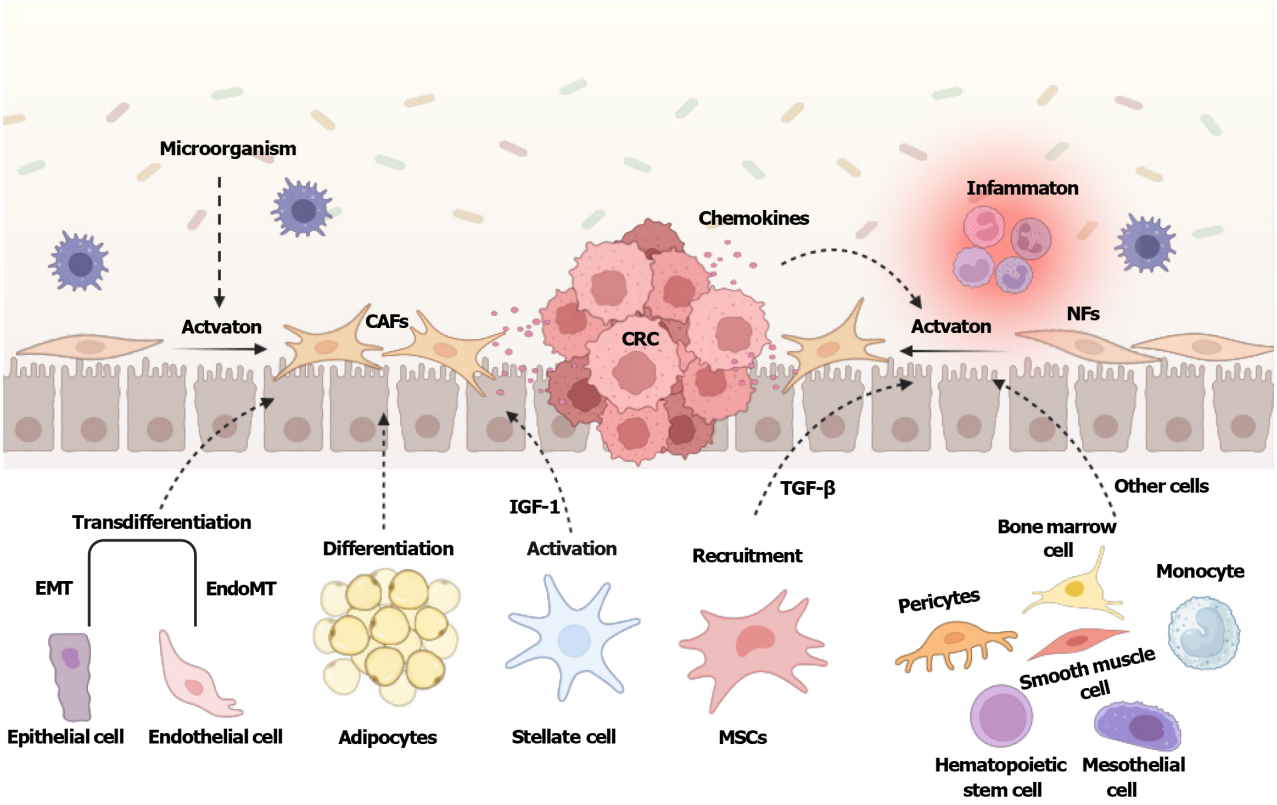

Figure 1 Origins of cancer-associated fibroblasts in colorectal cancer. Normal fibroblasts can be activated by various factors including inflammation, microorganisms, and chemokines, and transform into cancer-associated fibroblasts. In addition, epithelial cells, endothelial cells, hepatic stellate cells, adipocytes, mesenchymal stem cells, pericytes, monocytes, mesothelial cells, hematopoietic stem cells, bone marrow cells, and smooth muscle cells, are all potential precursors of cancer-associated fibroblasts. Created with BioRender.com (Supplementary material). CAFs: Cancer-associated fibroblasts; CRC: Colorectal cancer; TGF-β: Transforming growth factor-β; NFs: Normal fibroblasts; EMT: Epithelial-to-mesenchymal transition; IGF-1: Insulin-like growth factor-1; MSCs: Mesenchymal stem cells.

The heterogeneity of CAFs is continuously evolving with technological and temporal advancements. Single-cell sequencing and spatial transcriptomics have significantly enhanced our understanding of CAFs' diversity. However, a thorough classification of the functional diversity among different CAF subtypes in CRC remains incomplete, and more effective approaches for elucidating the identities and states of CAF subtypes are urgently needed[57,58].

ROLES OF CAFS IN CRC

CAFs and tumor proliferation and migration

In recent years, an increasing awareness has emerged regarding the pre-existing tumorigenic state of fibroblasts even prior to the onset of malignant cell transformation[13]. To delve deeper into the pathogenic intricacies of CRC, investigators isolated CAFs and NFs from fresh surgical specimens of colorectal adenocarcinoma patients. Additionally, co-culturing of these cells with colorectal tumor cells unveiled that tumor cells in conjunction with CAFs exhibited heightened proliferative and migrative capacities[59]. Mechanically, CAFs facilitate CRC proliferation and migration by secreting a variety of cytokines and small extracellular vesicles containing microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs)[60] (Figure 2). Furthermore, Hirashima *et al*[61] revealed that gene sets related to the Wnt signaling pathway were highly enriched in colorectal CAFs by analyzing the expression profiles of paired CAFs and NFs from CRC tissue. Subsequent *in vitro* experiment showed that cancer cell proliferation and migration were significantly stimulated by both recombinant Wnt5a protein and CAFs-secreted Wnt2 through activating Wnt signaling [62]. Interestingly, the strategic collaboration between CAFs and tumor-associated macrophages amplifies the migratory prowess of CRC cells[63], which indicates that the immune microenvironment including various immune cells may serve as pivotal orchestrators in propelling the biological function of CAFs.

CAFs and tumor immune suppression

On the other hand, the intricate crosstalks between CAFs and immune cells also lead to tumor immune evasion by mediating immune cell recruitment and functional differentiation within the TME[64] (Figure 2). In the context of CRCs, the MSCs, as precursors to CAFs, exacerbate tumor progression by intensifying the inhibition of immune cells. Studies found that the sialylation profile of stromal cells is an important mechanism by which MSCs/CAFs modulate T cell

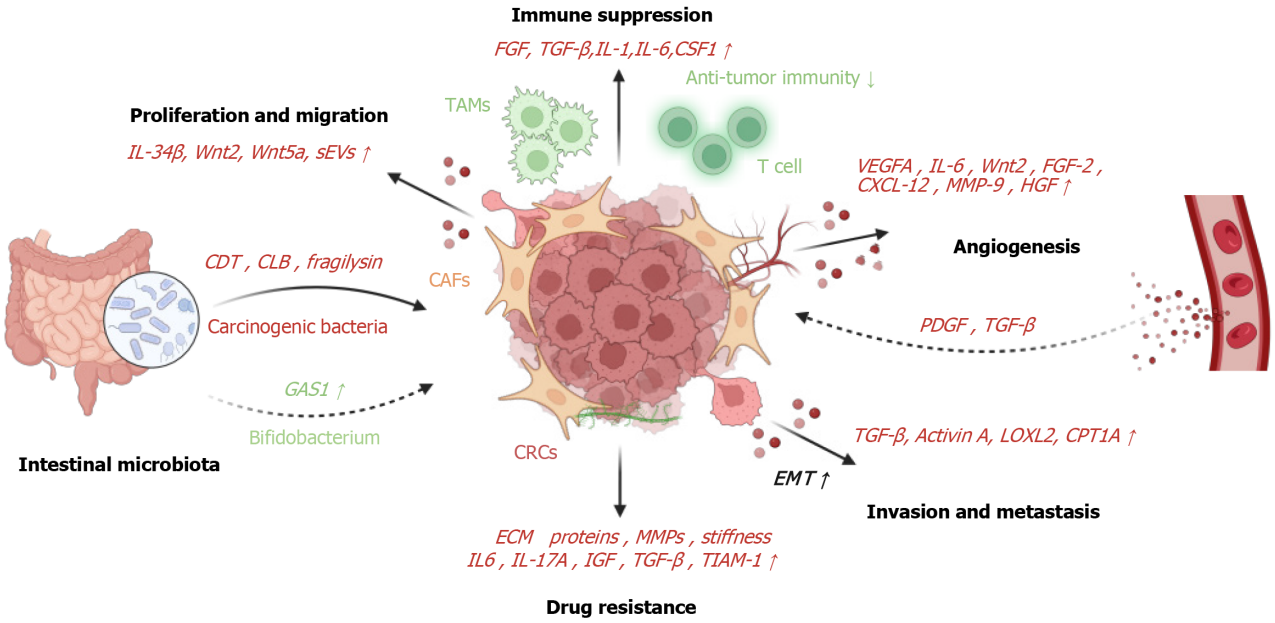

Figure 2 Roles of cancer-associated fibroblasts. Cancer-associated fibroblasts (CAFs) secrete a variety of cytokines, including interleukin (IL)-34, Wnt2, Wnt5a, and small extracellular vesicles, which actively promote colorectal cancer proliferation and migration. Additionally, CAFs intricately manage tumor immune evasion through a range of complex mechanisms, including the secretion of diverse cytokines and chemokines such as fibroblast growth factor, transforming growth factor-β (TGF-β), IL-1, IL-6, and colony-stimulating factor 1. And CAFs contribute to tumor initiation by releasing pro-tumor factors that stimulate angiogenesis, including vascular endothelial growth factor A, IL-6, Wnt2, fibroblast growth factor 2, CXC motif chemokine ligand 12, matrix metalloproteinase-9, and hepatocyte growth factor. In turn, the leaky vasculature within tumors releases pro-angiogenic factors such as platelet-derived growth factor and TGF-β through degranulation, which further activates fibroblasts. The secretion of TGF-β, activin A, and lysyl oxidase-like 2 by CAFs, along with the upregulation of carnitine palmitoyl-transferase 1A expression, promotes epithelial-to-mesenchymal transition in colorectal cancer, thereby enhancing the invasion and metastasis of colorectal cancer. Moreover, CAFs produce ECM proteins and remodel the matrix *via* matrix metalloproteinases, creating a physical barrier and increasing matrix stiffness and interstitial pressure. And CAFs secrete key soluble factors, including IL-6, IL-17A, and insulin-like growth factor-1. "Carcinogenic bacteria" secrete bacterial toxins such as cytolethal distending toxin, colibactin, and fragilysin, influencing the tumor microenvironment to foster tumor progression and immune evasion. Meanwhile, Bifidobacterium exhibits anticancer effects by activating CD143+ CAFs. Created with BioRender.com (Supplementary material). IL: Interleukin; sEVs: Small extracellular vesicles; FGF: Fibroblast growth factor; TGF-β: Transforming growth factor-β; CSF1: Colony-stimulating factor 1; TAMs: Tumor-associated macrophages; VEGFA: vascular endothelial growth factor A; CXCL-12: CXC motif chemokine ligand 12; MMP: Matrix metalloproteinase; HGF: Hepatocyte growth factor; CDT: Cytolethal distending toxin; CLB: Colibactin; CAFs: Cancer-associated fibroblasts; PDGF: Platelet-derived growth factor; GAS1: Growth arrest specific 1; CRC: Colorectal cancer; IGF: Insulin-like growth factor; TIAM-1: T-lymphoma invasion and metastasis-inducing protein-1; EMT: Epithelial-to-mesenchymal transition; LOLX2: Lysyl oxidase-like 2; CPT1A: Carnitine palmitoyl-transferase 1A.

exhaustion. Targeting stromal cell sialylation may overcome immunosuppression in the CRC TME[65]. The investigations spearheaded by Yang *et al*[66] illuminated the exacerbation of CAFs' pro-tumor role with the loss of the *BCL9* gene, culminating in the aberrant activation of the Wnt/β-catenin signaling pathway, thereby impeding T-cell-mediated anti-tumor immune responses.

Tumor-associated macrophages contribute to all aspects of tumor progression. Colony-stimulating factor 1 produced by tumor cells caused histone deacetylase 2-mediated downregulation of granulocyte-specific chemokine expression in CAFs. Treatment with colony-stimulating factor 1 receptor inhibitors disrupted this crosstalk and triggered a profound increase in granulocyte recruitment to tumors[67]. Moreover, colony-stimulating factor 1 receptor inhibitors have been utilized as agents targeting tumor-associated macrophages in clinical trials for solid tumors, including intestinal cancers [68]. However, their efficacy has been limited. This limitation has been attributed to CAFs' capability to counteract the therapeutic effects of these agents by recruiting polymorphonuclear myeloid-derived suppressor cells to tumor sites, thereby shaping an immunosuppressive TME[67]. Concomitantly, the involvement of pentraxin 3, fostering M2-like polarization of macrophages, surfaces in the context of CAF-mediated immune suppression, with elevated pentraxin 3 expression correlating positively with fibroblasts and inflammatory response signals in CRC patients, prognosticating unfavorable survival outcomes[69]. The pervasive influence of CAFs also extends to shaping the cytotoxicity of T lymphocytes, fortifying tumor cells in their evasion of the body's immune response[70].

A noteworthy revelation surfaces from recent research, underscoring the tumor-suppressive function of α-SMA+ CAFs within a genetically engineered mouse model of metastatic CRC. The α-SMA(+) CAFs in CRC exert tumor-restraining functions *via* bone morphogenetic protein 4/TGF-β1 paracrine signaling that serves to suppress Lgr5(+) CSCs and promote anti-tumor immunity, ultimately limiting CRC progression[71]. However, the nuanced impact of the depletion strategy, predominantly targeting α-SMA+ CAFs, on other α-SMA+ cells dispersed throughout the body, introduces an element of uncertainty regarding its potential perturbation of the observed outcomes. While there is a growing interest in cancer immunology, our comprehension of how CAFs participate in tumor immune surveillance is still in its infancy. More extensive investigations into CAFs are imperative to pinpoint promising target molecules or subsets of CAFs and to devise innovative therapies that can enhance the clinical efficacy of existing immunotherapies.

CAFs and tumor angiogenesis

Angiogenesis stands out as a pivotal step throughout diverse stages of tumor progression, playing a crucial role in the invasive growth of CRC. The significance lies in its ability to provide abundant blood vessels, furnishing oxygen and nutrients indispensable for the proliferation of tumor tissues. As a hallmark of malignant tumors, angiogenesis is closely associated with tumor growth, metastasis, and patient prognosis and is promoted by the most potent pro-angiogenic factor, vascular endothelial growth factor (VEGF), which stimulates angiogenesis by binding to its corresponding receptor VEGF receptor 2 (VEGFR2) on endothelial cells[72-74].

Neovascularization in cancer is governed not solely by tumor cells but also by stromal cells[75]. In fact, CAFs directly foster tumor angiogenesis by releasing pro-angiogenic factors and indirectly by generating the ECM[5,75]. In the context of CRC, cancer cells exhibit minimal VEGF secretion whereas CAFs represent a significant origin of VEGFA through the abundant release of IL-6[75,76]. The intricate interplay between colon cancer cells and the TME facilitates the transformation of NFs into CAFs, positively modulating IL-6 secretion, thereby amplifying VEGF secretion and fostering tumor angiogenesis[77]. Additionally, Unterleuthner *et al*[78] discovered that WNT2 secreted by CAFs plays a pivotal role in promoting the formation of tumor blood vessels in CRC. Silencing WNT2 in CAFs significantly diminishes the angiogenic potential of tumor vessels, highlighting that elevated WNT2 expression in CAFs renders tumors more susceptible to invasion and metastasis. Moreover, CAFs promote tumor initiation by secreting pro-tumor factors (Figure 2) that enhance angiogenesis, including VEGF-α, fibroblast growth factor 2, CXC motif chemokine ligand 12, MMP-9, and hepatocyte growth factor (HGF)[79]. In turn, the permeable vasculature within tumors leads to platelet extravasation and the subsequent release of pro-angiogenic factors such as PDGF and TGFβ through degranulation, which further activate fibroblasts[80]. Collectively, these studies offer a compelling rationale for considering CAFs as a viable therapeutic target to modify tumor vasculature.

CAFs promote tumor invasion and metastasis

In the intricate landscape of tumorigenesis, CAFs stand as instrumental architects, actively promoting the insidious progression of tumor invasion and metastasis[81,82]. As a substantial component of the TME, CAFs wield their influence in fostering the malignant behaviors of cancer cells. The multifaceted role of CAFs is underscored by their ability to induce EMT, a pivotal process that endows cancer cells with the traits essential for invasion and metastasis. Research illuminates the mechanistic intricacies, revealing that factors (Figure 2) such as TGF-β activation of colonic stromal fibroblasts and the secretion of activin A contribute to the heightened migratory capacity and EMT in colonic epithelial cells, thereby rendering CRC cells more prone to metastasis[83].

The dynamic interplay extends to specific molecular signaling pathways, as evidenced by studies elucidating the stimulation of EMT in CRC cells through the secretion of lysyl oxidase-like 2 by CAFs (Figure 2), activating the focal adhesion kinase signaling pathway[84]. Inhibition of this process presents a potential avenue for curtailing CRC cell invasion and metastasis. Additionally, the orchestration of EMT by CAFs involves regulatory elements such as myosin light chain 9, which influences the secretion of C-C motif ligand 2 and TGF-β, thereby shaping the TME and impacting CRC invasion and metastasis[85].

Beyond their involvement in EMT, CAFs exert a substantial impact on the metabolic landscape of CRC cells, enhancing their invasion and metastasis. Through the upregulation of key factors like carnitine palmitoyl-transferase 1A (Figure 2) [86], CAFs promote fatty acid oxidation while minimizing glycolysis, ultimately fostering a milieu conducive to tumor growth and invasion. Woven into this intricate narrative is the expression of WNT2 in CAFs, contributing to the invasion of CRC cells and unveiling additional dimensions to the role of CAFs in promoting metastasis[87]. As the exploration of CAFs' influence on tumor invasion and metastasis unfolds, their capacity to produce signaling molecules, including TGF-β, leukemia inhibitory factor, and HGF, emerges as another crucial facet[88]. These molecules act as potent drivers, propelling cancer cell proliferation and invasion behaviors. TGF-β, in particular, emerges as an effective inducer of EMT through paracrine signaling, endowing premalignant cells with mesenchymal properties that facilitate invasion and metastasis[89]. Furthermore, CAFs play a pivotal role in the colonization of distant organs during metastasis, either by creating a supportive microenvironment for cancer cells or by accompanying them in their journey[90].

Examining factors that foster invasion and metastasis through the lenses of EMT and metabolism is imperative. Concurrently, we need to delve into the repercussions of cancer cell EMT on CAFs subtypes. A crucial aspect to explore involves comprehending the influence of EMT-inducing transcription factors on stromal cells. Existing studies underscore a direct correlation between the expression of EMT transcription factors and the presence of CAFs[91]. Noteworthy is the work of Franci *et al*[92], who discerned predominant Snail expression in fibroblasts proximate to tumor cells in CRC. Furthermore, CRCs exhibiting mesenchymal gene expression traits display a heightened proclivity for distant metastasis, marked by the accumulation of CAFs in the stromal milieu. And findings indicate that fibroblasts within epithelial tumors exhibit elevated miR-200 expression and reduced levels of actin alpha 2 and fibronectin 1 compared to their mesenchymal counterparts[93]. This discovery unveils a novel mechanism for the heterogeneity of CRC CAFs, elucidating how miRNA transfer *via* extracellular vesicles contributes to this phenomenon. It also offers insights into why CRCs with augmented metastatic potential boast an abundance of CAFs.

CAFs and tumor drug resistance

Recent investigations underscore the pivotal role of the TME in shaping tumor cell resistance, elucidating the substantial impact of CAFs in promoting drug resistance across diverse cancers, notably CRC[94]. The intricate interplay involves CAFs's production of ECM proteins and matrix remodeling MMPs, forming both a physical barrier and elevating matrix stiffness and interstitial pressure (Figure 2). This dual effect impedes the efficient penetration of chemotherapy drugs and targeted therapies, contributing significantly to drug resistance[95]. Moreover, the secretion of key soluble factors

(Figure 2) by CAFs, including IL-6, IL-17A, and IGF, intricately mediates chemotherapy resistance and amplifies cytokine secretion post-treatment, consequently intensifying drug resistance[96,97].

Beyond their physical and soluble influences, CAFs play a pivotal role in immune suppression within the TME[13]. The accumulation of aberrant ECM components exacerbates immune suppression, adversely impacting the efficacy of immune checkpoint inhibitors. The involvement of the TGF-β signaling pathway is particularly noteworthy in the context of immune therapy resistance. It is intriguing to observe that the blockade of TGF-β signaling, in conjunction with receptor kinase inhibitors and anti-programmed cell death protein 1/programmed cell death ligand 1 immunotherapy, exhibits a synergistic effect in a murine model of CRC liver metastasis[98,99]. Notably, an elevated compound stromal score, characterized by three stromal components (CAFs, leukocytes, and endothelial cells), has the potential to anticipate resistance to radiotherapy in rectal cancer patients[100].

Regarding molecularly targeted medications, the release of HGF and IGF2 by CAFs plays a role in conferring resistance to tyrosine kinase inhibitors[101]. Notably, the concurrent inhibition of epidermal growth factor receptor (EGFR) and MET, or insulin receptor and IGF1 receptor, which facilitate the IGF2/insulin receptor/IGF1 receptor signaling pathway, has been shown to augment the therapeutic efficacy of an EGFR inhibitor in xenograft models of colon cancer, respectively[102]. In the realm of CRC, CAFs further exhibit their intricate influence by secreting IL-17A, which acts on the IL-17A receptor on CSCs. This action maintains CSPDCs' stem cell characteristics, upregulates nuclear factor-κB expression, and induces resistance in cancer cells[97]. Additionally, the secretion of exosomes by CAFs is implicated in promoting the stemness and chemotherapy resistance of CRC. The interaction with eukaryotic initiation factor 4A-III and the exosomal miR-625-3p blockade of the CELF2/WWOX pathway underscore the multifaceted mechanisms through which CAFs potentiate drug resistance[103,104]. Furthermore, CAFs contribute to chemotherapy resistance in CRC cells by inducing the overexpression of T-lymphoma invasion and metastasis-inducing protein-1, presenting T-lymphoma invasion and metastasis-inducing protein-1 as a promising therapeutic target[105]. In a co-culture setting, CAF-conditioned medium induces the overexpression of the *RBCK1* gene, augmenting the stemness and resistance of CRC cells[106]. This intricate web of interactions emphasizes the significant and varied roles of CAFs in fueling drug resistance in CRC, urging further exploration for targeted therapeutic interventions.

Relationship between CAFs and intestinal microbiota

As a crucial component of the intestinal barrier, the intestinal microbiota intricately weaves a biofilm, actively participating in intestinal functions and establishing a conducive survival environment for intestinal cells. Notably, this microbial consortium is implicated in various stages of CRC, ranging from benign precursor lesions (polyps) to *in situ* growth and metastasis. The concept of "carcinogenic bacteria" introduced in 2018, encompasses species like *Escherichia coli*, *Fusobacterium nucleatum*, and enterotoxigenic *Bacteroides fragilis*, underscoring their pivotal role in CRC pathogenesis. Concurrently, bacterial toxins such as cytolethal distending toxin, colibactin, and fragilysin exert their influence on the TME, fostering tumor development and immune escape. Noteworthy insights illuminate the intricate interplay between *Helicobacter pylori*, fibroblasts, and cancer cells, leading to the induction of Serpin E1 expression. This induction propels the transformation of NFs into CAFs, contributing to the onset of gastric cancer[107]. The complexity of these interactions emphasizes the multifaceted role of the intestinal microbiota in orchestrating the TME and influencing cancer progression.

Crucially, the nuanced roles of distinct intestinal bacteria must be acknowledged, as some confer beneficial effects on the human body. For instance, the work of Chen *et al*[108] highlights the positive impact of youth-associated Bifidobacterium, activating CD143+ CAFs, thereby initiating the Wnt signaling pathway and upregulating growth arrest specific 1 expression. This cascade of events manifests in anticancer effects, unveiling a promising therapeutic target for CRC[108]. These findings underscore the dynamic nature of the interactions between the intestinal microbiota, fibroblasts, and cancer cells, offering a profound understanding of the intricate molecular mechanisms shaping the TME and presenting potential avenues for therapeutic interventions.

TREATMENT OF CAFS IN CRC

Alongside surgical resection, the most current clinical approaches to treating CRC involve chemotherapy and radiotherapy, which exert diverse effects on the various cellular constituents of the TME[109]. A comparative study of CRC specimens from patients before and after undergoing cytotoxic treatment revealed a marked rise in CAFs[97]. CAFs exposed to chemotherapy were observed to prolong tumor cell survival and accelerate growth compared to untreated CAFs, indicating that CAFs may shield tumor cells from the growth-inhibitory effects of chemotherapy[109]. In contrast to the genetic instability often observed in malignant tumor cells of CRC, CAFs exhibit genetic stability. This characteristic distinction prompts the exploration of combined therapies targeting both CRC cells and CAFs, envisaged as a novel strategy to augment treatment effectiveness and overcome resistance in CRC. These strategies encompass three primary methods: (1) The elimination of "harmful" CAFs[110]; (2) The reprogramming of CAFs into "normal" fibroblasts or anti-tumor "beneficial" CAF subtypes[111]; and (3) The blockade of signals or ECM components derived from CAFs [112,113]. Successful implementation of these approaches necessitates a precise definition and classification of CAFs, coupled with an enhanced understanding of their diverse functions. Despite extensive research endeavors, several strategies targeting CAFs are yet to yield satisfactory clinical outcomes[14,114,115].

Currently, numerous anticancer drugs targeting CAFs are undergoing preclinical research or clinical trial phases. These drugs predominantly exert direct damage to CAFs by targeting specific surface molecules or impede the secretion of pro-cancer factors and associated signaling pathways in CAFs. The inaugural phase I clinical trial targeting

gastrointestinal cancers, employing autologous MSCs genetically modified to express herpes simplex virus-thymidine kinase, has demonstrated acceptable safety and tolerability. These MSCs facilitate the conversion of the pro-drug ganciclovir into its active cytotoxic metabolite. Furthermore, researchers are exploring the combination of TGF-β inhibitors or Hedgehog inhibitors with standard chemotherapies or immunotherapies[116]. This combination strategy aims to obstruct pro-tumorigenic signaling pathways pertinent to CAFs in gastrointestinal cancers[99,117,118]. Moreover, the differentiation of HSCs into CAFs *via* the C-X-C chemokine receptor type 4/TGF-β1 signaling axis promotes CRC liver metastasis. Consequently, blocking the C-X-C chemokine receptor type 4/TGF-β1 signaling axis emerges as a beneficial strategy for anti-metastasis treatment in CRC[119].

As research on the TME advances, exosomes have emerged as a promising avenue for therapeutic development. Among many miRNA molecules, miRNA-20a was found to inhibit the secretion of CXC motif chemokine ligand 8 from CAFs, thereby inhibiting tumor growth[120]. CAFs are also capable of secreting the lncRNAs CCAL and H19, thereby inducing drug resistance in cancer cells through the activation of β-catenin signaling[121,122]. Furthermore, CAFs release exosomal circSLC7A6 to stimulate the proliferation of CRC cells, an effect that can be inhibited by matrine, a compound derived from *Sophora flavescens*[123]. Additionally, CAFs secrete exosomal miR-93-5p and miR-21, which are transferred into CRC cells, consequently enhancing tumor resistance to chemotherapy[124-126].

Diverse attempts have been made to directly target specific subsets of CAFs. Some researchers have encapsulated drugs within lipid nanocapsules to directly target CAFs in the TME, discovering that paclitaxel and acetylcholinesterase are particularly promising for inhibiting CAF development[127]. Notably, a DNA vaccine inducing CD8 T cell killing of FAP+ CAFs has demonstrated the depletion of FAP+ CAFs and the inhibition of tumor progression in a CRC mouse model[128]. However, clinical trials evaluating anti-FAP monoclonal antibodies have not yielded the anticipated efficacy in advanced CRC patients[129]. Combining the chemotherapeutic drug oxaliplatin with the inhibitor PT-100 in a CRC mouse model significantly increased the sensitivity of tumor tissue to chemotherapy, concurrently reducing the recruitment of pro-tumor cells and angiogenesis[130]. Additionally, calcium/calmodulin-dependent protein kinase II has emerged as a pivotal mediator of TFG-β1-induced CAFs activation and participation in CRC cell signaling, positioning calcium/calmodulin-dependent protein kinase II as a promising target for future CRC treatment[131]. Furthermore, CAFs enhance the chemotherapy resistance of CRC cells by receiving signals through their receptor C-C motif chemokine receptor 5, suggesting that targeting C-C motif chemokine receptor 5 may offer a potential approach for treating CRC [132]. In the meanwhile, phosphorylated signal transducer and activator of transcription 3 in CAFs can be used as a tool to judge the prognosis of patients with CRC, and the activation of CAFs may be a therapeutic target for CRC[133]. Moreover, inhibitors of HGF activation, such as SRI 31215, offer a novel strategy to disrupt autocrine and paracrine oncogenic HGF/MET signaling, thereby preventing HGF-dependent cancer cell proliferation, EMT, and migration[134]. Simultaneously targeting HGF and EGFR can effectively block both primary and acquired fibroblast-mediated resistance to EGFR inhibitors in colon cancer cells.

CONCLUSION

In CRC, CAFs predominantly reside within the tumor or adjacent tissues, secreting factors that fuel tumor initiation, progression, invasion, and metastasis. Notably, CAFs play a pivotal role in aiding tumor cells in evading the body's immune responses, thereby fortifying resistance to radiation and chemotherapy. Consequently, the targeting of CAFs has emerged as an innovative and promising approach in the treatment landscape of CRC.

Anticipating future developments in the realm of CAFs, particularly in CAF subpopulation biology, there has been rapid and significant progress. A growing body of evidence underscores the crucial roles played by specific subgroups of CAFs in tumor initiation, development, metastasis, and resistance to treatment. Nevertheless, the heterogeneity in phenotype and function exhibited by CAFs introduces variability in their roles across different types of tumors and at various stages of the same tumor. Therefore, further exploration is imperative to unravel the nuanced functions of CAFs in different pathological subtypes of CRC and at distinct developmental stages.

Recent reports add an intriguing layer to our understanding, revealing that CAFs not only promote tumor cell development but also exhibit inhibitory effects on tumors. Investigating the underlying mechanisms and pathways through which CAFs themselves exert inhibitory effects represents a promising avenue for future research. The advent of modern scientific technologies, such as single-cell sequencing and spatial transcriptomics, has empowered researchers to delve into the study of CAFs subgroups at unprecedented levels. However, despite the valuable insights gained from single-cell technologies in identifying CAFs subgroups, comprehensive characterization and in-depth functional analyses remain essential to validate data and establish meaningful connections.

In the future trajectory of research, dedicated efforts should be directed towards comprehending the dynamic nature of CAFs, exploring their plasticity, deciphering the factors influencing their transformation, and investigating the potential reversibility of these changes. This concerted endeavor holds the promise of offering more precise and effective strategies for cancer treatment, ultimately paving the way for improved therapeutic outcomes and enhanced well-being for patients.

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FOOTNOTES

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