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REVIEW ESSAY

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The role of the tumor microenvironment in colorectal cancer and the potential therapeutic approaches

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Abstract

Background: Colorectal cancer (CRC) with a high prevalence is recognized as the fourth most common cause of cancer-related death globally. Over the past decade, there has been growing interest in the network of tumor cells, stromal cells, immune cells, blood vessel cells, and fibroblasts that comprise the tumor microenvironment (TME) to identify new therapeutic interventions.

Methods: Databases, such as Google Scholar, PubMed, and Scopus, were searched to provide an overview of the recent research progress related to targeting the TME as a novel therapeutic approach.

Results: Tumor microenvironment as a result of the cross talk between these cells may result in either advantages or disadvantages in tumor development and metastasis, affecting the signals and responses from the surrounding cells. Whilst chemotherapy has led to an improvement in CRC patients' survival, the metastatic aspect of the disease remains difficult to avoid.

Conclusions: The present review emphasizes the structure and function of the TME, alterations in the TME, its role in the incidence and progression of CRC, the effects on tumor development and metastasis, and also the potential of its alterations as therapeutic targets. It should be noted that providing novel studies in this field of research might help us to achieve practical therapeutic strategies based on their interaction.

KEYWORDS
blood vessel cells, colorectal cancer, potential therapeutic approaches, tumor microenvironment

Narges Zafari and Fatemeh Khosravi contributed equally to the current manuscript.

1 | INTRODUCTION

Colorectal cancer (CRC) is a prevalent and widespread cancer, the fourth most frequent leading cause of death, with one or two million newly diagnosed cases yearly.[1,2] Although the development of therapeutic strategies such as chemotherapy (CHT) and targeted agents (TA) has resulted in the improvement of patients' survival and mortality rates, metastatic CRC is still incurable, with only a 12% survival rate.[3–5] Furthermore, in early-stage patients, surgical resection of the tumor frequently results in relapse and is not applicable to advanced-stage patients.[3] In recent years, the limited knowledge of the factors underlying the progression mechanisms and lack of tumor targeting has led to a greater focus on the role of the tumor microenvironment (TME) in the development of many cancers, including: breast, cervical, ovarian, prostate, gastric, pancreatic, and CRC to find an effective therapeutic approach.[6] Tumors contain infiltrating inflammatory cells, proliferating cancer cells, blood vessels, tumor stroma, and an assortment of related tissue cells that comprise the tissue microenvironment.[7] The fate of cancer cells is influenced by specific molecular interactions between cancer cells and their microenvironment, which controls cellular and molecular events in adjacent tissues.[8]

The seed and soil theory was proposed more than a century ago.[9] Based on this theory, there is an interaction between the microenvironment and cancer cells in the distant organ, and it would be practical to investigate their crosstalk.[10] Despite the determination of molecular features of the cancer cells, there remains a long way to go to fully understand the role of the microenvironment in the original site of the tumor and in relation to metastasis to distant organs. Inflammatory cells, vascular cells, and cancer-associated fibroblasts (CAFs) are essential components of the TME, which results in the final phenotype of cancer cells, recurrence, metastasis, and drug resistance entity of CRC.[11,12] It has been shown that long-term targeting of cyclooxygenase-2 (COX-2) by nonsteroidal anti-inflammatory drugs, which is overexpressed in the majority of CRCs, reduces the risk of CRC.[13] This treatment results in mediating tumor cell proliferation, supportive tumor microenvironment, survival, and migration/invasion.[13] Another important characteristic of the TME is to reduce or suppress activated immune cells in response to the tumor invasion.[14] Therefore, enhancement of the antitumor response of the immune system by targeting checkpoint blockade pathways would be promising. There are a few FDA-approved drugs such as Pembrolizumab, Nivolumab, and Atezolizumab that target PD-L1 and PD-1 for producing tumor-specific T-cell responses.[15]

In this review, we will discuss the role of the tumor microenvironment in the incidence of CRC, its impact on tumor progression, and recent therapeutic and management approaches based on their interaction. Figure 1 showed the selection of articles used in constructing the manuscript. First, we searched PubMed, Scopus, and Google Scholar to find articles related to our main keywords, including colorectal cancer, microenvironment, therapeutic approach, and molecular mechanisms. Then, the titles and abstracts of articles were screened in order to include proper articles. To assort the included articles, we read their full texts and put them under the suitable headlines. Finally, we chose the most recent and frequently cited publications in order to summarize and include.

2 | THE MOLECULAR MECHANISMS BEHIND THE MICROENVIRONMENT IN TUMORIGENESIS

One of the most important characteristics of cancer cells is their ability to proliferate indefinitely and to survive in a variety of harsh conditions. Furthermore, tumor cells are supported by normal stroma called TME. TME has recently been shown to be responsible for tumor growth by providing specific circumstances such as maintaining cancer cell initiators and neutralizing metastatic factors. Inflammation and immune-related cells in the TME are other determining factors in the tumor-specific phenotype. Thus, understanding the cellular and molecular mechanisms underlying tumor microenvironment is critical for facilitating the identification of new therapeutic targets.

2.1 | The relationship of wound healing and tumor microenvironment

Involvement of TME and cells of TME, which are known as the stroma, reactive stroma, and cancer-associated fibroblasts (CAFs; also known as tumor stromal fibroblasts) during wound healing is a key event in tumorigenesis.[16] Some of the well-known underlying molecular mechanisms are fibroblast-to-myofibroblast differentiation, as well as activation of inflammatory components.[17,18] The repair of damaged tissue produces paracrine signals, which results in the activation of myofibroblast differentiation.[17] Transforming growth factor-beta (TGF-β) is the most important signal during this process.[19] Myofibroblasts, by inducing angiogenesis factor and ECM remodeling, play a vital role in the healing process.[16] During normal conditions, myofibroblasts would degrade by apoptosis; however, in cancerous states, they would resist as chronic wounds.[20]

Embryonic mesenchymal cells traditionally are considered as the direct origin of adult fibroblasts.[21,22] During fibrosis (pathological wound healing), one of the main promoters of fibroblasts' accumulation is the epithelial-mesenchymal transition (EMT), which is the loss of epithelial cells' features in order to gain mesenchymal cells' features and occurs in up to 40% of tumor-associated fibroblasts.[23,24] Integration of malignant epithelial cells into the tumor stroma after undertaking the EMT process can also increase the CAF population.[25] TGF- and BMP-7 collaboration also promotes it as a mediator and inhibitor, respectively.[26] STAT3 enables the epithelial-to-mesenchymal transition through stimulation of matrix metalloproteinases (e.g., MMP2, MMP7, and MMP9) and disintegration of the extracellular matrix. STAT3 also, by activation of hypoxia-inducible factor-1 (HIF1) and vascular endothelial growth factor (VEGF), plays a vital role in self-renewal maintenance of diversified types of tissue.[27–29]

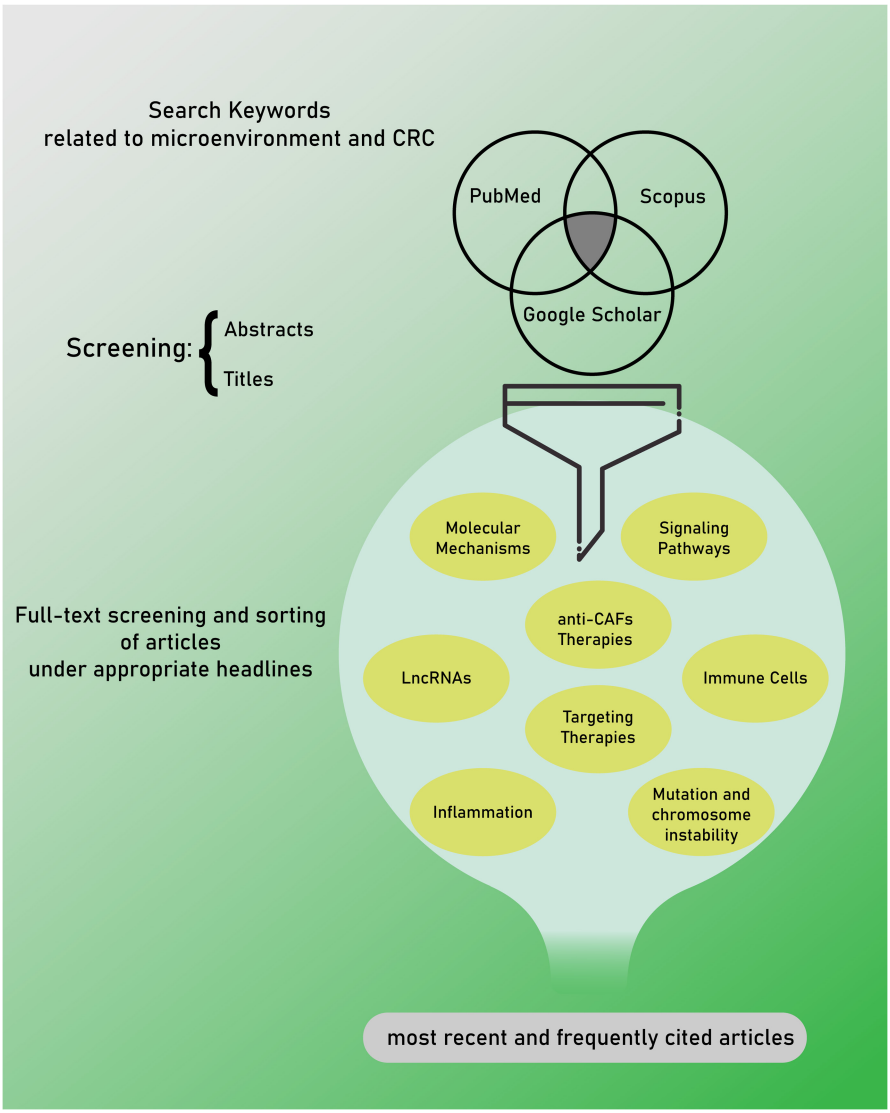

FIGURE 1 Articles selection process of the present study

During wound healing, the inflammation in the tumor microenvironment was enriched by GP130 cytokines via Th17 cell differentiation to induce the malignant feature of the epithelium, aberrant STAT3 activity, and suppress the immune system's antitumor response.[30] Here, tumor formation could be initiated by the continuous wound-healing process in TME and CAF (Figure 2). Therefore, myofibroblast formation could serve as a potential target for the therapeutic approach.

2.2 | Immune cells and tumor microenvironment

The weakness of the anti-tumor response may result from the lack of proper reorganization of a primary signal to pathogens, down-regulation of the immune system to avoid self-harm or the involvement of the microenvironment to hinder any assessment of the immune system to the tumor cells.[8,31,32] Regulating immune cell infiltration into the pre-metastatic niches or tumor is another way that direct tumor cells and TME interaction can affect inflammation.[33] Microenvironment cells stimulate the secretion of matrix remodeling enzymes, cytokines, chemokines, and growth factors.[34] Although cytokines are in charge of tumor suppression based on tumor microenvironment, they initiate cell transformation and progression in constant inflammation responses that result in a disrupted balance of pro- and anti-inflammatory cytokines.[35] Then, STAT3 and NF-κB pathways are activated to regulate the release of the cytokines and mediate the progression and inflammation response that per se becomes a promoting factor in releasing more cytokines.[36–38]

Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that has been identified to play a critical role in tumorigenesis. This cytokine can bind to one of two receptors, of which TNF-αR1 is constitutionally expressed while TNF-αR2 expression is mainly restricted to immune cells. The activation of TNF-α results in the activation of an antiapoptotic pathway induced by the cellular inhibitor of apoptosis protein-1 (cIAP1) and induced NF-κB.[39,40] TNF-α promotes tumor growth by producing reactive nitrogen species (RNS) and reactive oxygen species (ROS).[41,42]

Interleukin 6 (IL-6) is another pro-inflammatory cytokine which involves stimulating proliferation and inhibition of apoptosis in

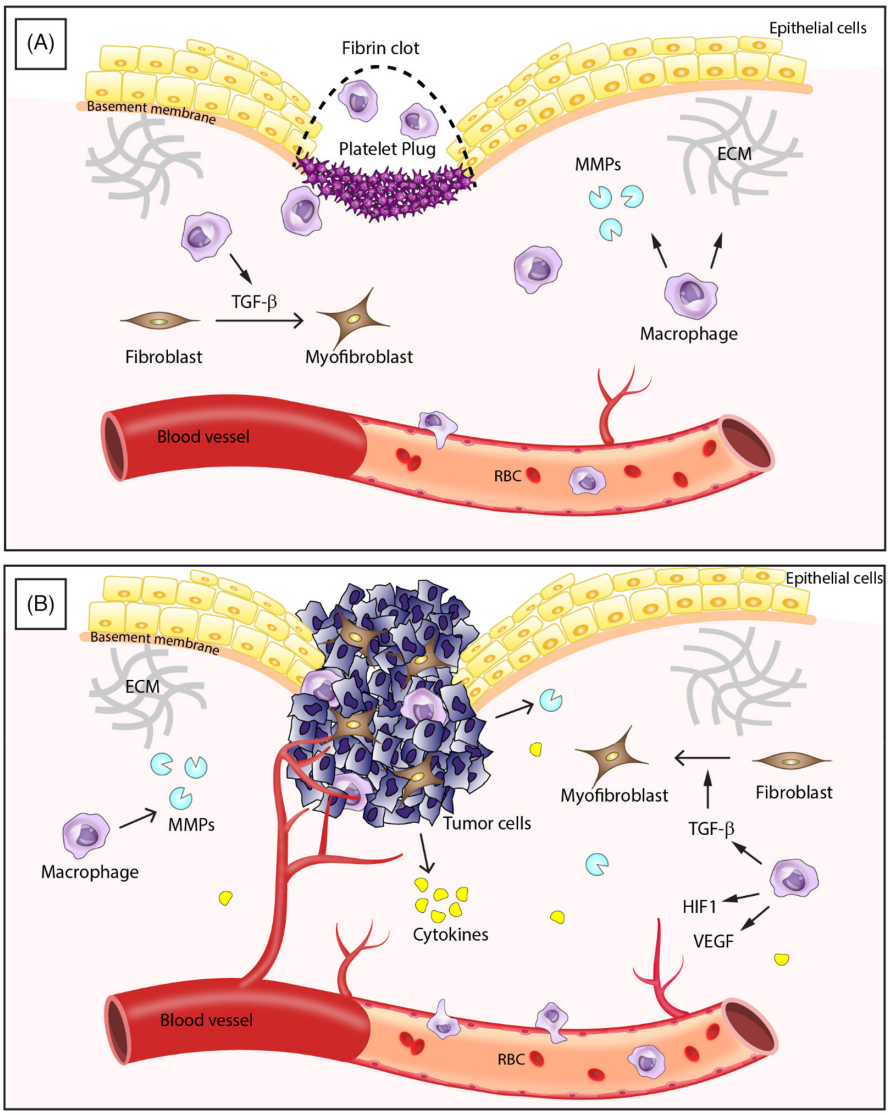

FIGURE 2 Processes involved in wound healing in the tumor microenvironment. VEGF, vascular endothelial growth factor; HIF1, hypoxia-inducible factor-1; TGF-β, transforming growth factor-beta; ECM, extracellular matrix; MMPs, matrix metalloproteinases; RBC, red blood cell

tumorigenesis. As IL-6 binds to the IL-6R receptor and glycoprotein 130 co-receptor (gp130), the Janus kinase (JAK)/STAT signaling pathway becomes active.[43–45] The IL-6R/JAK/STAT3 signaling pathway activation leads to the up-regulation of Oct4 gene expression. STATs family are transcription factors that their relation with the tumorigenesis process has been shown.[46] All in all, IL-6 has become an attractive target therapy. Targeting IL-6 by a monoclonal antibody named Siltuximab (CNTO 328) has been revealed to have favorable outcomes.[47,48]

IL-10 is an anti-inflammatory factor that is produced by different cells, including tumor cells and infiltrating-macrophages from tumors.[49,50] IL-10 binds to its receptors (Jak1 and Tyk2), and leads to the activation of STAT signaling pathway as well as inhibition of the NF-κB signaling pathway,[51] which results in the protumorigenic effect and down-regulated of pro-inflammatory cytokines, respectively. By suppressing the immune system, IL-10 contributes to tumor cells' escape from immune surveillance mechanisms.[52]

Through the initiation of the inflammatory response, anti-inflammatory cytokines suppress the signaling pathways as well as cancer progression. Hence, TGF-β and IL-10 have a complicated role in tumorigenesis. Therefore, it is of great importance to determine their role in the context of colorectal cancer in order to properly target them as a part of the therapeutic approach.

2.3 | Inflammation as a potential mechanism in tumorigenesis

One of the most important promoters of tumorigenesis in colon cancer is inflammation.[53] Inflammation starts as a response of the immune system to pathogens or tissue damage; however, perpetuating this response results in increasing the incidence of cancer due to the weakness of the anti-tumor response because it can release bioactive molecules from tumor microenvironment cells such as chemokines, cytokines, and growth factors—that contribute to constant proliferation and cell survival signals to prevent apoptosis-metalloproteinases,—as a modifier of extracellular matrix to initiate epithelial-mesenchymal transition

(EMT)—pro-angiogenic factors, and it can also facilitate other tumorigenesis mechanisms such as genome instability.[34,54,55] Although fibroblasts, immune cells, and endothelial cells produce a large portion of pro-inflammatory signals as tumor microenvironment components, they have also been shown to play an important role in tumorigenesis promotion through the secretion of cytokines and proteases from CAFs.[34]

It has been shown that fibroblasts adjacent to the CRC cells express IL-6, FAPα, and SPINK3 as an inflammation-induced factor in CRC.[47,53,56] Another function of IL-6 is the involvement in cell survival by stimulating the phosphorylation and acetylation of Ku70, production of sClusterin and organization of Bax-Ku70-sCLU in the cytoplasm. This process finally results in inhibition of the pro-apoptotic activity of Bax.[57] IL-6 expression also results in increased expression of VEGF and, eventually, angiogenesis stimulation while IL-6 and SPINK3 both have a regulatory role in various cellular functions such as differentiation, growth, proliferation, and motility.[56,58–60] The IL-6 family acts through IL6ST/gp130 and leads to phosphorylation of STAT3 at tyrosine 705 residue and makes STAT3 active. Finally, fibroblast-derived IL-6 results in the high secretion of SPINK1 in CRC cells via the STAT3 signaling pathway.[59] IL-6–STAT3 signaling is known as a promoter of cancer-related inflammation (CRI) by cytokines producing and stimulating angiogenesis and tissue transformation, while the SPINK1 signaling pathway is a mediator of CRI that has a critical role in tumorigenesis.[61] Hereto, lots of STAT3 inhibitors have been used to block its phosphorylation and hinder its activation. However, none of these inhibitors have revealed an appropriate outcome due to the absence of specificity, cell penetrance, and rapid degradation.[59–62]

As was mentioned earlier, in the tumor microenvironment, ROS is one by-product of inflammatory cells. ROS is one of the regulatory factors in chronic inflammation that can regulate other relevant factors in this process, such as activator protein 1 (AP-1), NF-κB, β-catenin/Wnt (wingless related integration site), chemokines, inflammatory cytokines, peroxisome proliferator-activated receptor-gamma (PPAR-γ), and growth factors.[63–66] In the presence of elevated ROS in the microenvironment, the secretion of VEGF and HIF1 would stimulate and activate cellular signaling related to migration and proliferation.[67,68] Therefore, targeting of ROS becomes another factor to consider as a therapeutic approach to modulate proliferative signaling and angiogenesis.[69,70] Figure 3 summarized the role of various inflammatory pathways in the TME.

2.4 | TGF-β signaling and tumor microenvironment

Stromal cells, which include immune cells and fibroblasts, are an important source of TGF-β in the tumor microenvironment. TGF-β attachment to TGF-β RII results in TGF-β RI activation and, eventually, activation of SMAD transcription factors.[71] SMADs family activation has various cellular consequences, such as cytostatic effects, invasion, cell proliferation, extracellular matrix synthesis, suppression of migration, and cell cycle.[51] However, the role of TGF-β varies according to cell type and stage of cancer. TGF-β suppression causes tumorigenesis in the early stages due to its role in the up-regulation of the cyclin-dependent kinase inhibitor (CKI) p21 and the down-regulation of c-Myc.[51] As the tumor starts to progress, TGF-β by activation EMT plays a critical role in increasing the invasion and metastasis.[72] Although targeting of TGF-β and has revealed favorable outcomes in progressive cancers, serious side effects have been reported heretofore.[73]

Activated TGF-β in the Tumor Microenvironment is involved in the differentiation of mesenchymal stem cells (MSCs) to cancer-associated fibroblast CAFs through activation of STAT3 by stimulating of TGF-β2 and then nuclear translocation of p-STAT3 due to the activation of JAK/STAT pathway. Activated CAFs also participate

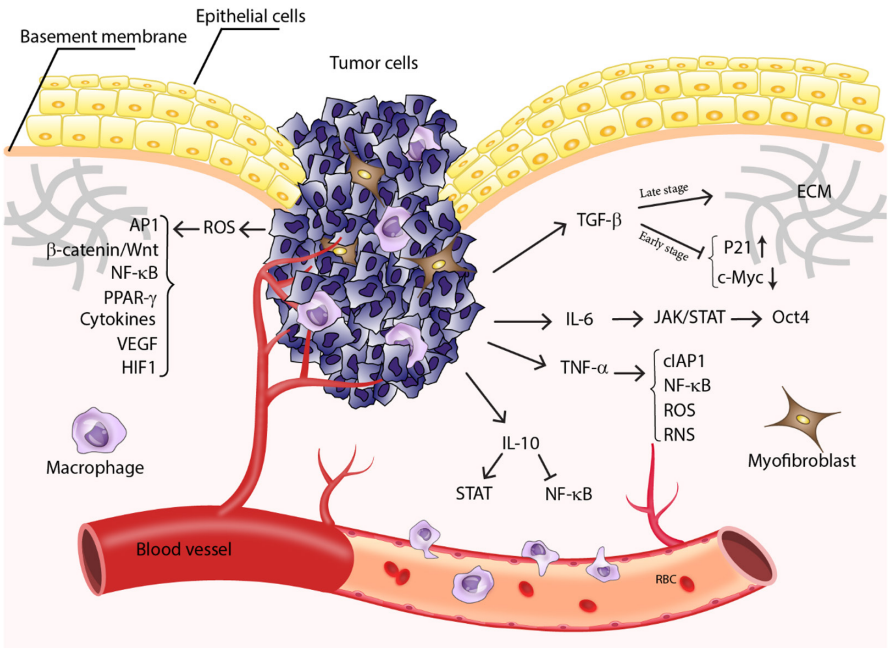

FIGURE 3 The schematic of inflammatory pathways involved in the tumor microenvironment. ROS, reactive oxygen species; AP1, activating protein 1; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; cIAP1, cellular inhibitor of apoptosis protein-1; RNS, reactive nitrogen species; IL-6, interleukin 6; PPAR-γ, peroxisome proliferator-activated receptor-gamma; NF-κB, nuclear factor-kappa B; VEGF, vascular endothelial growth factor; HIF1, hypoxia-inducible factor-1; ECM, extracellular matrix; IL-10, interleukin 10; JAK, Janus kinase; STAT, signal transducer and activator of transcription; RBC, red blood cell

in the acceleration of metastasis by increasing the production of chemokine CXCL12, interact with CXCR4+ CRC cells, activation of IL-11 induced-GP130/STAT signaling pathway, and positive feedback on TGF-β ligand production in the tumor microenvironment, therefore, CAF plays an major role in tumorigenesis and metastasis.[74]

2.5 | Estrogen regulatory impact on tumor microenvironment and immune surveillance

There is a hypothesis around the inhibitory role of estrogen on the inflammatory signal and thereupon modulation of the tumor microenvironment in CRC, but the exact underlying mechanism has not been understood yet.[75] The tumor microenvironment leads to the release of cytokines through inflammation; these cytokines increase the biosynthesis of steroid hormones by enhancing the expression of the 3b-hydroxysteroid dehydrogenase gene.[75] A genome-wide study showed that the transfected ERβ in SW480 cells results in the down-regulation of the IL-6 signaling pathway.[76] As mentioned previously, by considering the role of IL-6 in the STAT3 transcription factor's activation and promotion of CRC tumorigenesis, the potential consequence of ERβ expression could be the reduction of tumor progression in the microenvironment.[77] ERβ also plays a role in the anti-inflammatory response by suppressing IL-6, TNF-a, and CSF2 expression induced by TNF-a and enhancing CD4C T cell responses on monocytes and macrophages.[78,79] Estrogen signaling plays a role in tumor suppression in CRC via pro-apoptotic signaling activation by ERβ, adjusting the tumor microenvironment and immune surveillance mechanisms by inhibiting inflammatory signals.[80] Therefore, the absence of ERβ could result in tumorigenesis and then provides a suitable therapeutic target.

3 | INFLAMMATION/FIBROBLASTS ASSOCIATED WITH TUMOR MICROENVIRONMENT

The initial description of the chronic inflammatory responses' involvement in tumorigenesis was done by Virchow in 1863.[81] Since the incidence rate of CRC, Crohn's disease, or ulcerative colitis is higher in patients with inflammatory bowel disease (IBD) than in the unaffected population, and the important role of chronic inflammation in sporadic CRC's incidence, the CRC was introduced as an inflammation-dependent cancer.[82] The inflammatory response is initiated by the activation of specific oncogenes, which results in the exertion of immune cells and the generation of chemokines and cytokines.[83] The inflammatory microenvironment is responsible for invasion, fibroblast activation, matrix remodeling, angiogenesis, metastasis, and the survival of malignant cells.[84,85] B cell, lymphotoxin, and CD40 ligand as pro-inflammatory cytokines lead to the activation of the TNF family and NF-κB.[86] NF-κB participates in tumorigenesis and development by causing chromosomal instability, DNA damage, aneuploidy, mutation, and epigenetic changes, along with the production of reactive nitrogen and reactive oxygen species (ROS).[87] Nuclear transcription factors such as STAT3 and NF-κB produce numerous pro-inflammatory cytokines, proliferation modulating, survival, angiogenesis, and invasion in the nucleus, targeting critical genes in modulating cancer-promoting inflammatory responses and so have a great influence on producing the tumorigenic microenvironment.[86,88] Moreover, they also play a role in autoactivation by the chemokines' generation, and therefore, in the tumor microenvironment, they cause a sustained inflammatory response.[84] Alternatively, the loss of p53, which is the most prevalent mutation in colorectal cancer, is another promoting factor of NF-κB production, so it initiates epithelial-mesenchymal transition and inflammation in the microenvironment.[89] Another result of inflammatory factors' activation and the existence of oxidative stress is the prevention of MSH3 protein's (DNA mismatch repair protein) displacement from nuclear to cytosolic, which promotes inflammatory-associated microsatellite alterations in the tumor microenvironment.[90]

As we have already discussed, tumor microenvironment consists of a wide variety of cell types, including endothelial cells, leukocytes, and fibroblasts. As an initiator of the chronic inflammatory condition, epithelial cells can undergo an epithelial-mesenchymal transition in order to produce the fibrotic matrix.[91] Fibroblasts in the tumor microenvironment express α-SMA marker just like phenotype, are presented by myofibroblasts; and are known as cancer-associated fibroblasts (CAFs). CAFs can assist in the progression and development of tumors by raising a plethora of growth factors' secretion.[92,93] In the case of the exact origin of CAFs, there is controversy, as it is obvious that the most possible origin in the colon tissues of CRC patients is fibroblasts. In colon cancer, as well as various types of cancers, CAFs demonstrated functional heterogeneity, which could influence the clinical outcome of patients.[94] In colon cancer, CAFs secrete various cytokines and growth factors like hepatocyte growth factor (HGF) and make a colony of cancer stem cells.[95] On the other hand, cancer cells and CAFs increase the growth of CAFs by producing growth factors and accelerating the proliferation of tumors.[96] TGF-β derived from cancer cell make CAFs produce IL-11, to promote gp130/STAT3 signaling and help the tumor to more progression.[97] In CAFs, the expression of MMPs is associated with the basement membrane's degradation and PAR1 cleavage; therefore, CAFs also play a critical role in the invasion and migration of cancer cells.[98,99] Although the CAFs are the outcome of chronic inflammation, they can also influence the increased inflammation by modulating pro-inflammatory genes such as NF-κB.[100] All in all, CAFs play a various role in making the best conditions for the tumor to become malignant.

4 | CROSSTALK BETWEEN CANCER-ASSOCIATED FIBROBLASTS AND IMMUNE CELLS

Cancer is regarded as a promoting factor for inflammation because it results in severe immune cell reactions. A better understanding of

how the CAFs interact with immune cells is crucial for our understanding of the tumor-based prognostic and therapeutic aspects of many malignancies. The data suggest that CAFs interact with cancer cells and immune cells through different mechanisms.[101,102] For instance, several tumor-promoting factors such as chemokines and cytokines are secreted by CAFs, resulting in tumor cell survival, immune suppression, and resistance to therapy.[103] These immune cells include natural killer (NK) cells, macrophages, T cells, and dendritic cells which have a significant role in TME. There is a controversial issue regarding the role of immune cells in TME and controlling the growth of a tumor, which influences all aspects of cancer diseases, from tumorigenesis to treatment.[104,105] The interaction between immune cells and CAFs to regulate the TME has been summarized in some kinds of literature.[101,102,106] However, the importance of this issue convinced us to provide this section for a better understanding of the fundamental aspects of immunology's role in cancer.

In tumor tissue, fibroblasts have the ability to secret lots of immune suppressants such as TGF-B and VEGF. CAFs are thought to be the primary source of TGF-β in the TME,[102,107] and TGF-β inhibits NK cell and cytotoxic T lymphocyte (CTL) activation (CTLs) activation.[106] NK cells are the main cause of the tumor-infiltrating leukocyte population, which acts as the first immune response against tumors. Furthermore, TGF-β not only inhibits DAP12 (DNAX-activating protein of 12 kDa) transcription (a critical protein for NK cell signaling) by inducing miR-183, but it also inhibits NKp30 and NK Group 2D (NKG2D) expression.[108] Thus, NK cells are inhibited by CAFs through various signaling blockage pathways, which leads to tumor progression. The inhibiting properties of CAFs on the operation of NK cells may be exerted in different ways, including NK receptor activation, cytokine production, and cytotoxic activity.[8] Furthermore, CAFs decrease the cytotoxic effect of NK cells versus their tumor target cells via secretion of PGE2, perforin, IDO, as well as granzyme B.[101,108] Li et al. reported that the release of pro-inflammatory cytokine prostaglandin E2 (PGE2) by CAFs is a novel mechanism for the suppression of antitumor NK cell immunity in TME, which binds the pro-inflammatory response to immune tolerance.[109] Moreover, it has been suggested that inhibition of PGE2 confers chemotherapeutic properties in numerous cancers, especially CRC.[109–111]

Macrophages have a vital role in angiogenesis, tumor progression, and enhancement of tissue repair. Accumulation and infiltration of macrophages in TME are related to tumor development, worse prognosis, and metastasis.[112,113] According to the different phenotypes, classically activated macrophages (M1) and alternatively activated macrophages (M2) are the two types of tumor associated macrophages (TAMs). M1 macrophages activate the immune system by producing lots of inflammatory cytokines (TNF-α, IL-22, IL-12, and IL-6) and reactive oxygen species, TNF, and NO. M2 macrophages have an impact on the immune system by promoting tissue repair and angiogenesis, which are involved in malignant development.[114,115] Furthermore, M2 macrophages promote the production of immunosuppressive cytokines (IL-10, TGF-β, Arginase, and IDO) that inhibit inflammation and the immune response of cytotoxic $CD8^+$ T cells in the TME.[108,116] M2 macrophage and CAFs can interact with each other bilaterally, and M2 macrophage can facilitate the conversion of CAFs to myofibroblasts. Pieces of advice indicate there is an essential relationship between CAFs and TAMs, causing the tumor to develop. Notably, CAFs and TAMs are frequently identified in the same location in a number of tumor forms. CAFs have a significant role in immunosuppressive cancers because they promote monocyte recruitment to the TME (via stromal cell-derived factor-1 (SDF-1) and monocyte chemotactic protein-1 (MCP-1)) and monocytes divided into M2 macrophages with higher IL-10 expression.[117] Moreover, CAFs can secrete IL-6, CCL2/MCP-1, CXCL12/SDF1, and M-CSF (macrophage colony-stimulating factor which is also recognized as CSF-1) which leads to an increase in the influx of monocytes into the TME as well as M2 immunosuppressive differentiation.[117] Overall, the expression of these factors is considered as a poor prognostic factor for patients with many cancers, particularly colorectal cancer.

Another critical immune cell type is mast cells, which are involved in CAFs-TAE interaction. It has been documented that activation and accumulation of mast cells release a wide variety of chemokines and cytokines (such as IL-6, IL-10, IL-13, IL-17, VEGF, and TNF-α) and exacerbate the inflammation that modulates tumor growth and immunosuppression.[108,118] Evidence suggests that mast cells can be recruited and activated by different agents produced by different tumors. Activation of mast cells enhances CAFs differentiation and proliferation by secreting TGF-B, tryptase, IL-13, and adenosine, which are all favored in tumor progression and immunosuppression.[119] Adenosine, which is produced by both tumor cells and mast cells, inhibits T-cell function and has a critical role as an immunosuppressive factor in TME. Mast cells could also increase the expression of IL-13 and activate STAT-3, leading to M2 polarization and contributing to immunosuppressive effects.[118–121]

CAFs also participated in the gathering of neutrophils into the TME and increased the activation and survival of them via secreting IL-6 and STAT-3.[122] Then, in association with CAFs, tumor-associated neutrophils (TANs) expressed more programmed death-ligand 1(PDL1), IL-8, TNF-α, and CCL2, which all of them are linked to increasing the tumor cell migration and poor prognosis of patients in many cancers, especially colorectal cancer.[101,108,123] Moreover, these TANs derived factors have many roles in tumor cells; for example, they have the ability to facilitate invasion, proliferation, and migration as well as produce pro-angiogenic factors, leading to tumor vascularization.[108,124]

5 | TUMOR CELL MUTATIONS/ CHROMOSOME INSTABILITY AND TUMOR MICROENVIRONMENT

The TME surrounding tumors consists of various immune cells, vessels, and fibroblasts. There is an important relationship between TME and tumor cells that together leads to cancer development. So, it is important to recognize the abnormal genetic changes in TME, which might be critical factors in the development of colorectal cancer or metastasis by influencing signaling pathways in the process of

CRC pathogenesis, such as chronic inflammation. Therefore, understanding the genetic alternations that may promote CRC is important for identifying novel therapeutic targets and drug development. In the following paragraphs, some of the genetic mutations in TME that may have a role in the CRC's incidence are summarized.

5.1 | SLIT/ROBO signaling pathway and tumorigenesis

Previous studies have shown significantly overexpressed ROBO1 and ROBO4 in colorectal cancer compared to normal patients, and there is a relation between the expression of SLIT2 and ROBO1 and a high risk of metastatic incidence and poor prognosis in these patients.[125] ROBO1 and ROBO4 are chiefly expressed in tumor cells and the endothelial cells of tumor vessels, respectively.[125] The SLIT/ROBO pathway is critical for regulating tumorigenesis by modulating migration, tumor proliferation, tumor microenvironment, and angiogenesis; it could play both tumor-suppressor and oncogenic functions in this process. One of the main consequences of the overexpression of the SLIT/ROBO pathway is EMT, a major activator of metastasis and tumor invasion. The activation of ROBO1 by recombinant SLIT2 in colorectal epithelial carcinoma cells results in ubiquitination of E-cadherin by ubiquitin ligase Hakai that together lead to lysosomal degradation and then stimulate the EMT.[126] Moreover, the SLIT/ROBO pathway has a further role in the tumor microenvironment, such as angiogenesis and inflammation. The regulatory effect of SLIT2 on ROBO1 and ROBO4 results in the activation of ROBO4, then the blockage of VEGF, resulting in increased vascularization and permeability.[127] In the same way as SLIT2 regulated vascularization, it could affect inflammation by down-regulation of lipopolysaccharide or VEGF.[128,129] Taking these together, it is suggested that the SLIT/ROBO signaling pathway might play a role in the tumor microenvironment.

5.2 | PD-L1 gene locus and resistance to the adaptive immune response

In CRC, amplification of the PD-L1 gene locus has been reported recently, which is known as a cause of resistance to the adaptive immune response to local inflammatory signals.[130,131] Up-regulation of PD-L1 has a strong correlation with chromosomal instability, which is caused by mutation in the mismatch repair (MMR) gene (responsible for the occurrence of MSI).[130] Within the tumor microenvironment, the anti-tumor immune activation stimulated the secretion of IFN-γ, which results in abnormal expression of PD-L1.[132] CD8+ cells are an important anti-cancer immunity response to cancer cells and are produced by tumor-infiltrating lymphocytes (TIL).[133] Besides, infiltrating CD8+ cells are the main consequence of microsatellite instability, high neo-antigen content, or active chronic inflammation pathways.[134] Another possible mechanism under the up-regulation for PD-L1 is the constant expression of NF-κB, the major cause of chronic inflammation. Because the PD-L1 gene has a binding site for NF-κB on its promoter, continued activation of NF-B in cancer cells results in sustained expression of PD-L.[135] High PD-L1 expression bestows the advantage of an increased survival rate for colorectal carcinoma through a negative impact on the immune response.[136] It could be a useful tool to evaluate the prognosis of patients with high levels of microsatellite instability and provide them with the therapeutic benefit of PD-1/PD-L1 blockade.

5.3 | NF-κB, IL-6/STAT3, and inflammation

As we mentioned earlier, inflammation is one of the progressive factors in the incidence of CRC. There are lots of factors in the microenvironment that participate in the secretion of pro-inflammatory cytokines, among which NF-κB, IL-6/STAT3, and epigenetic changes help them to make it worse and irreversible,[137] are a contributing signal in promoting inflammatory response in the microenvironment, and we discussed their plausible epigenetic changes during tumorigenesis of CRC.[138] IL-6 induces DNA methylation mechanisms by increasing the expression levels of DNMT1; therefore, it suppresses the negative regulator of the STAT3 signaling pathway, which is SOCS3 (suppressor of cytokine signaling 3).[139] On the other hand, IL-6, in the same way, suppresses miR-27b expression, which targets CYP1B1 (cytochrome P450 enzymes) and results in altered metabolic competency of epithelial cells. Overall, their silencing leads to the incidence of CRC.[140] Another epigenetic component with the ability to silence SOCS3 is miR-196b-5p. As a result, overexpression of miR-196b-5p in CRC is associated with a poor prognosis and resistance to 5-fluorouracil (5-FU).[141] The activation of NF-κB by TNF-α, which is a leading factor in chronic inflammatory and tumorigenesis by regulation of the Wnt/β catenin signaling pathway. This pathway employs both anti and pro-inflammatory functions during the development of CRC, and constantly remains active due to the suppression of DACT3 (a negative regulator of Wnt/beta-catenin) by histone modification.[77] TNF-α also increases the expression of miR-105 and miR-19a, which activate NF-κB signaling and contribute to the progression of colitis, CAC, and CRC.[142,143]

5.4 | Long non-coding RNAs (lncRNAs) and tumor microenvironment

LncRNAs may play a regulatory role in tumor progression by affecting angiogenesis and metastasis through adjustment of the biological processes of endothelial cells as critical elements of stroma in TME.[131,144] For example, lncRNA APC1 decreases the stability of Rab5b mRNA through reduced production of exosomes in CRC cells, which results in the suppression of tumor angiogenesis by inhibition of the MAPK pathway in endothelial cells.[134] Another regulatory role of lncRNAs is the adjustment of activation, development, and differentiation of T cells. T cells are one of the major immune cells in

the TME, of which CD8+ (cytotoxic T-cell) with an anti-tumor role in the TME is a predominant percentage of T cells.[84,145,146] LncRNA SOX5 through adjustment of indoleamine 2,3-dioxygenase 1 (IDO1) expression by regulating the secretion of $CD8^+$T cells and cytotoxicity can impact on colorectal cancer progress.[147]

LncRNAs have a critical role in tumor microenvironment regulation by modulating angiogenesis, and cancer stem cell self-renewal.[148,149] Aberrant expression of SATB2-AS1 has been shown in CRC. The expression of SATB2-AS1 was down-regulated in tissue and cells of CRC patients, which has a positive correlation with progression and poor prognostic in patients. Besides, SATB2-AS1 is able to suppress the metastasis and regulate the immune response in the tumor microenvironment of CRC through the modulation of immune cell infiltration by cis-activating SATB2.[150] In addition, lncRNAs are another progressive factor in turning chronic inflammation into CRC. In comparison to normal CRC tissue, higher expression of LncRNA FEZF1-AS1 and abnormal expression of LncRNA AB073614 has been observed in CRC. LncRNA FEZF1-AS1 and lncRNA AB073614 cause the up-regulation of STAT3, which induces the transformation of inflammation into cancer and EMT in CRC, respectively[151,152] (see Table 1).

6 | THERAPEUTIC APPROACH OF COLORECTAL CANCER BY TARGETING TME COMPONENTS

Two factors influence tumor growth and progression: genetic and epigenetic alteration in tumor cells and the related and active interaction that reorganizes the components of the TME. Tumor cells, as the center of TME, employ sophisticated signaling networks to alter the purpose of cellular and non-cellular parts in order to exploit non-cancerous cells. A complicated network of various components is the source of intercellular communication, and the result of such interaction is tumor growth and progression, drug resistance, and ineffective treatment response. Recent developments in tumor biology have shown that understanding the various underlying mechanisms of tumor growth and progression requires a complete investigation of the complex interactions between tumor cells and their surrounding microenvironment. Understanding how cancer cells interact can help researchers create therapeutic strategies to predict and combat cancer cells' strategies for surviving and resisting anti-cancer treatments. As a result, a variety of approaches have been used to attack malignant tumors by interrupting their interactions with stromal cells, and we summarized a few of them in the following paragraph.

However, the most significant challenge in this field is recognizing and determining the heterogeneity of TIME by investigating a wide variety of patients with different cancer types at either the cellular or the molecular level. This can result in functional solutions for extensive clinical application, such as increasing the therapeutic effectiveness of targeting TIME components.

6.1 | Anti-cancer-associated fibroblast therapies

Anti-cancer-associated fibroblast treatments have recently received considerable attention. Although many reports have shown the pro-tumorigenic characteristics of CAFs, the therapeutic aspects of CAFs are still a challenging issue. In this regard, many drugs have been discovered and used with the aim of anti-CAFs therapies and have had anti-tumor effects in some clinical research. According to different specific targets, these agents can be divided into several classes.[153]

TABLE 1 A summary of dysregulated non-coding RNAs related to the TME of CRC

Non-coding RNA	Type	Clinical level	Regulated by/ Regulating	Reference
miR-183	miRNA	Up	TGF-β/DAP12	1
APC1	lncRNA	Up	Rab5b	75
SOX5	lncRNA	Up	IDO1	79
SATB2-AS1	lncRNA	Down	SATB2	139
FEZF1-AS1	lncRNA	Up	STAT3	140
AB073614	lncRNA	Up	STAT3	141
miR-27b	miRNA	Down	IL-6/CYP1B1	146
miR-196b-5p	miRNA	Up	SOCS3	147
miR-105	miRNA	Up	TNF-α	126
miR-19a	miRNA	Up	TNF-α	127

Abbreviations: APC1, adenomatous polyposis coli 1; CRC, colorectal cancer; CYP1B1, cytochrome P450 enzyme 1; DAP12, DNAX-activating protein of 12 kDa; FEZF1, FEZ Family Zinc Finger 1; IDO1, indoleamine 2,3-dioxygenase 1; IL-6, interleukin 6; lncRNA, long non-coding RNA; miR, miRNA, microRNA; RAB5B, member RAS oncogene family; SATB2, special AT-rich binding protein 2; SOCS3, suppressor of cytokine signaling 3; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-beta; TME, tumor microenvironment; TNF-α, tumor necrosis factor-alpha.

6.1.1 | Class 1 of anti-CAFs

Class 1 agents suppress signal transduction pathways and affect the interaction between CAF and the tumor. Inhibitors of VEGF, TGF-, VEGFR, IGF-1R, PDGFR, and HGF/MET are examples of this class. After binding to their receptors, TGF-, IL-6, and PDGF are important factors for activating fibroblasts as well as participating in cell signaling circuits.[154,155] Activation of these receptors leads to increase proliferation and invasive characteristics of CAFs. Along with the role of CAFs in secreting plenty of growth factors and pro-inflammatory chemokines and cytokines mentioned above, they can also increase IL-6, CCL2, and TGF-β, which help immune evasion by enrolling immune cells.[56,156]

CAFs are the main cellular source of TGF-β, which is known as an immunosuppressive cytokine and leads to polarization of immune cells (both adaptive and innate cells) to promote immunosuppressive cells.[156] Galunisertib (LY2157299) is an anti-cancer agent that targets TGF-β signaling and has been used in a variety of cancers.[157] Calon and colleagues reported that TGF-β inhibition may be associated with the prevention of CRC metastasis, particularly when patients are treated early phase of the disease.[97]

VEGF is highly expressed in advanced CRC. Neovascularization, supported by increased VEGF expression, is needed to provide nutrients and hematogenous supply for tumor spread.[158] It has been demonstrated that in colorectal adenocarcinoma, higher levels of VEGF have been linked to a higher risk of hepatic metastasis and a worse prognosis.[158,159] By restoring vessel integrity, expanding tumor perfusion, and decreasing interstitial fluid pressure, VEGF inhibitors increase the number of immune cells entering the tumor. Some of the anti-VEGF agents, including Aflibercept, Regorafenib, and Bevacizumab, have been used successfully in the treatment of malignant CRC.[160]

Another growth factor that activates c-Met (mesenchymal-epithelial transition factor) on cancer cells, HGF, is mainly secreted by fibroblasts.[93] Activation of the c-Met, which is a cell surface tyrosine kinase receptor, regulates signaling cascades, including cellular motility, angiogenesis, proliferation, development of cancer cells, and epithelial-mesenchymal transition.[161] Recently, anti-Met agents have become a topic of interest as a new strategy for both therapeutic management and prediction of CRC patients' prognosis. In this respect, several drugs have been used in different phases of trials to target the c-MET/HGF signaling pathway with different results. These drugs are divided into small-molecule tyrosine kinase inhibitors (TKIs), including NK4,[162,163] Cabozantinib,[164] as well as Onartuzumab and also monoclonal antibodies (mAbs). For a review of c-Met inhibitors in colorectal cancer, see ref (161).

6.1.2 | Class 2 of anti-CAFs

Class 2 anti-CAFs agents are more focused on CAFs and CAF products, and thus include inhibitors of MMPs, tenascin-c, cathepsin, and serine proteases.[153] Although clinical trials in this group are not too many, we discuss them in brief as the following.

Cathepsins are a group of globular proteases that belong to the cysteine, serine, or aspartic proteases and are not only identified as intracellular peptide hydrolases, but some of them also have extracellular functions. There are several cathepsin families, including cathepsin A-H, K L, O, S, V, and W. Cathepsins are synthesized and processed as inactive proenzymes to be converted to mature and active enzymes.[165,166] Since cathepsins are able to degrade extracellular matrix proteins, they are involved in colorectal cancer invasion and metastasis. Evidence suggests that some cathepsins are expressed in CRC and enhance development and tumor progression.[165-168] For instance, cathepsin S is a lysosomal cysteine protease with a critical role in cell migration, angiogenesis, and cancer cell invasion. This, in turn, can provide a valuable prognostic indicator and a possible target for noninvasive therapy. Burden et al. demonstrated that Fsn0503, which is a monoclonal antibody, could block CRC angiogenesis and tumor development in vivo and might improve the effectiveness of chemotherapy by inhibition of catepsin S.[168]

MMPs are zinc-dependent proteolytic metalloenzymes that have a significant role in the deterioration of ECM and are needed for metastasis and tumor development. During the inactive period, they are secreted and activated in the extracellular environment. Based on preclinical studies, different MMPs, including MMP1-13 and MT1-MMP, have been found abundantly in CRC. Although overexpression of some MMPs is related to bad prognosis and metastasis in CRC, overexpression of MMP-12 is associated with a higher improved survival rate in patients with CRC due to its inhibitory effects on angiogenesis.[169,170] Prinomastat/AG-3340 is an MMP inhibitor and effective against a variety of MMPs, including MMPs 2, 3, 9, 13, and 14. AG-3340 might be able to stop angiogenesis and tumor growth, which results in apoptosis in different cancers, especially colon cancer. However, the utility of this drug is limited due to its lack of effectiveness and unwanted side effects.[171] Curcumin is another anti-cancer agent that suppresses MMP expression and significantly inhibits MMP-9 activity in CRC.[172] Notably, the inhibitory effect of curcumin on AP-1 and NF-KB cell signaling results in down-regulation of MMP-9 expression.[173]

Serine protease inhibitors (serpins) belong to a protein superfamily, which can be used as a powerful strategy in cancer treatments. They have been classified into six groups: serine, glutamic acid, threonine, cysteine, aspartate proteases, and matrix metalloproteinase. SPINK1 (Serine protease inhibitor Kazal Type 1) is an inhibitor of trypsin kinase, which plays a role in cell proliferation, cancer metastasis, and inflammation. It seems that SPINK1 has participated in tumor progression and malignancy via EGFR signaling.[174] Overexpression of SPINK1 has been seen in 50% of patients with CRC and is related to a bad prognosis.[58] Thus, SPINK1 could be a useful biomarker for targeted therapy in CRC. FAP (Fibroblast activation protein) is a serine proteinase found in CRC cancers at both the protein and mRNA levels, and its expression levels are linked to

angiogenesis, collagen degradation, poor prognosis, and aggressive cancer progression stages.[58]

Moreover, it has been reported that FAP in CAFs by inducing tumor-promoting inflammation may be critical in controlling an anti-tumor immune response.[175] Consequently, treatment with anti-FAPα antibodies inhibited progression and tumor growth, which might be facilitated by T-cell immunotherapy.[101] In this regard, ValboroPro (Talabostat) was used in metastatic colorectal cancer, which prevents fibroblast activation protein (FAP).[176]

6.1.3 | Class 3 of anti-CAFs

Class 3 of anti-CAFs is COX-2, which is triggered by a huge number of cytokines and growth factors. COX-2 is overexpressed in many cancers, and COX-2 inhibitors can decrease the growth of tumor by several pathways such as the production of 1-PGE1 (inhibition of prostaglandin E1) in fibroblasts, and 2-down-regulation of HDM2, which is an oncogenic E3 ligase that targets P53 for degradation and ubiquitination.[153] On this point, NSAIDs, which are COX-2 inhibitors, have been used successfully in CRC treatment and have an anti-tumor effect on the progression of tumors (see Table 2).[177]

6.2 | Targeting the tumor vasculature

Angiogenesis is needed for the metastasis and growth of solid tumors in cancer, and it demands the balance of lots of inhibitory and stimulatory factors. Even though different mechanisms are responsible for the pathogeneses of angiogenesis, the inhibition of angiogenesis may be a practical therapeutic approach in the management of cancers. Measuring microvessel density (MVD) is commonly used to evaluate angiogenesis. Furthermore, MVD is based on endothelial markers such as CD31, endoglin (CD105), CD34, and von Willebrand's factor (Factor VIII related antigen or F. VIII Ag) and is also associated with the distant site, lymph node involvement, depth of invasion, and tumor metastasis stage.[183] There is a relationship between MVD and VEGF with a higher incidence of metastases and decreased survival of CRC. However, it is challenging to relate MVD and VEGF with overall survival (OS) as prognostic biomarkers for CRC patients.[183]

Inhibitors of angiogenesis such as antibodies or small molecules are used in the standard treatment of CRC. Bevacizumab (Avastin) is the first angiogenesis inhibitor with a specific effect on VEGF, which avoids its binding to specific receptors. Previous studies have demonstrated that adding bevacizumab to chemotherapy increases OS and response rate.[184,185] However, this kind of treatment is expensive and, in some cases, it could be accompanied by some side effects such as proteinuria, hypertension, as well as bowel perforation without producing an effective response.[186]

Endoglin, also known as CD105, is a TGF-β accessory receptor that is overexpressed in endothelial cells of tissues involved in angiogenesis. Consequently, CD105 is a good predictor of tumor-related angiogenesis. It has been documented that MVD determined by monoclonal antibodies to CD105 can be utilized to differentiate low-grade from high-grade dysplasia and also between high-grade dysplasia from CRC. On the other hand, MVD determined by monoclonal antibodies to CD34, cannot be utilized to differentiate between these pathologies.[187]

6.3 | Targeting the tumor microenvironment

In a patient with colorectal cancer, some special features of tumor cells can change the tumor microenvironment (TME) and vice versa. The TME consists of cellular components (fibroblasts, osteoblasts, mesenchymal stem cells, blood, fat cells, and immune cells and ECM). The TME has been proven to play a significant role in providing cytokines, growth factors, and other anti-apoptotic and pro-metastatic factors that modulate tumor cells' ability to migrate.[188]

TABLE 2 Pharmacological anti-tumorigenic agents against CAFs in CRC treatment

Class	Name	Target	Pathway	References
Class 1 of anti-CAFs	Galunisertib (LY2157299)	TGF-βRI kinase	TGF-β signaling pathway	97
	Aflibercept	VEGF	Angiogenesis	178
	Regorafenib			
	Bevacizumab (Avastin)			
	NK4	c-Met	c-MET/HGF signaling pathway	38,179,180
	Cabozantinib			
	Onartuzumab			
Class 2 of anti-CAFs	Fsn0503	Catepsin S	Proteolysis	181
	Prinomastat/AG-3340	MMPs 2, 3, 9, 13 and 14		182
	Curcumin	MMP-9		48
Class 3 of anti-CAFs	NSAIDs	COX-2	Inflammatory pathway	49

Abbreviations: CAFs, cancer-associated fibroblasts; COX-2, cyclooxygenase-2; CRC, Colorectal cancer; EGCG, epigallocatechin-3-gallate; HGF, hepatocyte growth factor; MMPs, matrix metalloproteinases; NSAIDs, nonsteroidal anti-inflammatory drugs; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor.

Several treatment approaches based on tumor microenvironment targeting have been established, including TGF-signaling pathway targeting, angiogenesis targeting, CAF targeting, cancer stem cell (CSC) therapies, and immunotherapy. In the following, some of these therapies and their targets will be discussed in more detail.

6.3.1 | Targeting TGF-β signaling in colorectal cancer

The multifunctional TGF-β has a crucial role in proliferation, embryonic development of normal tissues and differentiation as well as cellular immune responses, cell motility, angiogenesis, and extracellular matrix production.[189] Basically, cells in tissues synthesize and secrete this factor into the microenvironment where it attaches to special TGF-β receptors for paracrine and autocrine signaling. The TGF-β signaling pathway begins with the attachment of TGF-β molecule to its receptor and consequent activation of downstream molecules where they can move to the nucleus and change several genes' expression.[190] There are three major TGF-β receptors, each of which plays a specific role in transmitting the signal into the cytosol. Following TGF-β receptor II (TBR II) activation by TGF- I, TGF- receptor I (ALK5) is activated and a heterodimeric complex is formed.[191] TBRII is a fundamental active serine/threonine kinase while transphosphorylation of the glycine/serine-rich domain of TBRI by TBRII after complex formation, activates TBRI kinase. TBRIIIs, endoglin, which lacks kinase signaling motifs, also participates in the activation process of TGF-β1 kinase receptors as the accessory receptor.[192] Phosphorylated receptors then activate separate pathways, including canonical and non-canonical pathways. The canonical pathway is also referred to as the SMAD-dependent pathway in which SMAD2 and SMAD3 molecules are phosphorylated and then assembled into heterodimeric and trimeric complexes with SMAD4 molecules. The complex is then translocated to the nucleus to regulate the expression of TGF-β target genes.[193]

TGF-β has been shown to have dual activity in CRC, acting as a tumor suppressor factor in the early stages and increasing disease progression in the later stages. Kawata et al. reported in a study that TGF-β signaling has a positive effect on disease development and that its serum level predicts recurrence in CRC patients.[194] It has also been shown that increased TGF-β signaling in the tumor microenvironment is associated with a poor prognosis in CRC patients, and that stromal TGF-response causes an increase in ECM proteins, cytokines, and growth factors, many of which play important roles in metastasis and the development of various cancers.[194]

Several TGF-targeting therapeutic options are currently being studied in clinical trials, including monoclonal antibodies, chimeric proteins, small molecule receptor kinase inhibitors, vaccines, and antisense oligonucleotides (ASOs).[195] In the case of colorectal cancer, the first priority has been to block the receptor with small molecules such as Galunisertib (LY2157299), which inhibits TGF-RI kinase and thus blocks SMAD2 phosphorylation (NCT04031872, NCT02688712). In a study, Jonathan M. Yingling et al. reported that Galunisertib has anti-tumor activity, including suppressing mesenchymal phenotype and tumor cell migration, postponement of tumor growth, and reversal TGFβ-mediated immune-suppression.[195] It has been demonstrated that this molecule prevents the growth of hepatocellular, colon, lung, and breast cancers in animal models.[196]

6.3.2 | Targeting CAFs and angiogenesis in CRC

CAFs are also the most crucial elements of the tumor microenvironment that induce metastasis and tumor growth via various mechanisms. Basically, CAFs secrete many cytokines and growth factors in the tumor microenvironment, leading to the enhancement of cancer cell growth and invasiveness. In addition to CAFs, TAMs also exist in the tumor microenvironment and, together with CAFs, they prepare a better niche for cancer cells. IL-6 secreted by CAFs is one of the inflammatory cytokines primarily and helps the growth and invasiveness of cancer by activating STAT3.[197]

STAT3 is an important mediator for malignant progression in colorectal cancer. Retained STAT3 activation in CRC is actively contributed to immune cells and cancer-associated fibroblasts.[198] TGF-β-stimulated CAF and TAM induce STAT3 signaling in tumor cells by secretion of IL-11 and IL-6, respectively. In a study, E Sanchez-Lopez et.al investigated the potential of NT157, which is a new tyrphostin, for targeting cancer cells and their microenvironment at once in a sporadic CRC mouse model. NT157 at least inhibits IGF/1R/IRS and JAK/STAT3 as oncogenetic signaling pathways. By doing so, it was demonstrated that NT157 efficiently decreased tumor size and multiplicity.[197]

In another study performed by Jin et al. JAK/STAT3/IL-8 pathway was inhibited using (−)-epigallocatechin-3-gallate and curcumin's combination in order to stop microenvironment-induced angiogenesis. In this study, JAK/STAT3 signaling was repressed by curcumin combination with EGCG and subsequently inhibited the conditioned medium-induced transition of normal endothelial cells (NECs) to tumor endothelial cells (TECs).[199]

7 | CONCLUSIONS

With respect to the great heterogeneity in the TME of CRC and the following metastasis, there is a pressing need to consider targeted therapy. In addition, there are several therapeutic molecules that could be used to target TME components in preclinical investigations and also in clinical trials. We have evaluated studies reporting the cell composition and other various components in TME along with their characteristics and functions with respect to CRC to provide new diagnostic biomarkers and novel personalized therapeutic approaches.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this study.

DATA AVAILABILITY STATEMENT

All data used to support the findings of this study are included in the article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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