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REVIEW PAPER

The Tumor Microenvironment in Colorectal Carcinogenesis

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Abstract Colorectal cancer is the second leading cause of cancer-related mortality in the United States. Therapeutic developments in the past decade have extended life expectancy in patients with metastatic disease. However, metastatic colorectal cancers remain incurable. Numerous agents that were demonstrated to have significant antitumor activity in experimental models translated into disappointing results in extending patient survival. This has resulted in more attention being focused on the contribution of tumor microenvironment to the progression of a number of solid tumors including colorectal cancer. A more complete understanding of interactions between tumor epithelial cells and their stromal elements will enhance therapeutic options and improve clinical outcome. Here we will review the role of various stromal components in colorectal carcinogenesis and discuss the potential of targeting these components for the development of future therapeutic agents.

Keywords Colon cancer · Stroma · Tumor microenvironment · Tumor infiltrating cells · Extracellular matrix

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Introduction

Colorectal cancer (CRC) is the second or third leading cause of cancer-related mortality in United States [1]. In the past decade, therapeutic development has improved survival rates for patients with metastatic CRC, and many more treatment options exist for advanced disease. Many of these treatment options for advanced disease now include a combination of chemotherapy with targeted therapy. However, the fact that metastatic CRC remains incurable prompts investigators to explore a deeper understanding of the factors underlying cancer progression. The limited success achieved by only targeting tumor cells highlights the importance of understanding the role of the tumor microenvironment and its precise contribution to carcinogenesis.

A major contributor to the tumor microenvironment is inflammation and inflammatory mediators. The recognition of chronic inflammation as the seventh trait acquired by tumor cells necessary for survival, growth, and metastasis [2–4] has intensified studies on the role of intratumoral inflammatory cells and proinflammatory cytokines in cancer progression. Chronic inflammation is now recognized as both a tumor initiator and promoter, and it has long been studied in relation to proinflammatory prostaglandins in colon cancer [5, 6]. Clinical studies have shown that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDS) reduces the risk of CRC by 40–50% [7], in part, by targeting cyclooxygenase-2 (COX-2), an enzyme required for prostanoid synthesis. COX-2 is overexpressed in the majority of CRCs [8, 9], and COX-2-derived prostaglandin E_2 (PGE_2) mediates various tumor-promoting effects [6, 10, 11]. PGE_2 is the most abundant PG found in CRC tissue, and it has well demonstrated proneoplastic effects [12–14]. PGE_2 promotes tumor growth by inducing tumor cell proliferation, survival,

migration/invasion [15–18] and by enhancing the development of a supportive tumor microenvironment.

In CRC, the multistep process from normal colonic epithelium to an adenomatous polyp and ultimately to an invasive colon carcinoma is associated with or supported by the tumor microenvironment. The tumor microenvironment essentially consists of tumor-infiltrating cells, vasculature, extracellular matrix (ECM), and other matrix-associated molecules. Transformed epithelial cells modulate the functions of stromal cells with the overall purpose of facilitating their own growth, survival, invasion, and metastasis. This dependence or "addiction" of the cancer cells to the stromal components opens novel avenues for the development of potential therapeutic agents.

In this review we will discuss the interactions of tumor epithelial cells, stromal cells, and noncellular components of stroma in promoting colorectal carcinogenesis. The role of stroma in metastasis will not be covered in this review as it has been discussed in other recent reviews [19].

Tumor-Infiltrating Cells

Local inflammation at the site of a solid malignancy results in the accumulation of a variety of cells, and it is now generally accepted that these cells are intimately linked to the promotion of tumor growth. Colon carcinomas, similar to most other solid tumors, are infiltrated by different cells such as tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), mast cells, cancer-associated fibroblasts (CAFs), monocytes, neutrophils, CD8 and CD4 T-cells, dendritic cells (DCs), natural killer (NK) cells, endothelial cells, endothelial progenitor cells (EPCs), platelets, and mesenchymal stem cells (MSCs) [20] (Fig. 1). Two important factors for this infiltration are inflammation and soluble chemoattractants secreted by both tumor cells and stromal cells [21–25]. Inflamed stroma has been shown in mouse models to promote the progression of colonic adenomas to adenocarcinomas [26]. The initial role of these stromal cells is not necessarily tumor promotion, in fact data exists to support the notion that these cells may have some antitumor properties [27]. With time, the dynamic interaction between stromal and tumor cells changes in favor of tumor progression as it influences and exploits stromal cells to promote tumor cell proliferation, survival, and metastasis [27]. As a more complex architecture evolves, the function of the stromal cells changes spatially and temporally in the tumor. Some of these are reversible changes while others are irreversible, such as genetic alteration in stromal cells, including loss of heterozygosity (LOH) and microsatellite instability (MSI) as seen in colorectal cancer [28].

Tumor-Associated Macrophages

TAMs are derived from blood monocytes that are recruited to the tumor by growth factors, chemokines, and angiogenic factors such as colony-stimulating factor-1 (CSF-1), CCL2, CCL3, CCL4, CCL5, vascular endothelial growth factor (VEGF), and angiopoietin-2 [29–31]. The presence of low interleukin (IL)-12 and high IL-10 levels in the tumor microenvironment induce the differentiation of monocytes into TAMs [32].

Macrophages are highly plastic and can be activated to either M1 (anti-tumor) or M2 (pro-tumor) polarization states depending on the microenvironment stimuli [33–36]. The classic activation state (M1 polarization) happens in response to microbial products (e.g., lipopolysaccharide) or interferon-γ (IFN-γ), following which the M1 macrophages produce high levels of IL-12, IL-23, nitric oxide (NO) and oxygen intermediates (ROIs), as well as develops a high capacity to present antigens. The M1 macrophages are part of the Th1 response and are potent effectors against intracellular pathogens and tumor cells.

Alternatively, signals such as IL-4, IL-13, IL-10, immunoglobulin complexes, Toll-like receptor (TLR) ligands, and M-CSF induce a M2 polarization state [37–40]. The M2 macrophages express high levels of scavenger receptor-A (CD163) [41, 42] and mannose receptors (CD206) [43, 44] and have low IL-12 and high IL-10, IL-1 decoyR, and IL-1RA and CCL17 and CCL22 chemokines. The M2 macrophages, as part of the Th2 response, are involved in scavenging debris [45], promoting angiogenesis, tissue remodeling and repair [35]. M2 macrophages are also known to induce the differentiation of regulatory T-cells [46].

TAMs with M2 polarization are a major tumor-infiltrating cell population [3, 47] and are a vital component of inflammation-associated carcinogenesis. High TAM density in tumors is now recognized as a poor prognostic sign in various tumors, including CRC [29, 48, 49]. TAMs promote tumor growth and metastasis through inducing angiogenesis and enhancing tumor cell migration/invasion and ECM breakdown (Fig. 2) [50–54]. Macrophage depletion, either by pharmacological treatment with clodronate liposomes or by genetic manipulation, such as in $Csf1^{op/op}$ mice lacking CSF-1, leads to decreases in tumor macrophage infiltration, angiogenesis, tumor growth, and metastasis [55–58].

The influence of signaling molecules on TAMs has been well studied. One in vitro study demonstrated that activated macrophage-conditioned medium containing tumor necrosis factor (TNF)-α, IL-1β, and IL-6 induced human colon cancer cell proliferation and migration [23]. Colon tumor cells also stimulate macrophages to produce IL-6, which in turn induces STAT3-mediated IL-10 production in tumor cells [59]. It has been established that elevated IL-10 levels

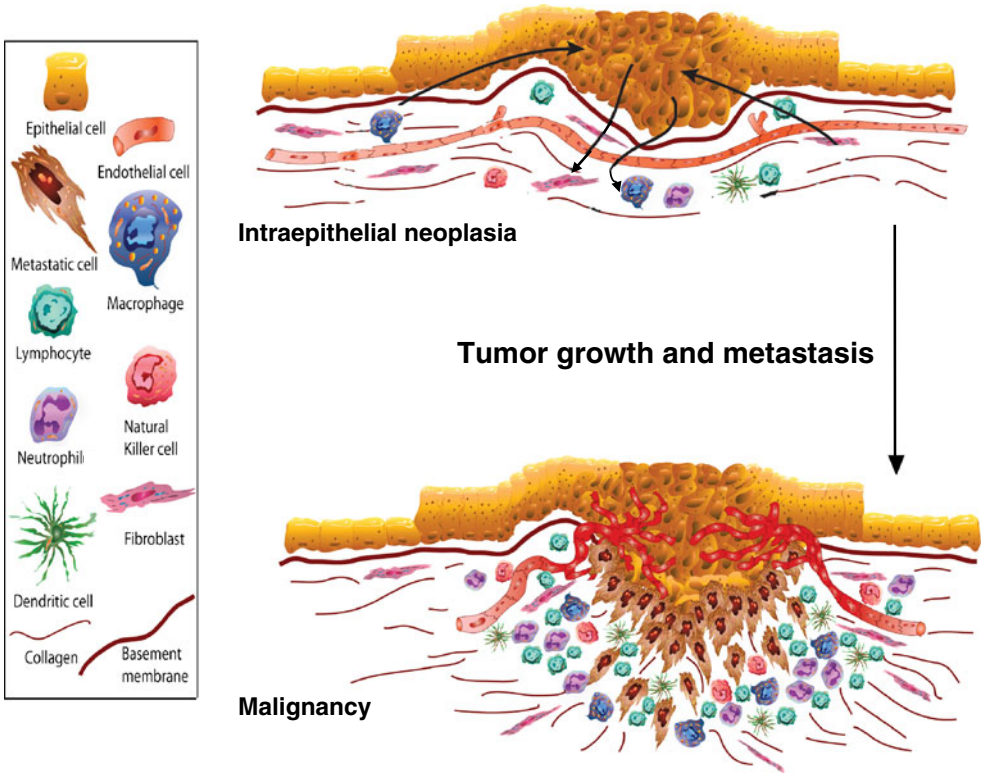

Fig. 1 The models of a cross talk between transformed epithelial cells and stromal cells in promoting cancer progression. Following the initiation of epithelial tumors, reciprocal interactions between transformed epithelial and stromal cells play a key role in switching a microenvironment from normal to one that supports tumor growth and spread. The tumor microenvironment, which is associated with massive infiltration of dysregulated immune cells as well as changes of their functionality, can promote tumor growth, angiogenesis, and metastasis. Tumor-infiltrating cells predominantly include tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), CD4 T-cells, CD8 T-cells, CD4 regulatory T-cells (Tregs), mesenchymal stem cells (MSCs), cancer-associated fibroblasts (CAFs), endothelial progenitor cells (EPs), mast cells (MCs), and platelets (PLTs). These cells are able to maintain tumor associated inflammation, angiogenesis, and immunesuppression, which in turn promotes tumor growth and metastasis

[60] are associated with a poor prognosis. The uptake of surface sulfoglycolipids—sulfatide SM4s-coated apoptotic cancer cells—by macrophages results in enhanced macrophage secretion of IL-6, transforming growth factor (TGF)-β1 and expression of P-selectin [61], which contributes to the development of M2 TAMs. Clinically, it has been shown that the presence of surface SM4s on colon carcinoma cells is associated with a poor prognosis, possibly due to low immunoreactivity of the tumor. TAMs in the stroma also strongly express COX-2, and the relationship between COX-2 and colonic adenoma formation [62] is well established.

TAM and Angiogenesis

Colon carcinoma cells induce TAMs to secrete VEGF, which promotes angiogenesis as well as metastasis [53, 63, 64]. TAMs also express many other pro-angiogenic factors, such as basic fibroblast growth factor (bFGF), TNF-α, IL-1β, IL-8 (CXCL8), COX-2, platelet derived growth factor-β (PDGF-β), hepatocyte growth factor (HGF), matrix metalloprotease (MMP)-7, and MMP12 [50–53, 65, 66]. The angiogenic factors secreted by both tumor and the stroma cells interact with respective receptors on endothelial cells, activating tumor-associated angiogenesis [67, 68]. Recent in vivo parabiosis experiments demonstrated that CD31, F4/80-positive monocyte/macrophages are recruited to the site of tissue injury and incorporated into newly formed vessels, directly contributing to angiogenesis [69].

TAMs, Epithelial-to-Mesenchymal Transition, and Invasion

Colon carcinoma cells are known to produce CSF-1 [24, 70], which recruits macrophages to the tumor periphery where they secrete promotility and angiogenic factors that facilitate tumor cell invasion and metastasis [21]. TAMs contribute to the epithelial-to-mesenchymal transition (EMT), which is an initial event for cancer metastasis [71, 72]. In colon carcinoma spheroids, TGF-β1–induced EMT is accelerated dramatically in the presence of TNF-α-producing macrophages [73, 74]. TGF-β, which is produced by both colon cancers [75, 76] and macrophages

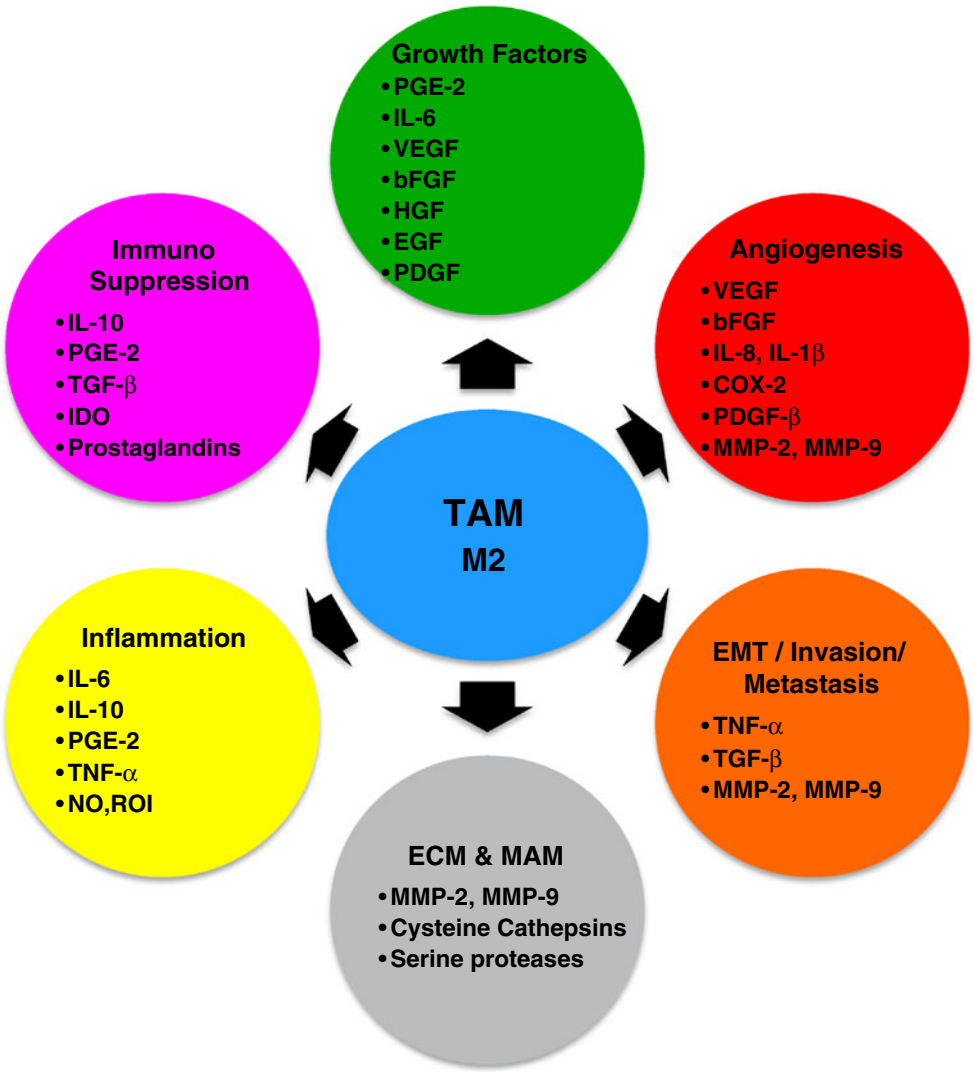

Fig. 2 Multiple functions of tumor-associated macrophages (TAMs). TAMs are one of the most important components of tumor stroma. M2 cells, differentiated TAMs, facilitate tumor growth by contributing to tumor inflammation, angiogenesis, the epithelial-to-mesenchymal transition (EMT), tumor cell invasion, intravasation, extracellular matrix and matrix-associated molecule formation (ECM and MAM) as well as immunosuppression. They accomplish this by either direct contact with other cells or producing various growth factors, chemokines, and angiogenic factors such as inteleukin (IL)-10, IL-8, IL-6, IL-1β, prostaglandin E_2 (PGE_2), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), indoleamine dioxigenase (IDO), nitric oxide (NO), reactive oxygen intermediates (ROI), matrix metalloprotease (MMP)-2, MMP), epidermal growth factor (EGF), basic fibroblast growth factors (bFGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor-β (PDGF-β)

[77], plays a significant role in the process of EMT and involves the activation of Smad2 and Smad3 [78, 79]. Essentially, the TGF-β/Smad pathway induces high mobility group A2 (HMGA2) gene expression, resulting in the regulation of SNAIL1 gene expression, which then leads to EMT [80, 81]. In addition, cancer cells can induce stromal cells (including macrophages) to secrete MMPs (MMP2 and MMP9) [24, 82, 83], cysteine cathepsins [84–86], and serine proteases [87–90] that aid in cell invasion and intravasation by cleaving cell-adhesion molecules such as E-cadherin and the ECM.

TAM and Immunosuppression

CRC is associated with a cytokine phenotype that is immunosuppressive [91]. Suppressive mediators—such as proinflammatory PGs, IL-10, TGF-β, and indoleamine dioxigenase—produced by TAMs can suppress T-cell activation and proliferation [77]. The TAMs are also known to be poor antigen-presenting cells (APCs). In addition, M2 macrophages can directly induce T-regulatory (Treg) cells by cell–cell contact via membrane-bound TGF-β1 expressed on the Treg cells [46, 92], resulting in suppression of antitumor T-cells and other inflammatory cells such as monocytes [93, 94]. A low ratio of T effector to Treg cells in CRC tissue is known to predict a shortened disease-free survival [95].

Myeloid-Derived Suppressor Cells

MDSCs [96] are a heterogeneous population of immature myeloid cells that have suppressive affect on adaptive immune responses [97]. In pathological conditions, such as cancer and some autoimmune diseases, there is a partial block in the differentiation of immature myeloid cells (iMCs) resulting in expansion of MDSCs characterized by up-regulation of arginase-I and inducible nitric oxide synthase (iNOS). Numbers of MDSCs are increased in the blood of mice

and patients with cancer, including CRC [98], by up to 10-fold [99–102].

Murine MDSCs express the following markers: $CD11b^{+}CD14^{+/-}$ $Gr1^{+}MHCII^{low}$ $CD124^{+}$ [102], while human MDSCs are Lin^{-} $HLA\text{-}DR^{-}$ $CD33^{+}$ or $CD11b^{+}CD14^{-}$ $CD33^{+}CD86^{-}$ [103]. The ability to suppress the function of T-cell and NK cells provides the most effective way of identifying MDSCs [96]. The expansion of MDSCs is influenced by pro-myelopoetic factors produced by colorectal carcinoma cells [104], such as stem cell factor (SCF), M-CSF, PGs, IL-6, GM-CSF, and VEGF[105], while the activation factors produced by MDSCs are produced by both activated T-cells and stromal cells and include IFN-γ, TLR ligands, IL-4, IL-13, and TGF-β. The suppressive effect of MDSCs has been associated with the metabolism of L-arginine, a substrate for the two key enzymes, arginase-1 and iNOS (which generates NO). Arginase-1 depletes arginine in the microenvironment, which affects T-cell proliferation. The generation of reactive oxygen species (ROS) and NO by MDSCs leads to the production of peroxynitrite, which results in nitrosilation of T-cell receptors and immunosuppression [106]. There is also evidence indicating that MDSCs promote the development of Foxp3-positive Treg cells [107]. MDSCs isolated from murine tumors also express high levels of MMPs compared with MDSCs from normal mice [108]. Being immature cells, they are also more plastic, expressing endothelial markers such as CD31 and VEGFR2 [108], and thus have the potential to incorporate themselves into the tumor endothelium. Some MDSCs also differentiate into mature TAMs [102, 109].

MDSCs are also known to express PGE_2 receptors such as EP2, and PGE_2 partially mediates MDSC induction via activation of EP2 receptors [110, 111]. In a mouse model of 4T1 mammary carcinoma, PGE_2 induced the differentiation of MDSCs from bone marrow stem cells, whereas PGE_2 receptor antagonists blocked this differentiation. Although there are high levels of PGE_2 in the colonic tumor microenvironment, the role of PGE_2 in MDSCs has not been well studied [13, 15, 98].

Mast Cells

Mast cells are key effector cells in allergic diseases, but it has become apparent that they also contribute to other pathologies, including autoimmune diseases and cancer. In the majority of human tumors, higher mast cell infiltration is associated with increased vascularity, enhanced tumor growth, invasion, and poor clinical outcome [112–114]. Recent CRC studies revealed that a lower number of mast cells was associated with hypovascularity and better survival in CRC patients [115, 116]. Stem cell factor (SCF) produced by tumor cells in vivo has been implicated in the accumulation of mast cells in the periphery of growing tumors [117].

Activated mast cells release many proangiogenic and growth stimulatory factors such as VEGF [114, 118, 119], bFGF [119, 120], heparin [121, 122], histamine [123, 124], TNF-α [125, 126], angiopietin-1 [127], and proteases [128, 129]. Mast cell infiltration into tumor tissue can trigger the angiogenic switch and induce angiogenesis. Then, as the tumors grow bigger, tumor cells take control of angiogenesis and become mast cell independent [130].

A recent study by Gounaris et al. demonstrated that colonic polyps in *APC* mutant mice are infiltrated with proinflammatory mast cells and their precursors. Depletion of mast cells through either pharmacological treatment or the generation of chimeric mice programmed to have genetic lesions in mast cell development leads to a profound regression of existing polyps, suggesting that mast cells are an essential component for preneoplastic polyp development [131]. The number of mast cells is markedly higher in primary CRCs than in adjacent healthy tissues [132]. Additionally, there are many more mast cells in poorly differentiated tumors than in well-differentiated tumors [133].

Mast cell-produced proteases such as mMCP-4 (chymse) and mMCP-6 (tryptase) are involved in ECM remodeling [130], which is subverted in the tumor microenvironment, resulting in tumor growth and metastasis. Human tryptase-positive mast cells are abundant in the invasive front of colonic adenocarcinomas, and tryptase has been suggested to be the agonist for protease-activated receptor-2 (PAR-2). Yoshii et al. demonstrated that tryptase activated PAR-2 in a human colon carcinoma cell line, which in turn led to the production of PGE_2 and the induction of cell proliferation [134]. Interestingly PGE_2 has also been found to induce the production of VEGF-A in mast cells.

Mast cells can also modulate immune responses by dampening immune rejection or directing immune cell recruitment, depending on local stimuli [135]. They are known to activate T-cells via release of TNF-α or cell–cell contact via OX40L, and they also express B7 and CD28 costimulatory molecules [136]. The mast cell-derived cytokine IL-5 promotes eosinophil recruitment and survival around tumors and is thought to modulate their ability to kill tumor cells [137]. Additionally, in skin, TNF-α released from mast cells and histamine [138] activates local keratinocytes to produce PGE_2, which triggers the release of IL-10 by DCs, and this plays an immunosuppressive role [139].

There is still debate about pro- vs. antitumor effects of mast cells in tumors. A mouse model deficient in mast cells developed 50% more adenomas than littermate controls as well as 33% larger tumors. There was no increase in tumor cell proliferation, but apoptosis was significantly lower [140]. The difficulty in interpreting the significance of the presence of mast cells in malignant neoplasms is partly due to differences between mast cells in mice and humans [135, 141, 142] as well as coexpression of cell-surface markers

that are shared by other immature myeloid cells [131]. iMCs in the tumor express CD34, CCR1, MMP2, and MMP9 [143], which are also expressed by mast cells during development [144–147]. Additionally mast cells express CD45, c-kit, sca-1, and low levels of CD11b, which are expressed by other infiltrating myeloid cells [148, 149].

Cancer-Associated Fibroblasts

CAFs are the main cellular constituents of reactive stroma in primary and metastatic cancer and play a key role in CRC development [150, 151] (Fig. 3). CAFs are still poorly understood and are mostly defined on the basis of the expression of α-smooth muscle actin (α-SMA) [152], fibroblast-activated protein (FAP), fibroblast-specific protein-1 (FSP1/S100A4), neuron-glial antigen-2 (NG2), and PDGF β-receptor [151]. Studies have shown that patients whose colon tumors have high levels of stromal FAP are more likely to have aggressive disease progression and have a higher potential to develop metastases or recurrence [153]. Microarray expression analysis of CAF and normal skin fibroblasts showed that CAFs from metastatic CRC clustered tightly into one group that included genes for growth factors, COX-2, and TGF-β2, whereas genes from normal skin fibroblasts clustered into another group [154].

Local tissue fibroblasts and fibroblast precursors stimulated by PDGF and TGF-β are generally considered to be the source of CAF. An analysis of CAF from CRC metastasis suggested that the majority of CAF in liver originates from resident liver fibroblasts [155]. In addition, mouse experiments have demonstrated that bone marrow-derived precursors such as MSCs also contribute to CAF population [156].

CAFs are a source of growth factors—such as EGF, TGF-β, and HGF—that promote tumor growth and metastasis [150]. Besides classical growth factors, CAFs express chemokines, insulin-like growth factor (IGF)-1, IGF-2, PDGF, secreted frizzled related protein, cell-surface molecules like integrin-α11 or syndecan-1, and proteases such as MMP2 and ECM constituents like osteopontin that stimulate tumor cell proliferation, survival, and migration/invasion [157–160]. In an in vitro colon cancer cell coculture system, CAFs was shown to enhance tumor cell proliferation [154]. CAF-derived chemokines such as

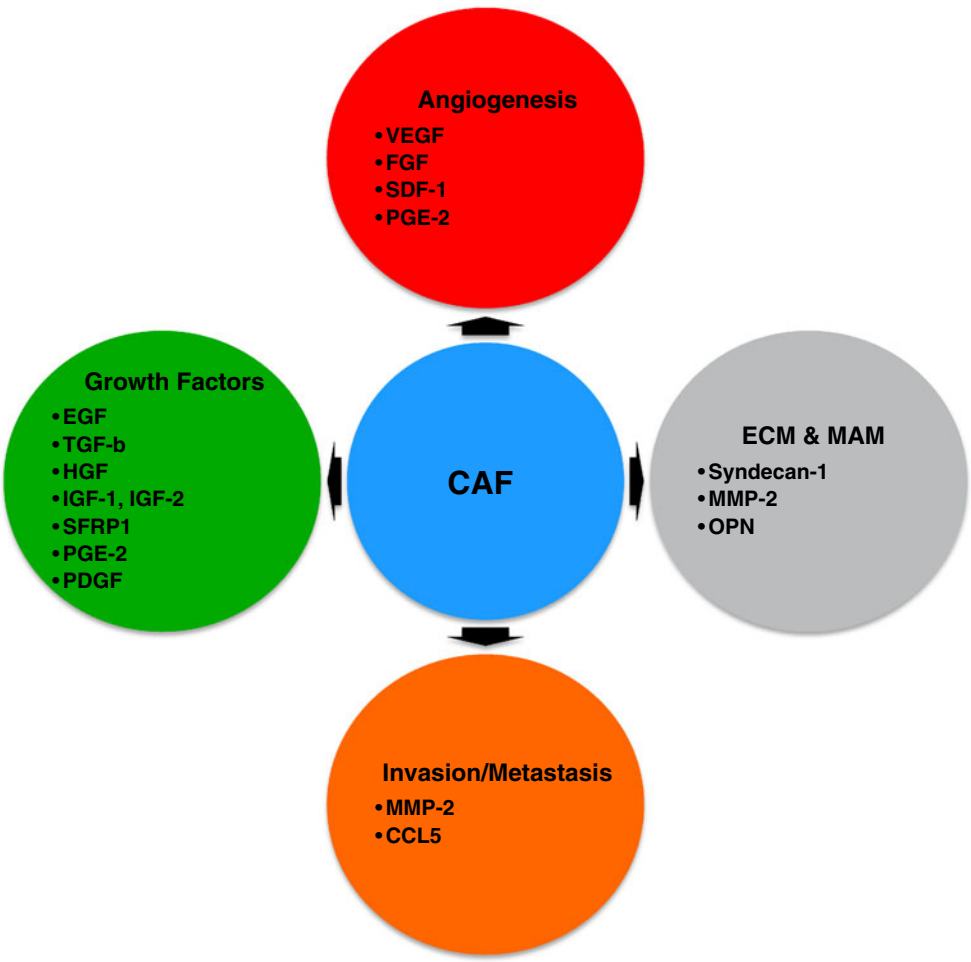

Fig. 3 Roles of cancer-associated fibroblasts (CAFs) in colon carcinogenesis. CAFs are the chief constituent of tumor stroma. They facilitate tumor growth by secreting growth factors; promoting angiogenesis, tumor invasion, and metastasis; and are involved in the production of extracellular matrix (ECM) and matrix-associated molecules (MAMs). The figure depicts the contributions of various CAF-derived molecules. They include prostaglandin E_2 (PGE_2), transforming growth factor-β (TGF-β), matrix metalloprotease-2 (MMP2), epidermal growth factor (EGF), hepatocyte growth factor (HGF), basic fibroblast growth factors (bFGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor-β (PDGF-β), secreted frizzled related protein (SFRP1), chemokine ligand 5 (CC5), osteopontin (OPN), and stromal cell-derived factor-1 (SDF-1), which is also called CXCL12

CXCL12 [161] or CXCL14 [151] recruit bone marrow-derived cells, macrophages, and other immune cells into the growing tumor, which also contributes to tumor growth.

The release of VEGF, FGF, and CXCL12 by CAF plays a central role in the promotion of tumor growth and angiogenesis. CAF-derived CXCL12 not only stimulates tumor cell growth directly through the CXCR4 receptor but also serves to recruit endothelial progenitor cells (EPCs) into tumors, thereby furthering neoangiogenesis [162]. Stromal myofibroblasts surrounding colon adenocarcinomas are also an important source of COX-2 [163], suggesting that myofibroblasts could be important target cells for NSAIDs and selective COX-2 inhibitors in the chemoprevention of CRC [62] [164].

A majority of sporadic CRC cases are initiated by constitutive Wnt activation, due to mutations in either the APC tumor suppressor gene or β-catenin [165, 166]. The tumor microenvironment is thought to play a central role in the transformation of epithelial cells by locally modifying Wnt/β-catenin signaling activity [166, 167]. In CRC, the CAF-derived Wnt ligands PDGF and PGE_2 can activate Wnt signaling and contribute to EMT as well as maintenance of the cancer stem cell phenotype [168–171]. The relationship between COX-2/PGE_2 and β-catenin activation with regards to tumor progression and metastasis has been well summarized in a recent review [11].

Also in human CRC, CAFs and pericytes of the tumor vasculature usually express high levels of PDGF-R, while cancer cells express PDGF-A and -B but not PDGF-R. The expression of PDGF-Rβ in the stroma is associated with advanced stage of disease and an increased metastatic potential [172, 173]. The blockade of PDGF-R signaling pathways in tumor-associated stromal cells using drugs such as imatinib [172] inhibits the progressive growth and metastasis of colon cancer cells [173]. Interestingly PDGF-C up-regulation in CAF is associated with increased resistance to anti-VEGF therapy in animal models [174, 175].

TIE-2-Expressing Monocytes (TEMs)

TIE-2, an angiopoietin receptor thought previously to be restricted mainly to endothelial cells and hematopoietic stem cells [176], is expressed by a subset of monocytes that are distinct from classical inflammatory monocytes [177]. In cancer patients these TIE-2-expressing monocytes (TEMs) are observed in blood and the tumor microenvironment, where they represent the main monocyte population and are distinct from TAMs. Interestingly, TEMs are hardly ever detected in nonneoplastic tissues [177]. While only 1% to 2% of total leukocytes are TIE-2^+, a substantial fraction (20%) of circulating monocytes express TIE-2 in mice and humans harboring tumors [177, 178]. In mice, circulating TIE-2^+CD45^+ hematopoietic cells are mostly $CD11b^+Gr\text{-}1^{low/neg}$, whereas in humans they express CD14, CD16, and CD11c [176, 179].

TEMs have been found in many tumors, including colon, kidney, and lung tumors [177, 180]. TEMs promote tumor angiogenesis and growth [20, 176, 181]. Studies have shown that monocyte chemokines such as CCL3, CCL5, and CCL8 but not CCL2 play a role in TEM recruitment. Importantly, the TIE-2 ligand angiopoietin-2 (Ang-2) expressed by hypoxic tumor cells and tumor endothelial cells is the dominant factor in this recruitment [177–179]. Inhibition of Ang-2 expression has been shown in murine colon cancer models to decrease angiogenesis and tumor growth [182].

Neutrophils

Neutrophil infiltration has been observed in both acute and chronic inflammatory states. Interestingly, increased levels of neutrophils are found in patients with different cancers including gastric and colon cancer [183, 184]. Neutrophils are an important component of oxidative stress-associated pathogenesis of chronic inflammatory bowel disease (IBD)-related CRC [185]. CXCL1 and CXCL8 are neutrophil chemokines involved in the recruitment of neutrophils in various tumors, including gastric and colon carcinomas [183, 186].

Recent data has suggested that neutrophils significantly affect tumor angiogenesis [187]. Factors such as oncostatin M released by neutrophils can stimulate tumor cells to produce VEGF [188]. In CRC patients, neutrophil-derived MMP-9 releases biologically active VEGF (165) from the ECM by the cleavage of heparan sulfates [189]. Stimulation of neutrophils by TNF-α, GM-CSF, platelet activating factor, and CXCL8 induces degranulation and the release of proangiogenic factors such as VEGF, CXCL8, and CXCL1 from intracellular stores [190–192].

Data suggests that neutrophil-derived factors can promote genetic mutations leading to malignant transformation [187]. The genotoxic capacity of neutrophils, which is a crucial etiological factor in carcinogenesis, is mediated by the induction of oxidative DNA damage through the release of ROS and myeloperoxidase-related metabolic activation of chemical carcinogens [193]. Activated human neutrophils are able to synthesize carcinogenic N-nitrosamines that also contribute to colon carcinogenesis during chronic inflammation [194]. These N-nitrosamines promote human colon carcinoma cell adhesion to the microvascular endothelial wall by production of ROS [195]. Neutrophils also play a crucial role in postoperative adhesion and the growth of spilled tumor cells after surgical peritoneal trauma. Prevention of peritoneal neutrophil influx has been shown to reduce local tumor recurrence in at least one study [196].

Neutrophils are also known to have antitumor properties. Factors secreted by neutrophils such as ROS, proteases, and cytokines such as TNF-α and IL-1β can kill tumor cells directly [197, 198]. Recent data from animal models of cancer have indicated that TGF-β promotes tumor-associated neutrophils (TANs) to acquire a protumor phenotype in the tumor microenvironment (called N2-TAN). By contrast, TGF-β blockade leads to the acquisition of an antitumor N1-TAN phenotype (similar to M1 TAMs) by the infiltrating neutrophils. The N1-TANs are hypersegmented and more cytotoxic to tumor cells, and they express higher levels of proinflammatory cytokines (IL-12, TNF-α, GM-CSF, and VEGF) and promote $CD8^+$ recruitment as well as activation by producing T-cell-attracting chemokines (e.g., CCL3, CXCL9, and CXCL10) [199]. They can also activate DCs via cell–cell contact and through secretion of TNF-α [200]. By contrast, N2 neutrophils do not produce high levels of such proinflammatory agents but do produce large amounts of arginase, which inactivates T cell effector functions in the same way that has been proposed for M2 TAMs [200]. Thus, TANs are capable of being pro- or antitumorigenic, depending on the tumor microenvironment [201].

Lymphocytes and Dendritic Cells

Tumors without signs of early metastatic invasion have been shown to contain increased immune cell infiltrates and markers of T-cell migration, activation, and differentiation [202]. In a study of colon cancer tissues, the type, density, and location of T-cells within the tumor samples were found to be a better predictor of patient survival than were histopathological results currently used to stage CRC [203, 204]. Although some tumor-infiltrating CD8 T-cells are reactive to tumor antigens, they are largely ineffective in arresting tumor growth due to the immune inhibitory microenvironment and unfavorable cytokine milieu for the activation of T-cells and maturation of antigen-presenting DCs [205].

$CD4^+CD25^+FOXP3^+$ Tregs are also expanded in tumors and are capable of suppressing the proliferation of other T-cells by direct contact or IL-10 and TGF-β production. Treg cells that expand in colonic polyps produce IL-17, which promotes mastocytosis and a tumor-promoting inflammatory response [206, 207]. Tregs also express COX-2 and produce PGE_2, which suppresses effector T cells. NSAID treatment increases MHC II protein (HLA-DP, -DQ, -DR) levels and infiltration of $CD4^+$ T-helper cells and $CD8^+$ cytotoxic T cells into both tumor stroma and epithelium, along with a decrease in molecules associated with immunosuppressive Treg cells, such as FOXP3 and IL-10 [208, 209]. In mouse models of CRC, Tregs also inhibit the ability of tumor-infiltrating DCs to mediate TNF-related apoptosis-inducing ligand (TRAIL)-induced tumor cell death [210].

The role of B-cells in human CRCs is not well characterized, but B-cell-deficient mice exhibit spontaneous regression of MC38 colon carcinoma cells. Studies involving BCR-transgenic mice indicated that B-cells may inhibit antitumor T-cell responses by antigen-nonspecific mechanisms [211].

NK cells mediate an innate immune response and represent the first line of defense against pathogens [212]. They are rich in perforins and granzyme-containing granules and can mediate potent antitumor cytotoxicity in vitro. NK cells also mediate immune surveillance by promoting apoptosis in colon cancer cells by increasing the production of TRAIL [213]. The paucity of NK cells in the tumor milieu is a well-known mode of tumor immune evasion [214]. Additionally, serum from patients with CRC has been shown to contain elevated levels of soluble MHC class I chain-related molecules, which are responsible for down-modulation of the receptor NKG2D on NK cells. Only $NKG2D^+$ NK cells have been found to be tumoricidal in vitro and in vivo [215].

Colon carcinoma cells also evade immune surveillance by increased expression of Fas ligand (FasL), which binds to its receptor on immune cells to trigger apoptosis. Reduced FasL expression by tumor cells is associated with increased lymphocyte infiltration [216]. Interestingly, the PGE_2/EP2 signaling plays a role in the up-regulation of FasL expression in colon cancer cells and immune escape [217].

DCs, both myeloid DCs (MDCs) and plasmacytoid DCs (PDCs), are professional APCs and are capable of inducing primary and secondary T- and B-cell responses as well as immune tolerance [218]. MDCs originate from immature DCs (iDCs) in bone marrow and lack the mature DC markers CD1A, CD83, CD40, and CD86 but express CD11c, CD33, and HLA-DR. Tumor-derived factors such as VEGF, β-defensin, CXCL12, HGF, CXCL8, and PGE_2 [219] recruit iDCs into the tumor but inhibit their maturation [220], resulting in few mature MDCs in tumors but abundant iDCs. The iDCs promote tumor angiogenesis by secreting proangiogenic cytokines and functioning as a source of endothelial progenitors [221]. However, mature DCs pulsed with tumor cell lysate can induce tumor-specific cytotoxic T lymphocyte (CTL) activity against colon tumor growth both in vitro and in vivo [222].

Platelets

Platelets are normally associated with hemostasis. However, they also play a vital role in tissue repair and the maintenance of endothelial function. Studies have suggested that increasing platelet counts may be linked to tumor progression [223]. Other evidence points to a role of platelets in tumor metastasis and angiogenesis [224, 225]. In cancer patients, platelets are generally activated by thrombin [225], which also stimulates tumor cell growth. Additionally they can be

activated by ADP or by direct contact with molecules on the surface of tumor cell membranes [226]. Platelet activation results in the generation of thromboxane A_2 and the release of the storage contents from both alpha granules and dense granules that include proangiogenic factors such as VEGF, PDGF, and CXCL12 [227, 228]. Platelets also contribute to colon cancer metastatic spread by accumulating on embolic tumor cells, thus protecting them from clearance by the immune system [229] and by facilitating circulating tumor cell arrest and adhesion to the endothelium [230, 231].

Mesenchymal Stem Cells

Colon tumors contain numerous multipotent cells, including MSCs, EPCs, and pericyte progenitor cells in addition to cancer stem cells [232] that can be enriched using CD133 and CD44 markers [233]. Chief among these are the MSCs, which are multipotent nonhemopoietic cells that reside in the bone marrow and can differentiate into different types of mesenchymal cells. They are characterized by the expression of a large number of adhesion molecules and stromal cell markers such as CD73, CD105, CD44, CD29, and CD90 and the absence of hematopoietic markers (CD34, CD45, and CD14) or endothelial markers (CD34, CD31, and vWF) [234–236]. MSCs produce a large number of cytokines and growth factors, and they express growth factor receptors and ECM proteins (fibronectin, vimentin, and laminin) [236]. In bone marrow, MSCs and MSC-derived stromal fibroblasts support hematopoiesis. However, in primary tumors, they are present in large numbers and contribute to the formation of tumor-associated stroma [237]. They also promote tumor growth and metastasis [238], in part by their immunosuppressive effects [239, 240] and proangiogenic properties [241]. MSC-derived fibroblasts produce growth factors and proangiogenic factors such as PDGF, FGF, and CXCL12. MSCs can also be differentiated into endothelial and pericyte-like cells, which promote tumor growth [241]. In addition, MSCs have been postulated to play a role in promoting the survival of the cancer stem cells [242].

Tumor Vasculature

The induction of angiogenesis is an important early event in the development of most cancers and is an integral part of tumor growth and survival [243]. The microvascular density of a tumor has prognostic significance and predicts survival in patients with CRC [244]. Tumor hypoxia is a dominant player in this process, which leads to the activation of hypoxia inducible factor-1 and subsequent expression of angiogenic factors such as VEGF, bFGF, and PDGF by the tumor cells [245]. PGE_2 directly induces colon cancer cells to produce VEGF [246, 247] and thus is a target for therapeutic intervention. Stromal cells—including TAMs, mast cells, CAFs, TEMs, neutrophils, MSCs, and others—also contribute proangiogenic factors and promote angiogenesis, as was discussed earlier in this review. Lymphangiogenesis also follows a path similar to angiogenesis during colon carcinogenesis [248]. VEGF-C, VEGF-D, and angiopoietin-1 are potent lymphangiogenic factors produced by tumor and stromal cells [249–251]. VEGF-C expression is also associated with lymphatic spread of colorectal carcinomas [252].

Extracellular Matrix and Matrix-Associated Molecules

The ECM is a highly organized three-dimensional structure with many physiological and pathological roles. In addition to maintaining tissue integrity, the ECM not only regulates cell migration, cellular differentiation, and proliferation but also provides a reservoir of cytokines and growth factors. Alterations to the ECM composition during tumor development are critical for tumor initiation and progression. The ECM is composed of five classes of macromolecules, including collagen, laminins, fibronectin, proteoglycans, and hyaluronans. Depending on the tissue and the microenvironment, they exist in various isoforms. The ECM can be divided into two main groups: basement membrane (BM) and interstitial or stromal matrix. BM is thin sheets of specialized ECM that surround epithelial or endothelial cells, nerves, and muscle cells and then separate these cells from the interstitial stroma [253]. BM can act as a mechanical barrier and organizer of tissue structure, as well as regulate cell growth, differentiation, polarity, and gene expression [254]. The BM is composed of a dense network of collagen type IV and laminin. Invasive growth of epithelial cancers is a complex multistep process that involves dissolution of the BM. The stromal matrix is composed of the polysaccharide gels, proteoglycans, and various fibrous proteins, while the matrix-associated molecules include intestinal receptors, proteases, phosphoproteins, mucins, lectins, and others.

Laminin

Laminins are major proteins in the BM, composed of an α-chain, a β-chain. and a γ-chain that are involved in cell differentiation, migration, and adhesion. In CRC, the $\alpha4\beta4$ integrins promote tumor cell migration on laminin-1 as it stabilizes actin-containing motility structures [255]. Laminin-332 (formerly laminin-5), composed of 3 subunits ($\alpha3\beta3\gamma3$), interacts with at least two integrin receptors expressed by epithelial cells and plays a crucial role in

signaling, adhesion, and migration. Laminin-332 is commonly lost in carcinomas but is expressed in premalignant tumors. In human colon and pancreatic tumor cells, Smad4 functions as a positive transcriptional regulator of all three genes encoding laminin-332 [256]. Inactivation of tumor suppressor Smad4, which is a genetically late event that occurs upon transition from premalignant stages to invasive and metastatic spread of cancer cells, can therefore lead to a loss of laminin-332. Abnormal expression of laminin-332 and its integrin receptors is also a hallmark of certain tumor types and is believed to promote invasion of colon, breast, and skin cancer cells [257].

Collagens

Fibrillary collagen type I is the most abundant protein in the human body and is essential for the integrity of soft tissues. Collagen type III is present in the wall of blood vessels and most organs and copolymerizes with collagen type I. Type I collagen down-regulates E-cadherin and β-catenin at cell-cell junctions. Furthermore, type I collagen inhibits differentiation, increases clonogenicity, and promotes expression of stem cell markers CD133 and Bmi1. Type I collagen promotes expression of a stem cell-like phenotype in human CRC cells through α2β1 integrin [258].

Fibronectins

Fibronectins are abundant high-molecular-weight adhesive glycoproteins present in the ECM (insoluble form) and in body fluids (soluble form). Fibronectin has the ability to bind other ECM proteins (collagen), cell-surface receptors (integrins), blood components (fibrin), and glycosaminoglycans and is important for cell migration. Fibronectin can promote invasion of Colo320 cells via focal adhesion kinase (FAK) [259]. FAK is overexpressed in a variety of cancers, including breast, colon, prostate, ovary, and lung cancer [259].

Proteoglycans

Colorectal carcinomas have been found to have altered expression of many proteoglycans [260, 261]. Syndecan-1, a transmembrane heparan sulfate proteoglycan, plays an important role in cell-cell and cell-ECM adhesion and functions as a growth factor coreceptor. Syndecan-1 is highly expressed by normal epithelial cells. The Syndecan-1 expression is down-regulated in human colon carcinomas, and this has been correlated with the transformed phenotype, EMT, TNM stage, and metastasis to local lymph nodes [260]. In contrast, versican and decorin are significantly increased in CRC.

Hyaluronan

Hyaluronan is a multifunctional anionic polysaccharide that has a structural role in many connective tissues. Hyaluronan is associated with the pericellular matrix surrounding proliferating and motile cells in normal and pathological systems, where it has both structural and signaling functions [262, 263]. Hyaluronan enhances colorectal tumor cell proliferation and motility in vitro and in vivo [264, 265]. Inhibition of hyaluronan production in SW620 colon carcinoma cells blocks matrigel invasion [266]. Interaction of hyaluronan with its receptor CD44 stimulates ERBB2 activation [267] in HCT116 colon carcinoma cells, leading to increased cell survival [268] as well as cell proliferation, adhesion, and invasion [265]. Moreover, the interaction between constitutive hyaluronan and CD44 mediates an ErbB2-PI3K/AKT-β-catenin signaling axis which induces COX-2 expression in colon carcinoma cells [269]. COX-2 inhibition reduces the ability of colon cancer cells to adhere to and migrate on ECM [270].

Integrins

Integrins are the largest family of cellular receptors for molecules in the ECM such as fibronectin, laminin, and collagen [271]. The binding of integrins to the ECM influences such cellular functions as adhesion, migration, and the sequestration of growth factors. In colon cancer cells, activation of integrins with collagen causes an increase in COX-2 promoter activity and expression via a PKC-α-Ras-NF-κB signaling cascade [272]. Increased expression of the COX-2 protein by integrin is responsible for an elevated generation of ROS and increased cell migration [272]. Poorly differentiated colon cancers are characterized by increased integrin-mediated ECM interactions, whereas disruption of this integrin-mediated adhesion leads to apoptosis and involves reduced PI3K activity [273].

Metalloproteases

The ECM turnover depends on various types of proteinases, of which MMPs are the principal ECM degrading enzymes [274]. These enzymes play an important role in cancer growth, invasion, and metastasis. The expression of MMP1, -2, -3, -7, -9, -13, and MT1-MMP is elevated in human CRC. The expression levels of some MMPs are correlated with stage of disease and/or prognosis [275]. For example, the increased expression of MMP3 in CRC correlates with low levels of microsatellite instability and a poor prognosis [275]. In contrast to other MMPs, overexpression of MMP12 is associated with increased survival in CRC, presumably as a result of an inhibitory

effect on angiogenesis [275]. Colon tumor cells can induce the secretion of MMP2 and MMP9 by stromal cells via direct contact or paracrine regulation [82, 276]. Increased levels of neutrophil-derived MMP9 have been observed in the transition from colon adenoma to adenocarcinoma. MMP9 releases biologically active VEGF [165] from the ECM of CRC by the cleavage of heparan sulfates [189].

Tissue inhibitors of metalloproteinases (TIMPs) also regulate ECM remodeling through the inhibition of MMPs. Interestingly, TIMP-1-expressing cells are more resistant to chemotherapy than are *TIMP-1* gene-deficient cells [277]. In CRC patients, high levels of TIMP-1 in tumor tissue and plasma are strongly associated with shorter survival time [278].

Mucins

Mucins are heavily glycosylated proteins that have been suggested to play a critical role in tumor malignancy. MUC1 and MUC15 expression is up-regulated in CRC [279]. Increased MUC1 expression at the invasive front in CRC correlates with poor prognosis [280]. Overexpression of MUC15 enhances cell proliferation, cell-ECM adhesion, colony-forming ability and invasion in HCT116 cells [281].

Osteopontin

Osteopontin is a glycophosphoprotein that is expressed and secreted by numerous human cancers. Osteopontin interacts with a number of integrin receptors and has pivotal role in tumor cell adhesion, chemotaxis, apoptosis, invasion, migration, and anchorage-independent growth [282]. The elevated expression of osteopontin has been observed in a variety of cancers and linked to tumor metastasis and a poor prognosis for patients [283]. Osteopontin appears to regulate colon cancer cell motility though its interaction with CD44 [284]. Osteopontin expression also reduces intercellular adhesion, an important characteristic of metastatic cancer cells. Overexpression of osteopontin in a poorly tumorigenic human colon cancer cell lines resulted in enhanced tumorigenicity in vivo with increased proliferation and angiogenesis [285]. Interestingly, COX-2 inhibitors down-regulate osteopontin expression by repressing two components of the osteopontin regulatory network: the orphan nuclear receptor NR4A2 and Wnt/β-catenin signaling [286].

Galectin

Galectin-3 is an endogenous lectin that binds glycan epitopes of cell membrane and some extracellular glycoproteins such as integrins and laminin, and its expression is elevated in CRC patients [287]. Galectin-3 is involved in several biological activities, including regulation of tumor progression via modulation of the cell cycle, adhesion, and metastasis [287]. Galectin-3 has been implicated in a Wnt/β-catenin signaling pathway essential for colon carcinogenesis [288]. Galectin-3 levels have been shown to be correlated with β-catenin levels in a variety of colon cancer cell lines [288]. In contrast, galectin-9 suppresses tumor metastasis by inhibiting the binding of ligands on vascular endothelium and ECM to adhesive molecules on tumor cell membranes [289]. It also suppresses the binding of hyaluronic acid to CD44 on Colon26 cells [289].

Other Extracellular Matrix Proteins

Periostin is a unique ECM protein, the deposition of which is enhanced by mechanical stress and the tissue repair process. Periostin is secreted by pericryptal and CAFs in the colon [290]. Betaig-h3/TGFβI (transforming growth factor, beta-induced gene) is an ECM protein secreted by colon cancer cells, and its expression is associated with high-grade human CRC. Ectopic expression of the betaig-h3 protein enhances the aggressiveness and alters the metastatic properties of colon cancer cells in vivo. Mechanistically, betaig-h3 appears to promote extravasation, a critical step in the metastatic dissemination of cancer cells, by inducing the dissociation of VE-cadherin junctions between endothelial cells via the activation of a αvβ5-Src signaling pathway [291]. In contrast, inhibition of betaig-h3 expression dramatically reduces metastasis [291].

Summary

A complex stromal system promotes the growth and survival of CRC cells. The tumor microenvironment is quite distinct from the normal tissue microenvironment and is composed of a particular phenotype of stromal cells—such as M2-TAMs, N2 neutrophils, and CAFs—that are adept in supporting tumor cell growth, survival, and metastasis. Therapeutic targeting of stromal cellular components, including inflammatory cells such as TAMs, MDSCs, CAFs, MCs, and neutrophils, vasculature, ECM, and matrix-associated molecules, must be considered in the future. Some currently used therapeutic agents, such as selective COX-2 inhibitors and NSAIDS, already target the stromal production of PGE_2 in addition to targeting the colon cancer cells, while bevacizumab and other anti-VEGF agents target the tumor vasculature. Application of agents targeting various stromal components in a synergistic manner along with targeting the tumor cells would potentially lead to the development of more effective treatments for CRC.

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