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Stromal Contributions to the Carcinogenic Process

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Abstract

Tumor-associated stromal cells are dynamic characters that endorse the carcinogenic process in a multitude of ways. The tumor microenvironment plays a crucial role throughout the tumor progression, which includes initiation, growth, invasion, and metastasis. The tumor microenvironment consists of cellular and non-cellular components. Tumor-associated stromal cell types include the microbiome, immune cells including macrophages, dendritic and T-cells, cells associated with blood and lymphatic vessels including pericytes and endothelial cells, fibroblasts, neuronal cells, and adipocytes. The non-cellular components of the microenvironment include matrix proteins and secreted factors. The development of therapies that target the mechanisms by which stromal cells contribute to successful tumorigenesis is major goal of upcoming cancer research. The purpose of this review is to present a comprehensive discussion of the role of each of the tumor-associated stromal cell types in the carcinogenic process with a special focus on target development and therapeutic intervention.

Keywords

tumor-associated stroma; carcinogenesis; microbiome; TAM; endothelial cells

INTRODUCTION

Cancer is one of the foremost health problems worldwide and has been the second leading cause of death in the United States since the 1940s. In spite of our increasing knowledge of the many aspects of carcinogenesis, malignancy is expected to surpass heart disease in the next few years as the single most common cause of death in the United States [1]. To combat this major threat to human health, it is vital that we explore cancer as a multi-faceted, dynamic occurrence.

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Tumor formation begins when cells become genetically abnormal and undergo rapid, unchecked proliferation. However, a tumor is not solely composed of cancer cells; it is a heterogeneous collection of both cancer cells and surrounding non-cancer or stromal cells that work in concert with one another to promote unrestricted growth, infiltration, and propagation of malignancy throughout the body. These non-cancer cells in the vicinity of the tumor will hereafter be referred to as the cells of the tumor microenvironment (TME) or tumor-associated stroma.

Many studies and reviews over the past decade have stressed the significance of the TME in cancer growth, progression, and metastasis [1,2]. In this paper, we will describe the various tumor-associated stromal cells that contribute to the carcinogenic process with a focus on the molecular signals that represent current and potential therapeutic targets (Figure 1). As we discuss these individual players, we briefly review several general principles associated with tumors and their milieu including theories of metastasis, the structure and function of the extracellular matrix, inflammation, and immunosuppression.

Paget's Seed and Soil Hypothesis and the Importance of the Microenvironment

In 1889, Stephen Paget proposed a theory to explain why some cancers, independent of the distance from the primary tumor and relative blood supply, display a preference for certain metastatic sites. The “seed and soil” hypothesis suggests that metastatic cancer cells (“seeds”) grow selectively in particular organs (“soil”). Paget’s theory also accounts for the predilection of disseminated tumor cells to flourish at one site and to remain dormant in another. For example, although head and neck squamous cell carcinoma (HNSCC) arrive in both the lungs and bone marrow, they quickly achieve metastatic growth in the former but remain latent in the latter [3]. Another theory of metastasis is the anatomical and mechanical hypothesis, which proposes that metastasis occurs as a result of blood and lymph flow away from an organ that deposits cancer cells in nearby lymph nodes and organs (e.g., gastrointestinal cancer metastasizing to the liver) [4]. Today, the general consensus is that both theories hold merit in the process of tumor metastasis, with either one playing a larger role depending on the specified tumor [4].

Regardless of the mechanism of metastasis, the tumor stroma as a whole plays an important role in the metastatic process. A study by Qian et al. [5] disclosed how nasopharyngeal carcinoma, which frequently metastasizes to lymph nodes, prepares a sentinel lymph node for metastasis by restructuring the nodal vasculature via lymphangiogenesis and angiogenesis. Likewise, chemokines and hormones such as parathyroid hormone-related peptide released into the microenvironment prepare bone sites for successful metastasis by breast and prostate cancer [4].

The Structure of the Microenvironment

Explicating the structure and contents of the TME is a fundamental step in understanding how tumor cells thrive and invade deeper into tissues. In addition to microorganisms and leukocytes, the cellular components of the microenvironment may also consist of fibroblasts, vasculature made up of pericytes and endothelial cells, stromal nerves consisting of neuronal cells, and adipocytes [6,7]. The aforementioned cell types are dynamic characters that live

within the stroma and interact with one another, as well as with tumor cells, in various ways. The non-cellular component of the stroma is the extracellular matrix (ECM), which is composed of the interstitial matrix and basement membrane. The interstitial matrix consists of collagens, proteoglycans, and glycoproteins, while the basement membrane is composed of fibronectin, laminins, type IV collagen, and linkage proteins.

In healthy adults, the function of the ECM as a whole is to provide a stable tissue architecture allowing growth of stem cells and prevention of cancer invasion. Conversely, an aberrant ECM has been shown to promote angiogenesis and tumor metastasis [8]. It is also important to note that cellular inhabitants of the stroma, such as tumor-associated fibroblasts (TAFs) and various immune cells, are believed to contribute to the development of an abnormal ECM [8]. In short, an aberrant ECM may be endorsed by cellular players and often accompanies successful tumorigenesis. Several studies characterizing the therapeutic targets and agents that affect tumor progression facilitated by the stroma are outlined in Table 1.

Inflammation and the Microenvironment

Inflammation both promotes the initial development of cancer and encourages its progression. Chronic, low-grade inflammation in particular repetitively inflicts cell damage and stimulates cells to repair and multiply, leading to initial carcinogenesis [9].

Inflammation secondary to infectious agents (i.e., *Helicobacter pylori* and gastric cancer), immune-mediated diseases leading to chronic inflammation (i.e., irritable bowel disease and colon cancer), subclinical inflammation, and inflammation caused by environmental carcinogens (i.e., smoking leading to lung cancer) are all examples of conditions that promote the formation of cancer [10]. The inflammatory process brings macrophages and other lymphocytes into the stroma. These cells produce reactive oxygen species and reactive nitrogen species leading to DNA damage and mutation, generating a setting ideal for the promotion of angiogenesis, epithelial-to-mesenchymal transition (EMT), and secretion of chemokines and growth factors such as IL-8 and IL-10 which stimulate tumor growth directly [11]. Angiogenesis, the branching and growth of new blood vessels from existing capillaries, is spurred on by an inflammatory microenvironment and is necessary for successful tumorigenesis. Inflammation is often seen not only within the TME, but also within a growing tumor. Intratumoral inflammation is a common finding and has been associated with poorer outcomes for patients with some types of cancer. For example, a greater amount of inflammation within malignant prostate tumors has been correlated with more aggressive disease [12]. Ultimately, inflammatory processes create a peculiar microenvironment filled with inflammatory mediators and cells that encourage cancer growth.

THE MICROBIOME

Origin

The human body is home to more than 100 trillion microorganisms, including bacteria, Eukarya, fungi, and viruses, that together constitute the microbiome or microbiota. The gastrointestinal tract, including the oral cavity, contains the majority of indwelling bacteria,

which help to break down food, absorb nutrients, synthesize vitamins, and regulate the immune system [13]. These populations of microbes are highly diversified not only within an individual but also from one person to the next [14]. Micro-organisms are acquired and altered through exposure during birth, lifestyle choices, diet, medications, and genetics [13].

Contributions to Carcinogenesis

Changes to the normal flora have been associated with disease states including cancer. The loss of beneficial microbes through antibiotic use can promote malignancy [13]. Additionally, the introduction of certain microorganisms into the body has been linked to some malignancies; in fact, one-fifth of cancer cases globally are associated with infectious agents [15]. Some oncogenic viruses include some types of human papilloma virus that lead to anogenital and esophageal cancers, Hepatitis B and C, which are associated with hepatic malignancy, and human herpesvirus 8, which causes Kaposi's sarcoma [15,16]. Certain fungal and viral infections, specifically *Candida* and Epstein-Barr virus, respectively, are considered to be risk factors for oral squamous cell carcinoma [17]. One of the best known of the oncogenic microbes is the gram-negative organism *H. pylori*, which is associated with chronic gastric inflammation, peptic ulcer disease, and gastric cancer [18]. Additional connections between bacteria and cancer are *Streptococcus gallolyticus* (formerly known as *Streptococcus bovis*) and colon cancer as well as *Salmonella typhi* and hepatobiliary cancer [17]. New relationships between oncogenic organisms and human cancers continue to emerge.

Some proposed mechanisms by which microbes may impact carcinogenesis are through modulation of the immune system, promotion of cellular signaling that alters inflammation, the release of exotoxins that directly influence mucosal cells and cell signaling, and indirect transformation of dietary components and xenobiotics into carcinogens [14,15]. *Citrobacter rodentium*, a bacterium functionally similar to *Escherichia coli*, induces crypt hyperplasia and an increased risk of neoplasia, mimicking the development of colonic adenocarcinoma. The underlying cellular mechanisms include activation of Wnt/ β -catenin and NF- κ B as well as phosphatidylinositol-3-kinase (PI3K)/Akt and the Notch pathway [19]. Similarly, *H. pylori* infection has been found to dysregulate β -catenin signaling, increasing epithelial cell proliferation and contributing to the formation of gastric cancer [19]. These molecular pathways are critical for the regulation of cellular growth and division and may be equally important in carcinogenesis.

Several other microbes have been implicated in the pathogenesis of colorectal cancer (CRC) via different mechanisms. For example, studies suggest that superoxide-producing *Enterococcus faecialis* stimulates macrophages to release factors that trigger DNA damage [20]. Additionally, enterotoxigenic *Bacteroides fragilis* produces *B. fragilis* toxin, which cleaves E-cadherin to promote tumor cell proliferation, increases expression of the MYC protooncogene, and triggers NF- κ B signaling [20]. Furthermore, genotoxic *E. coli* that possess the polyketide synthase (pks) island promote CRC. Deletion of the pks island led to a decrease in tumor numbers, DNA damage, and bacterial invasion in a murine model [20]. Finally, Fusobacterium species, most commonly *F. nucleatum*, are more frequently found in

tumor samples compared to controls [15,21]. Continued exposure of mice to *F. nucleatum* moderately increased the incidence of both small and large bowel tumors [20].

Implications and Therapeutic Targets

Some bacteria have the potential to modulate the immune response and increase the efficacy of anticancer therapies. The addition of bacteria from the *Bacteriodes* and *Burkholdia* genus into germ-free mice increased their response to cytotoxic T-lymphocyte-associated protein (CTLA) 4-inhibiting antibodies, increasing T-cell activity to improve the immune response [22]. Similarly, the presence of *Bifidobacterium* increased the efficacy of PDL1-blocking antibodies and slowed the rate of melanoma tumor growth in mice [22]. Research has demonstrated that when bacterial lipopolysaccharide (LPS), a toll-like receptor (TLR)-4 agonist, is released into the serum following total-body irradiation, the innate immune system is triggered via stepwise activation of host dendritic cells and T-cells, leading to tumor regression in mice [13]. Thus far, developed therapies that utilize TLRs have been found to be insufficiently effective. Therapies that utilize laboratory-designed, tumor-specific T cells appear to be more promising [13]. A better understanding of how the microbiota influences cancer could potentially lead to the development of probiotics and beneficial bacteria that could improve health and stave off cancer [15].

Immunosuppression in the TME

Although the TME is home to many immune cells, including dendritic cells, macrophages, T-lymphocytes, occasionally B-lymphocytes and rarely natural killer (NK) cells, immunosuppression is the rule. Successful tumorigenesis requires that cancer cells be insulated from the immune system, a feat that is accomplished by recruiting cancer-promoting leukocytes and inhibiting leukocytes with anti-tumor activity. For example, the presence of cancer-associated regulatory T-cells (Treg) and myeloid-derived suppressor cells (MDSC) in the TME can impair the activities of tumor-infiltrating cytotoxic T-cells, which are capable of identifying and destroying tumor cells [23,24]. In fact, more Tregs in the TME has been linked with a poorer outcome in some cancers, while the infiltration of tumors by cytotoxic T-cells is generally correlated with a better prognosis [25–27]. Although we will not specifically elaborate on the contributions of T-, B- or NK cells in this paper, it is important to note that both reducing Treg-generated immunosuppression in the TME and improving cytotoxic T-lymphocyte access to and function within the tumor are major areas of research with strong therapeutic potential [23,27]. The contributions of two other vital immune cells, tumor-infiltrating dendritic cells and tumor-associated macrophages, will be discussed more thoroughly in the coming sections.

DENDRITIC CELLS

Origin

Dendritic cells (DCs) are classically known the stellate, antigen-presenting cells that connect the innate and adaptive immune responses [24]. DCs possess both MHC class I and 2 molecules, release a variety of cytokines, and are capable of interacting with T-cells, B-cells and NK cells [25]. All DCs are derived from hematopoietic stem cells in the bone marrow and while a small percentage of DCs appear to develop from lymphoid progenitors, the

majority have been shown to be of myeloid lineage [28]. In addition to being categorized by their level of maturity and activation status, DCs differentiate into various subtypes including conventional or myeloid DCs, plasmacytoid DCs, or Langerhans' cells in the skin and microglia in the brain [25,29]. The terms cancer-associated DCs and tumor-infiltrating DCs (TIDCs) have been used to refer to DCs within the TME [25]. These TIDCs, which possess few costimulatory molecules for antigen presentation and are often functionally immature, are believed to develop as a result of tumor and stromal-cell production of various cytokines including IL-6, CSF-1, VEGF, COX-1 and -2, and PGE₂ [29].

Contributions to Carcinogenesis

The major role of TIDCs in the carcinogenic process lies in their failure to properly activate the adaptive immune response. TIDCs exhibit decreased CD40 and MHC class II molecule presentation, which impairs their ability to activate B and T cells [29]. Instead of priming lymphocytes to attack malignant cells, TIDCs often induce a state of anergy upon antigen presentation, which allows the tumor to avoid the immune system. The immunosuppressive functions of TIDCs have been associated with several factors including increased expression of co-inhibitory molecules such as B7-H1 and B7-D and secretion of arginase I and tumor growth factor β (TGF β), which hinder T-cell function and encourage the development of Treg. Increased production of IL-10 by DCs has also been linked to T-cell suppression [29]. Additionally, TIDCs have been shown to produce pro-angiogenic factors including matrix metalloproteinases (MMPs), VEGF, and basic fibroblast growth factor (bFGF) [24].

Implications and Therapeutic Targets

Improving the antigen-presenting capacities and decreasing the regulatory effects of DCs, thereby increasing the anti-tumor activities of the innate and adaptive immune systems, are the primary goals of DC-related therapies. Studies support a variety of combined mechanisms for accomplishing these aims, including anti-VEGF therapies to decrease DC immunosuppressive activity, blockage of IL-10 receptors with activation of pattern recognition receptors to increase T-cell activation, delivery of TLR3 ligands and antibody-mediated activation of CD40 to up-regulate co-stimulatory molecules, and directly targeting TIDCs with nanoparticles to activate toll-like receptors and increase immune activity [24]. Interestingly, injection of a tumor with *Toxoplasma gondii* infected and altered TIDCs to activate a vigorous antitumor response [24]. DC vaccines, DCs loaded with tumor antigens administered to cancer patients to bolster the antitumor immune response, are still being investigated and need to be further enhanced to increase effectiveness [30]. DC-based therapies are a promising and growing area of immunotherapy research.

MACROPHAGES

Origin

From tumor initiation to seeding and metastasis, tumor-associated macrophages (TAMs) are key players within the tumor microenvironment [31]. Literature is replete with evidence of the many functions of TAMs and their role in tumor growth promotion, angiogenesis, lymph-angiogenesis, immunosuppression, tumor seeding, metastasis, and chemotherapeutic resistance. It is widely understood that macrophages are derived from circulating bone

marrow monocytes; however, the exact origin and recruitment of TAMs is as complex as the tumor microenvironment itself [32]. Recent studies have shown that macrophages may originate from conventional hematopoietic stem cells, fetal yolk sac, and the fetal liver [33].

Macrophages are drawn to hypoxic tissue. As cancer cells multiply, the tumor mass enlarges, increasing the demand for oxygen and decreasing the oxygen tension within the core of the tumor. Low oxygen tension and necrosis trigger the release of hypoxia-inducible factors 1 and 2 and the subsequent, dependent expression of factors that recruit macrophages into tumor tissues [34]. Macrophage recruitment to the tumor site is accomplished by a variety of macrophage chemotactic factors produced by both stromal and tumor cells such as CCL2, CCL5, CCL7, CCL8, CXCL12, VEGF, and CSF-1 [35,36].

Macrophages can have a variety of morphologic and phenotypic differences within the tissue environment depending on the activating stimulus [36,37]. Although several types of macrophages have been identified [38], two major groups exist: M1 and M2. M1 macrophages are pro-inflammatory, phagocytic, and possess anti-angiogenic and anti-tumor properties. M1 macrophages are activated by lipopolysaccharide and IFN- γ and can produce known pro-inflammatory cytokines IL-1, IL-6, IL-12, IL-23, TNF- α [38], CXCL9, and CXCL10 [33]. Conversely, M2 macrophages are immunosuppressive, promote tumor angiogenesis and metastasis, are activated by IL-4, IL-13, CSF-1, IL-10, and TGF- β , and produce high levels of IL-10 and low levels of IL-12. The term TAM was once synonymous with the M2 phenotype; however, recent studies have proposed that TAMs might share M1 and M2 polarization [38].

Contributions to Carcinogenesis

TAMs hinder the tumoricidal activity of lymphocytes while supporting Treg activity through the production of immunosuppressive cytokines such as IL-10 and TGF- β [39]. TAMs also release TNF α , IL-6, and IL-1 β , which lead to inflammation, DNA damage, and oncogenic transformation [11,33]. Inhibition of macrophage-induced inflammation has been shown to reduce tumor growth in hepatoma-bearing mice [40]. Furthermore, the CSF-1/CSF-1R complex is often overexpressed in tumors plays a major role in macrophage-induced inflammation, angiogenesis, and metastasis [41]. CSF-1 has been shown to activate NF-kB in TAMs in murine tumor models [42], up-regulating the production of chemokines and growth factors that create an inflammatory microenvironment and supporting tumorigenesis and tumor progression [11]. The binding of CSF-1 to CSF-R causes proliferation of TAMs and the release of proangiogenic factors such as TNF- α , bFGF, EGF, and CXCL8 [33,42]. High levels of CSF-1 have been correlated with high microvascular density and overexpression of CSF-1 can accelerate tumor progression, angiogenesis, and metastasis [42]. Additionally, deletion of the CSF-1 gene has been found to lead to TAM depletion, delayed tumor angiogenesis, and reduced pulmonary metastasis [33]. Furthermore, special monocytes in possession of the angiopoietin receptor Tie-2 appear to have potent pro-angiogenic properties [33,43]. For example, Tie-2⁺ macrophages injected into tumor cells developed more vascularization than the original tumor cells alone or injected with Tie-2^{neg} macrophages [43]. TAMs also produce CCL18, which promotes angiogenesis and resistance

to anti-VEGF therapies in breast cancer. CCL18 may be a novel target in the development of anti-angiogenic therapies [44].

TAMs support lymphangiogenesis via the production of pro-lymphangiogenic factors such as VEGF-C and VEGF-D [33,45]. Infiltration of a high number of TAMs in lung adenocarcinoma equated to poor prognosis and increased peritumoral lymphatics [45,46]. Furthermore, high concentrations of macrophage derived VEGF-C showed higher lymphatic densities in oral squamous cell carcinoma [45,47]. TAMs are also responsible for the secretion of various MMPs, including MMP2 and 9 which have been linked to poor prognosis and decreased survival in breast cancer [48]. A gastric cancer study suggests that in addition to MMP2 and 9, CCL5 secreted by TAMs encourages invasion and tumor cell migration [49]. Macrophage-secreted proteolytic enzymes including MMPs, plasmin, cathepsin B, and urokinase-type plasminogen activator (uPA) break down the ECM and basement membrane to promote angiogenesis and metastasis [50]. The pro-carcinogenic activities of TAMs are illustrated in Figure 2.

Implications and Therapeutic Targets

Several studies have revealed a positive correlation between density of TAMs and poor prognosis [31,51]. CSF1R receptor blockers have shown to be promising in preclinical trials as anti-macrophage recruitment drugs [52,53]. Along the same lines, anti-CCL-2 antibodies have been shown to decrease the metastasis of breast cancer in mice and when stopping anti-CCL-2 treatment there was increased angiogenesis, metastasis and mortality due to an influx of monocytes and pro-tumoral cytokines [54]. Additionally, an immunotoxin targeting folate receptor β (FR β), a marker unique to activated macrophages and TAMs, was able to successfully reduce both TAM numbers and tumor growth [55].

Many new therapies targeting macrophages focus primarily on blocking recruitment of macrophages to the tumor site and re-programming TAMs from an M2 phenotype to an M1 phenotype. The use of TLR9 ligand CpG and anti-IL-10 antibodies has been shown to reprogram TAMs to a more “classical” phenotype with increased anti-tumor effects [52,56]. CD40 agonist antibodies also promote the reprogramming of TAMs and are showing promising results in pancreatic, lymphoma, and melanoma patients [57]. In superficial bladder cancer, intravesicle injection of *Mycobacterium bovis* has been shown to trigger cytotoxic activity in macrophages to prevent disease relapse [57]. Inhibition of I κ B Kinase β , the major activator of NF- κ B, led to re-education of TAM promoting direct tumoricidal activity through phagocytosis and NO production and indirectly through IL-12 production leading to NK cell mediated tumor death [58]. The use of histidine-rich glycoprotein (HRG) within the TM also promotes the tumor-suppressing M1 phenotype and normalized the tumor vasculature [59]. Antibodies to the pattern recognition receptor MARCO also skew TAMs toward the M1 phenotype to reduce tumor growth and metastasis, and also appear to enhance the effectiveness of anti-CTLA4 antibody therapy in CRC and melanoma [39].

Nanoparticles (NPs) are another up-and-coming tactic for targeting TAMs. By means of enhanced permeation and retention effects, NPs carrying drugs are able to pass through leaky tumor vessels and accumulate within tumors. Thioguanine delivered via NPs has been shown to be more effective than free thioguanine in depleting MDSCs in vivo [57].

Additionally, TAMs' ability to penetrate tumors while carrying NPs may prove useful for delivering drugs to hypoxic areas. NPs are also being investigated as vehicles for gene therapy. NP-delivered siRNA has the potential to modify the behavior of TAMs and induce antitumor activity [57]. While NP therapies may surmount some obstacles in cancer treatment, they may also generate hurdles of their own, such as buildup and potential toxicity [57]. Another current limitation in targeting macrophages includes an incomplete understanding of the mechanisms behind human TAM behavior, as the majority of information is based on murine models [60]. Overall, macrophage-based treatment options appear to be promising, particularly as components in combination therapy.

PERICYTES

Origin

Pericytes are believed to be primarily of mesodermal origin, although those located in the head region may be derived from ectoderm [61]. Pericytes are supporting cells that are closely opposed to the outer surfaces of the endothelial tubes within the BM of vascular capillaries. They are branched, elongated cells with projections and are important regulators of vascular development, stabilization, maturation, and remodeling [61,62].

Emerging studies have recently highlighted that these little cells can have a big impact. Pericytes may play a role in recruiting myeloid derived suppressor cells into the tumor microenvironment [63]. A lack of pericytes have been linked to increased endothelial cell proliferation, irregularities in vessel diameter, and increased vessel permeability [64].

Contributions to Carcinogenesis

Pericytes can both limit and promote angiogenesis [65]. Pericytes have been implicated in remodeling of the interstitial matrix, initiation of angiogenic sprouting, and stabilizing and directly interacting with endothelial cells [65,66]. Degradation of the basement membrane and surrounding ECM allows for the migration of endothelial cells, which is necessary for angiogenesis. Studies have suggested that pericytes are stimulated by tumors themselves and hypoxic conditions to secrete activated MMP1, 2, and 9 [66].

Pericytes are widely distributed throughout the body, ranging from a frequency of 1:100 in skeletal muscle to 1:1 in the retina with the highest pericyte coverage within the central nervous system (CNS) [67]. It has been hypothesized that the pericyte–endothelial interface relates to vessel function. For example, high coverage in the CNS could play a role in the creation of the blood brain barrier, while low coverage around vessels in the lungs and kidneys allow for easier gas exchange, transport of nutrients and filtration [68]. Interestingly, tumors with high pericyte coverage are more resistant to anti-tumor therapies, while tumors with low pericyte coverage exhibit increased angiogenic sprouting and cancer cell dissemination [69].

Implications and Therapeutic Targets

While their distinct contributions to carcinogenesis remain understudied, pericytes have potential as a target for cancer immunotherapy. The wide variation in pericyte coverage

among tumors makes selecting effective therapeutic options more difficult. In preclinical trials, antagonism of VEGFR and PDGFR β in high-pericyte tumors may make the cancer more susceptible to other treatments, while agonism of VEGFR, PDGFR β , and Tie-2 in low-pericyte tumors appears to limit angiogenesis and reduce vascular permeability [69]. Pericytes also appear to play a role in the regulation of immune cells via the release of growth factors, cytokines, chemokines and adhesion molecules and tumor-associated pericytes may support tumor survival through immunosuppression. In a study on pancreatic islet cancer in mice, an Rgs5 gene deletion supported pericyte maturation, the restoration of normal vasculature within tumors, and improved cytotoxic T-lymphocyte migration leading to an immune-mediated attack on the tumor [62]. Another study demonstrated that both Rgs5 and PD-L1 were up-regulated in pericytes exposed to tumor fragments, both of which appear to protect tumors from T-cell mediated destruction [62]. The development of drugs that reduce the immunosuppressive functions of Rgs5 and PD-L1 expressing pericytes is an avenue for future research.

ENDOTHELIAL CELLS

Origin

Like pericytes, endothelial cells (ECs) are an integral part of both normal and tumor-associated vasculature. Embryologically, ECs arise from the mesoderm to line the walls of newly formed vessels. In tumorigenesis, endothelial cell recruitment is necessary for the formation of new vessels and lymphatics to supply a growing tumor. However, the origins of these tumor-associated ECs have been much debated. There are three methods by which tumors recruit ECs to improve their blood supply: via “angiogenic sprouting” and the utilization of existing stromal populations of EC’s, through the summoning of EC precursors from the bone-marrow, and from epithelial tumor cells that become “tumor-derived endothelial cells” (TDECs) [70]. TDECs have been identified in certain types of cancer, such as glioblastoma and neuroblastoma [71,72]. In contrast to normal endothelial cells, TDECs are characterized by genetic instability, which suggests that they may be more prone to develop resistance to anti-angiogenic therapy [73].

Contributions to Carcinogenesis

Whether physiologic or tumor-mediated, one cannot separate the direct and indirect interactions between pericytes and ECs. Communication between ECs and pericytes support tumor angiogenesis via Ang-1/Tie2, TGF- β and PDGFB-PDGFR- β signaling [65]. Angiogenesis begins with the destabilization of the vascular pericyte-EC interaction, followed by sprouting of new vasculature by EC migration and decreased pericyte coverage, and finally stabilization of the new vascular wall by pericytes, all stimulated by angiogenic factors and proteases [74]. A key paracrine loop involving PDGF and PDGFR has been shown to develop between ECs lining new vessels in the requirement of pericytes. Interestingly, FGF-2 signaling primes endothelial cells to respond to PDGF-BB stimulation, which results in positive feedback to the FGF-2 signaling system. In murine studies, this interaction generates the formation of disorganized and unstable vasculature that supports tumor growth [75]. Recruited pericytes then stabilize and promote EC survival through VEGF and Angiopoetin-1 [62]. However, tumor angiogenesis is often defective leading to

tumor vascular that tends to be disorganized, tortuous, excessively branched, and leaky with and irregular basement membrane [62]. One aspect of defective angiogenesis has been thought to be due to poor PDGF signaling from the endothelial cells themselves, as the presence of PDGF in the stroma is not enough for proper attachment of pericytes to ECs [74]. Likewise, poor pericyte-EC interaction has been shown to enhance metastatic potential in mice. In a study involving mice deficient in neural cell adhesion molecule (NCAM), a molecule that is necessary for strong pericyte-EC association, Xian et al. [76] demonstrated destabilization of tumor vessels due to dysfunction of pericyte-endothelial interactions leading to increased vessel permeability and likelihood of tumor metastasis.

VEGF-A is a major contributor to angiogenesis along with vascular endothelial growth factor receptors 1 and 2 (VEGFR-1, VEGFR-2) [45]. The VEGF family works to promote the proliferation and maturation of endothelial cells. When proangiogenic molecules become dominant, the “angiogenic switch” occurs and new vessels are born. Likewise, hypoxia stimulates angiogenesis through stabilization of hypoxia-inducible factor (HIF)-1 α [77]. Vascular endothelial cells have been shown to express a variety of integrins including α 1 β 1, α 2 β 1, and α 5 β 1, which studies have shown are crucial to angiogenesis. For example, inhibiting the functions of α 1 β 1 and α 2 β 1 hinders angiogenesis in vitro. Additionally, α 5 β 1 integrins are exceedingly up-regulated in the setting of malignancy [77].

Vascular endothelial growth factors are, paradoxically, also responsible for the growth and maturation of lymphatic endothelial cells. VEGF-C and VEGF-D, which are secreted by the tumor and activated macrophages, and their corresponding receptor VEGFR-3 are the most notable promoters of lymphangiogenesis [45,78]. Some pro-angiogenic factors, such as PDGF, FGF-2, and EGF, also promote the growth and proliferation of lymphatic endothelial cells. VEGF-C is the strongest promoter of lymphangiogenesis, triggering degradation of the ECM via the secretion of MMP9 as well as the up-regulated release of chemokine ligand (CCL) 21 by lymphatic endothelial cells [45]. CCL21 release from lymphatic endothelial cells appears to pro-chemotactic, eliciting the migration of tumor cells towards newly formed lymphatic vessels which may lead to dissemination and metastasis [45]. Additionally, CCL21 appears to regulate the release of VEGF-C by tumor cells via its receptor, CCR-7. Furthermore, VEGF-C has been shown to up-regulate the expression of Bcl-2 on endothelial cells, which has been positively associated with the incidence of lymph node metastases in OSCC [45]. Via this paracrine loop, lymphatic endothelial cells are able to promote lymphangiogenesis and tumor metastasis.

Implications and Therapeutic Targets

VEGF and the VEGF receptor are obvious targets that are currently used in the treatment of cancer. Drugs like bevacizumab, sunitinib, axitinib, and sorafenib have had a major impact in the treatment of cancer. However, VEGF drugs have the potential to increase invasiveness of tumor cells and metastasis by encouraging the proliferation of tumor cells that are resistant to VEGF-based therapies [77]. Integrins are another possible target for anti-angiogenesis therapy, particularly in combination with radiation or other drugs. Cilengitide, a cyclic RGD-peptide inhibitor of α v β 3 and α v β 5 integrins, has undergone clinical trials as a treatment for glioblastoma. While the glioblastoma trials have had mostly poor results

[79], this drug has shown recent promise in the treatment of invasive gliomas in animal models [80] as well as in malignant bone disease by blocking αv integrins on osteoclasts [79]. Cilengitide has also been shown to diminish cell growth, cell proliferation, and cell survival and inhibit focal adhesion kinase-Src-Akt and Erk signaling pathways [77]. Volocixamab, a monoclonal antibody that binds to human and rabbit $\alpha 5 \beta 1$ integrins, is able to trigger apoptosis and prevent capillary tube formation in vitro to inhibit signaling cascades [77].

FIBROBLASTS

In normal tissue, the primary role of the fibroblast is to secrete various components of ECM and create the BM. During carcinogenesis, fibroblasts can become mutated and begin to function abnormally, promoting tumor promotion, growth, angiogenesis, invasion, and metastasis. Terminology used to describe fibroblasts within the tumor microenvironment includes tumor-associated fibroblasts (TAFs), cancer-associated fibroblasts (CAFs), peritumoral fibroblasts, and reactive stromal fibroblasts [81].

Origin

The exact origins of TAFs are unknown, but they are thought to originate from a heterogeneous population of cells. It has been postulated that they can originate from resident fibroblasts, adipocytes, or bone marrow-derived mesenchymal cells, as well as from epithelial cells through epithelial to EMT or endothelial cells via endothelial to mesenchymal transition (EndMT) [82,83].

The major activator and regulator of TAFs is TGF- β , which has been shown to induce activation of resident fibroblasts as well as induce differentiation of various other origins including adipocytes, epithelial and endothelial cells [81]. Likewise, TAFs themselves have been shown to drive EMT through paracrine secretion of TGF- β [84].

Resident fibroblasts are converted to TAFs by stimulation from reactive oxygen species (ROS) [83]. Similarly, bone marrow mesenchymal stromal cells can convert resident fibroblasts to TAF through transforming growth factor B (TGF- β). TAFs originating from human adipose tissue derived stem cells and endothelial cells undergoing transition to mesenchymal origin with “fibroblast-like morphology“ do so under the influence of TGF- β as well [82,85]. The constitution of TAFs include myofibroblasts, which are activated fibroblasts that congregate within the tumor microenvironment [86].

Contributions to Carcinogenesis

VEGF released by TAFs plays a crucial role in promoting angiogenesis, both physiologically and pathologically [87,88]. In colon cancer, stromal fibroblasts secrete high levels of IL-6 in response to cancer cells and inflammation through direct stimulation by IL1- β and TNF- α . Under IL-6 stimulation, stromal fibroblasts were found to generate high concentrations of VEGF and promote angiogenesis. Likewise, use of anti-IL-6 antibodies suppressed angiogenesis and tumor growth in vivo [89].

TAFs have also been shown to promote cancer growth through secretion of hepatocyte growth factor (HGF) which binds to c-Met receptor up-regulating various pathways within the tumor [90]. Up-regulation of HGF and/or c-Met have been seen in breast, lung, stomach, pancreatic, and head and neck cancers [91]. Specifically, TAF-secreted HGF causes epithelial cell dissociation and induces a more invasive phenotype [92]. In HNSCC, high levels of HGF correlated with increased tumor survival, growth, angiogenesis, invasion and metastasis and is an overall predictor of poor outcome [91].

In tumors resistant to anti-VEGF therapy, it appears the PDGF-C may play a role in continued angiogenesis and tumorigenesis. Crawford et al. [93] was able to show both VEGF-dependent and independent mechanisms of tumor promotion, specifically by enhancing angiogenesis in murine lymphoma models. Although all TAFs secrete high levels of PDGF-C, it appeared to be upregulated in TAFs resistant to VEGF therapy. Ultimately, this points out the ability of TAFs to modulate angiogenesis despite use of anti-VEGF therapy [93]. FGF plays a large role in human physiological development to include angiogenesis. In regard to tumor angiogenesis, it has been reported that FGF acts through VEGF-independent pathways. Stromal cell-derived factor (SDF) 1 also known as CXCL (chemokine (C-X-C motif) ligand) 12 is a major factor secreted by TAF which recruit endothelial progenitor cells in to the tumor microenvironment, promoting angiogenesis and tumor growth, a function that is mimicked in physiologic wound healing [87]. Likewise, breast tumors containing CAF-treated anti-SDF-1 antibodies showed diminished tumor growth and size. SDF-1 has also been shown to directly promote breast tumor cell growth through paracrine signaling through binding to CXCR-4. Anti-CXCR-4 antibodies decreased, to a large degree, SDF-1-mediated tumor growth in murine studies [94].

TAFs encourage EMT through the release of TNF- α , which encourages migration and invasiveness of tumor cells, as well as through remodeling of the ECM through MMP9 and MMP2 [81]. A study on HNSCC revealed that CAFs secreted high levels of pro-MMP2, which is subsequently activated by tumor released membrane type 1 metalloproteinase (MT-1-MMP). TAF-conditioned media has also been shown to promote migration of tumor cells in HNSCC [90]. A paracrine interaction between tumor cells and CAFs lead to up-regulation of MMP9, which is secreted and activated by OSCC tumor cells [95]. A later study on OSCC found that thrombospondin (THBS) –1 released by fibroblasts further stimulated the production of MMP9 and other MMPs, supporting destruction of the ECM and cancer invasion [96]. TGF- β enhances MMP9 secretion and also triggers TAFs to secrete IL-11, which may play a role in tumor progression and metastasis [81,97]. Figure 3 demonstrates some of the many TAF-secreted factors that promote cancer.

Implications and Therapeutic Targets

Four major therapeutic targets that may impact TAFs include SDF-1/CXCL12, VEGF-A, PDGF-C, and HGF. High levels SDF-1/CXCL12 have been shown to be a predictor of poor prognosis in patients with ovarian carcinoma [98]. Given the large effect that VEGF-A plays in promotion of angiogenesis, blocking its effects would seem a promising target. Upregulation of platelet-derived factor C (PDGF-C) occurs in a subset of resistant TAF. Anti-PDGF C antibodies are able to block angiogenesis created by this subset of TAFs [87].

Therefore, blocking both VEGF-A and PDGF-C concurrently could make large impacts into cancer growth through angiogenesis. However, studies have shown that this combination therapy to cause large amounts of toxicity, and further research is required [93]. The effects of HGF can be inhibited by c-Met tyrosine kinase inhibitors (TKI) *in vivo*, but further research is needed to evaluate the impact in human subjects [91]. Additionally, a DNA vaccine targeting fibroblast activation protein (FAP) led to destruction of TAFs through cytotoxic T-cells, thereby leading to suppression of tumor growth and metastasis in both breast and colon cancer in murine models [99]. Other potential therapeutic targets include THBS1 and IL-11 [81,96]. Overall, the data suggest that targeting various aspects of TAFs can lead to decreased tumor growth and further studies are needed to elucidate both effective and safe treatments to reduce the quantity and effects of TAFs in the tumor microenvironment.

NEURONAL CELLS

Origin

Neuronal cells are of ectodermal origin and are most relevant in the discussion of tumors that form within the central nervous system and in other nerve-rich regions, such as the head and neck, prostate, and pancreas. Cancers that form in these areas of the body have the tendency to interact with stromal nerves, which may be evidenced by perineural invasion (PNI). A recently proposed and more specific definition describes the tumor should covering at least 33% of the circumference of the nerve or invading any of the three tissue layers [100]. The invasion of tumor cells into stromal nerves has negative implications for disease prognosis. The study of PNI also provides opportunities to identify new targets in the treatment of cancer.

Contributions to Carcinogenesis

Various molecules called neurotrophins or neurotrophic factors present in the TME appear to promote the growth of neurites and interaction of stromal nerves and tumor cells. Neurotrophic factors are key promoters and regulators of PNI. Some of the major neuronal growth factors include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4) [100–102]. Interestingly, each of these factors binds to a tropomyosin receptor kinase (Trk) and a p75 receptor; NGF binds to TrkA, BDNF and NT-4 to TrkB, and NT-3 to TrkC [103].

Some of the aforementioned neurotrophins have been recently studied and found to promote carcinogenesis. With regards to NGF, hyperglycemia appears to encourage the proliferation and invasion of pancreatic cancer cells and increased the expression of nerve growth factor (NGF) in these cells. Likewise, Schwann cell migration is inhibited by hyperglycemia and a pathologic regeneration of neurites was noted within a hyperglycemic environment [104]. With regards to BDNF, a recent study showed both BDNF expression alone and increased expression of both BDNF/TrkB at the invasive tumor front correlated with poor prognosis [105]. BDNF has likewise been shown to stimulate HSNCC EMT, cell migration, and invasion [106]. Lastly, the BDNF/TrkB pathway has been linked to increased progression and metastasis in CRC [103]. Additionally, neurturin (NRTN) is a neurotrophic factor that

binds to a glial-cell-line-derived neurotrophic factor receptor alpha-2 (GFRa-2) in pancreatic cancer and pancreatic neuropathy. Neurturin and GFR-2a are upregulated in pancreatic cancer and have been shown to sustain proliferation and increase the invasiveness of pancreatic cancer. Likewise, neurturin can alter neuronal structure leading to enhanced invasion of nerves [107]. NT-3 and NT-4 impact perineural invasion as well as metastasis to the brain. Neurotrophin 3 (NT-3) has a dual function of regulating metastasis to the brain and decreasing the immune response of the brain to tumor cells in breast cancer [108]. Both NT-3 and NT-4 have been demonstrated to be upregulated in pancreatic ductal adenocarcinoma [102,109]. NT-4 and its receptor TrkB may encourage tumor cell invasiveness in HNSCC [102]. Glial cell line-derived neuronal factor (GDNF) is an additional neurotrophin that appears to promote cancer progression. GDNF enhances the migration of lung, pancreatic, glioma, chondrosarcoma, and HNSCC cells [110]. In a study on the behavior of HNSCC, increased levels of GDNF were found to increase the expression of MMP9 and MMP13, which increased the migration of tumor cells into the stroma [110]. In progressive OSSC of the tongue, tumor cells, macrophages, and vascular endothelial cells overexpress MMP2 and MMP9. These MMPs degrade collagen IV, an important scaffold for basement membrane proteins, and are associated with increased tumor cell invasiveness [111]. Ultimately, MMP2 and MMP9 appear to play an important role in allowing cancer cells to penetrate stromal nerves [100]. Other neurotrophins that promote neuronal cancer invasion include pleiotropin (PTN) and syndecan-2. PTN is another neurotrophin that has been linked to increased incidence of PNI in pancreatic cancer. PTN is highly expressed in cancer cells and is released upon cell death to bind to N-syndecan, its receptor on stromal neurites, and stimulates neural outgrowth toward tumors [112]. Syndecan-2, a protein upregulated in pancreatic adenocarcinoma, has been found to induce a more invasive and migration of cancer cells through the K-Ras pathway [113].

Implications and Therapeutic Targets

PNI is recognized as a key prognostic indicator of poor prognosis, decreased survival, and an increase in local recurrence in a variety of tumors. Although there is much research to be done in understanding the mechanisms promoting PNI, further studies are needed to develop effective therapeutic targets. In human oral cancer blocking GDNF decreased tumor migration, most likely through downregulation of MMP2 and 9 [110]. In murine models, antibodies and RNA inhibitors targeted against NGF have been shown to decrease cell proliferation and angiogenesis in breast cancer [100]. Anti-PTN antibodies have been shown to block neurite outgrowth in vitro, indicating their potential benefit in the treatment of pancreatic cancer. However, more studies are needed to evaluate PTN impact in neuronal outgrowth and create further treatment through blockade of its receptor N-syndecan [112]. Inhibition the BDNF/TRKB pathway in HSNCC has been shown to decreased tumor progression [106]. Because the interaction between stromal neurons and cancer cells is highly complex and has a strong negative prognostic impact in a variety of cancers, more studies are needed to better understand the process of perineural invasion and develop more treatments to target specifically those factors that promote PNI.

ADIPOCYTES

Origin

It was originally believed that all adipocytes were derived from the mesoderm, specifically from mesenchymal stem cells (MSCs). However, more recent research suggests adipocytes may also be formed from neuroectoderm [114]. In adults, adipocytes are believed to arise from adipocytes progenitors in the stroma and bone marrow hematopoietic stem cells (BMHSCs) [114]. Stromal adipocytes become cancer-associated adipocytes when they are activated by tumor cells and inflammation, losing various markers of expression like hormone-sensitive lipase (HSL), APN, and resistin and exhibiting increased expression of pro-inflammatory cytokines, growth factors, and adipokines [115,116]. Interestingly, some cancer-associated adipocytes appear to regress and take on a fibroblast-like phenotype, creating a desmoplastic appearance in the stroma [116,117].

Contributions to Carcinogenesis

Increased adiposity is associated with chronic inflammation and the promotion of cancer. The major pro-inflammatory adipokines include CCL2, TNF- α , IL-6, IL-8, PAI-1, and leptin [117,118]. Adipocytes overexpress CCL2, which interacts with CCR2 receptors, triggering chronic inflammation in adipose tissue through recruitment of macrophages. Likewise, elevated expression of cyclooxygenase-2 (COX-2) is associated with CCL2 upregulation, which is also thought to aid in macrophage migration [119]. It has also been shown that genetic deletion or inhibition of CCL-2, leads to decreased macrophage recruitment to the tumor site in mice, supporting the pro-inflammatory, pro-cancer role of CCL-2 [120]. Additionally, adiponectin (APN), an anti-inflammatory cytokine, is decreased in cancer states. Its presence has been shown to inhibit inflammation by blocking NF- κ B, inhibit growth and induce apoptosis [121].

Lipid-rich adipocytes in the tumor microenvironment provide an abundant energy supply for transformed cancer cells. In cancers growing in adipose-rich tissues, fat stored in adipocytes may be utilized to fuel cell signaling, tumor growth and progression [119]. For example, in ovarian cancer, adipocytes have been revealed to promote tumor growth by directly donating fatty acids to cancer cells for energy [120]. Although primarily released by other stromal cells such as fibroblasts, HGF is also released by adipocytes and has been shown to promote tumor cell invasion and growth via angiogenesis [121]. Leptin has mitogenic, anti-apoptotic, and angiogenic properties and has been reported to promote breast cancer through both estrogen-dependent and independent pathways [121]. Collagen VI, which is found abundantly in adipocytes, is also important for the growth and promotion of breast cancer. Type VI collagen, particularly the alpha3 domain, is up-regulated in the stroma surrounding a tumor and has been associated with tumor growth and progression, proliferation of fibroblasts, decreased apoptosis, and increased migratory and invasive activity of cells that possess the neuron-glia antigen 2/chondroitin sulfate proteoglycan 1 (NG2/CSPG) receptor [122].

Research has revealed intimate crosstalk between adipocytes and breast cancer cells. Breast cancer cells co-cultured with adipocytes showed increased invasiveness through the

increased release of IL-6, which decreased E-cadherin and β -catenin expression on breast cancer epithelial cells and increases tumor cell scattering in vitro [115]. Additionally, overexpression of IL-6 and IL-1 were seen at the protein level. Further supporting the pro-invasive effects of IL-6, treatment with murine IL-6 antibodies had a negative impact on tumor invasion. High levels of IL-6 were also correlated with increased tumor size and lymph node involvement. Likewise, MMP11 has been shown to be up-regulated in vivo, while MMP9 and MMP2 levels remained normal [115].

Implications and Therapeutic Targets

Given the pro-inflammatory and pro-tumor effects that result from increased adiposity, possible avenues for future therapy involve primary prevention of cancers through targeting the aforementioned aberrant pathways. Monoclonal antibodies that target CCL2 and its receptor, CCR2, have been developed and are being tested with mixed results so far [123]. COX-2 inhibitors such as Celecoxib may have therapeutic benefits in prostate cancer patients [123]. NSAIDs, which also block COX-2 pathways, have been shown to have anti-carcinogenic properties through promoting apoptosis and modulating the immune response [123]. Metformin is being studied for use in the primary prevention of breast cancer [117]. The use of antibodies to IL-6, IL-8, CCL2, and TIMP-1 has been shown to decrease attraction between adipocytes and ovarian cancer cells [120]. Ultimately, further research is still needed in developing treatments that are effective and tolerable in humans.

CONCLUSION

The TME is a vibrant, ever-changing atmosphere brimming with a multitude of cellular components, each of which plays a role in tumor initiation and progression. Thus, in order to develop effective therapeutic approaches, it is critical to study the tumor in the context of its associated stroma. Although the cellular composition of tumors at various sites may differ, the major stromal cell types discussed in this paper are associated with the majority of solid malignancies. The majority of studies discussed typically evaluate the effect of one stromal cell type on the tumor. In order to develop targets for therapy, it is critical to develop in vitro and in vivo models that incorporate multiple stromal cell types and assess their concerted effects on tumors. A variety of therapeutic techniques for targeting the tumor stroma are being developed, including agonistic or antagonistic antibodies, small molecules inhibitors, immune-checkpoint blocking inhibitors, vaccines, immunoconjugates including immunotoxins, and liposomes and nanoparticles as vehicles for drugs or gene therapy. With the advent of therapeutic approaches targeting tumor-stroma interactions, the stage is set for the development of approaches that effectively abrogate the carcinogenic effects of the microenvironment on tumor progression and response to therapy.

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Abbreviations

APN	adiponectin
α-SMA	smooth muscle actin
BDNF	brain-derived neurotrophic factor
bFGF	basic fibroblast growth factor
CCL	chemokine ligand
COX	cyclooxygenase
CRC	colorectal cancer
CSF	colony-stimulating factor
CXCL/R	chemokine (C-X-C motif) ligand/receptor
DC	dendritic cell
EC	endothelial cell
ECM	extracellular matrix
EMT	epithelial-to-mesenchymal transition
EndMT	endothelial-to-mesenchymal transition
FGF	fibroblast growth factor
GDNF	glial cell-line derived neurotrophic factor
HGF	hepatocyte growth factor
HNSCC	head and neck squamous cell carcinoma
HRG	histidine-rich glycoprotein
IL	interleukin
MMP	matrix metalloproteinase
NK	natural killer cell
OSCC	oral squamous cell carcinoma
PDGF	platelet-derived growth factor
PD-L1	programmed death ligand
PGE₂	prostaglandin E ₂
PNI	perineural invasion
PTN	pleiotropin

SDF	stromal cell-derived factor
TAF	tumor-associated fibroblast
TAM	tumor-associated macrophage
TDEC	tumor-derived endothelial cell
THBS	thrombospondin
TIDC	tumor-infiltrating dendritic cell
TLR	toll-like receptor
TME	tumor microenvironment
VEGF	vascular endothelial growth factor

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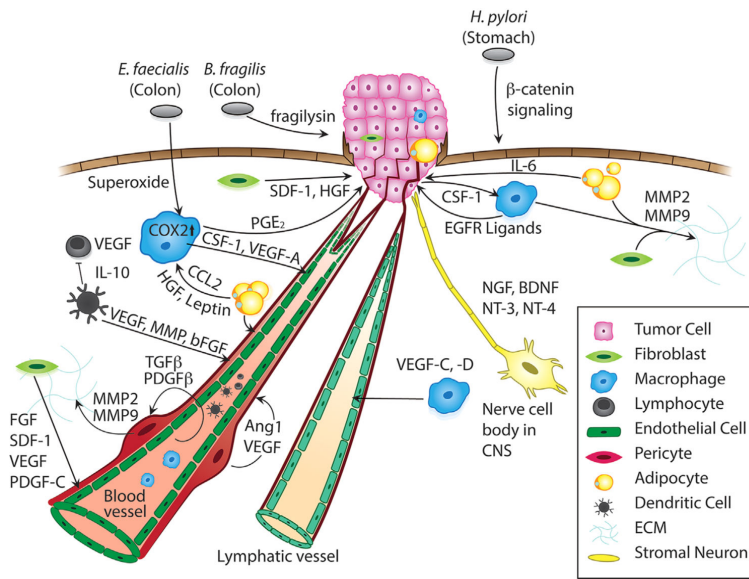


Figure 1.

Schematic depicting key stromal molecular mediators influencing tumor progression. Stromal cells release a wide variety of signaling molecules that target other stromal cells, tumor cells, and the extracellular matrix to generate an atmosphere conducive to cancer growth and metastasis. Additionally, the figure depicts examples of bacteria within the microenvironment that support tumorigenesis in the gastrointestinal tract. *B. fragilis* in the colon produces fragilysin, which directly promotes cancer cell proliferation through cleavage of tumor-suppressor protein E-cadherin. *E. faecialis* up-regulates COX2 expression in macrophages, generating DNA damage associated with carcinogenesis. *H. pylori* facilitates dysplasia and tumor formation via activation of β -catenin signaling within the gastric epithelium. Ang1, angiopoetin 1; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; CCL2, chemokine ligand 2; COX2, cyclooxygenase 2; PGE₂, prostaglandin E₂; CSF-1, colony-stimulating factor 1; EGFR ligands, epidermal growth factor receptor ligands; HGF, hepatocyte growth factor; IL, interleukin; MMP, matrix metalloproteinase; NGF, nerve growth factor; NT, neurotrophin; PDGF, platelet-derived growth factor; SDF-1, stromal cell-derived factor-1; TGF β , tumor growth factor β ; VEGF, vascular endothelial growth factor.

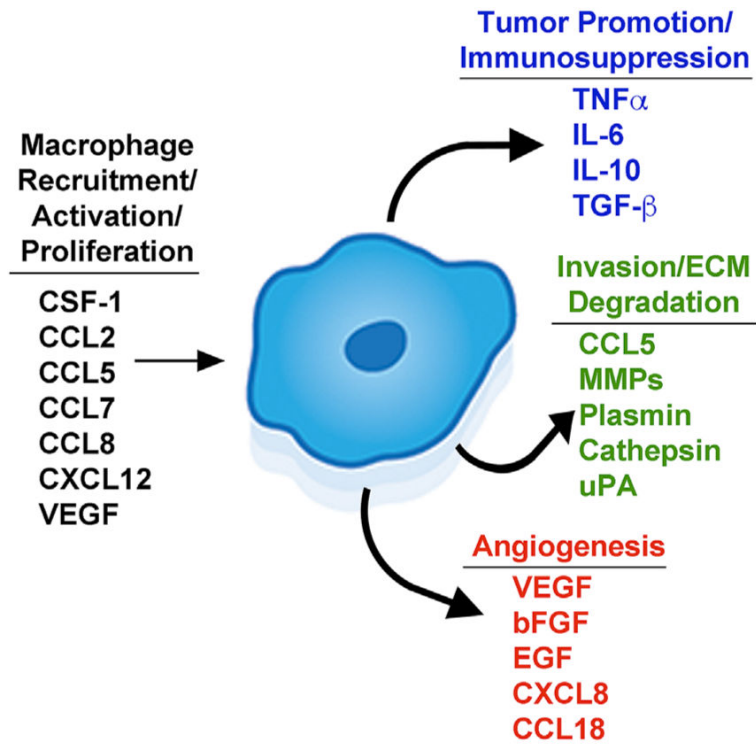


Figure 2. Schematic illustrating the factors that recruit and activate tumor-associated macrophages (TAM). In addition, TAM-secreted factors and their effects on the tumor and the microenvironment are described.

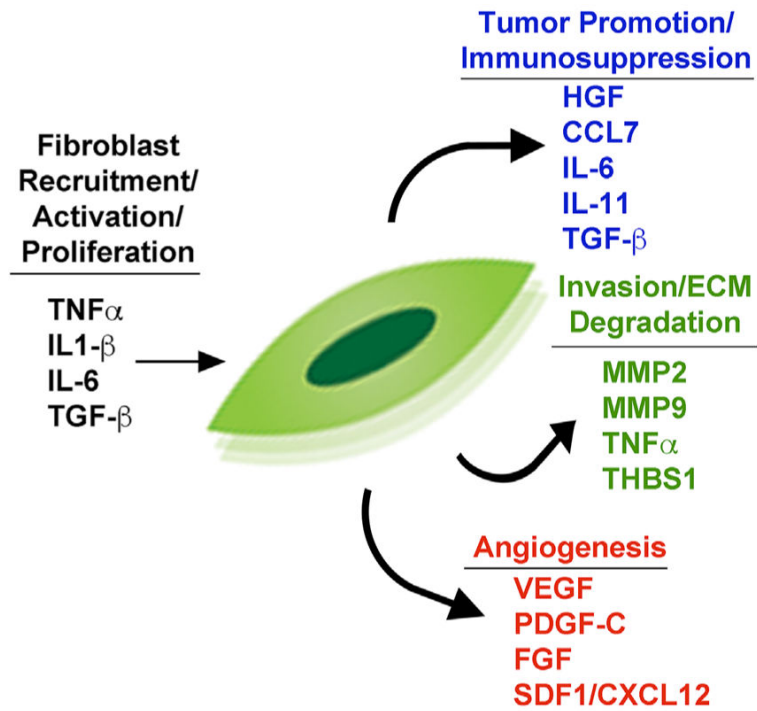


Figure 3. Schematic illustrating the factors that recruit and activate tumor associated fibroblasts (TAFs). In addition, TAF-secreted factors and their effects on the tumor and the microenvironment are listed.

Table 1

Putative Therapeutic Targets and Agents Interfering With Stroma-Facilitated Tumor Progression

Cell type	Potential therapeutic targets and agents	References
Microbes	Beneficial bacteria (Bacteroides; Bifidobacterium)+immune-checkpoint blocking inhibitors (anti-CTLA-4 antibodies; anti PD1/PD-L1 antibodies); TLR agonists	[13,15,22]
Dendritic cells	Anti-IL-10 antibodies; TLR ligands and agonistic CD40 antibodies, anti-VEGF therapies, intratumoral injection of <i>T. gondii</i> ; DC vaccines	[24,30]
Macrophages	Anti-CCL2 antibodies; CSF1 and CSF1R antagonists; TLR ligand CpG and anti-IL-10 antibodies; Ikk Kinase β inhibitors; HRG; FR β -targeted therapies; anti-CCL5 therapies; anti-CCL18 therapies; intravesicle installation of <i>M. bovis</i> ; agonistic CD40 antibodies Anti-MARCO antibodies	[39,44,49,52–59]
Pericytes	VEGFR and PDGFR- β antagonists; VEGFR, PDGFR- β , and Tie-2 agonists; anti-RSG5 and anti-PD/PD-L1 therapies	[61,68]
Endothelial cells	$\alpha v\beta 1$, $\alpha v\beta 2$, $\alpha 5\beta 1$ integrin inhibitors; anti-VEGF and VEGFR agents	[76,78]
Fibroblasts	Anti-CXCR-4 antibodies (SDF-1/CXCL12 inhibition); anti-VEGF-A antibodies and VEGF-R inhibitors; anti-PDGF-C/ PDGF-R inhibitors; MMP inhibitors; anti-IL6 antibodies; anti-HGF therapies; anti-FAP antibodies; Anti-TGF β and TGF β R inhibitors; anti-IL-11 therapies; anti-THSB1 therapies	[80,86,90,95–98]
Neuronal cells	NT3 and NT4 targeted therapies; GDNF inhibitors; anti-NGF antibodies; anti-PTN antibodies and N-syndecan inhibitors; BDNF inhibitors	[99,105,109,111]
Adipocytes	Anti-IL-6 antibodies; anti-IL-8 antibodies; anti-CCL2 antibodies; anti-TIMP-1 antibodies; COX2 inhibitors, APN	[119,120,122]

APN, adiponectin; BDNF, brain-derived neurotrophic factor; CCL, chemokine ligand; CD, cluster of differentiation; COX, cyclooxygenase; CSF, colony stimulating factor; CSF1R, colony stimulating factor 1 receptor; CTLA, cytotoxic T-lymphocyte-associated protein; CXCL, C-X-C chemokine ligand; CXCR, C-X-C chemokine receptor; FAP, fibroblast activation protein; FR β , folate receptor beta; GDNF, glial cell line-derived neurotrophic factor; HRG, histidine-rich glycoprotein; IL, interleukin; MMP, matrix metalloproteinase; NGF, nerve growth factor; NT, neurotrophin; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth receptor; PD1, programmed cell death protein; PD-L1, programmed cell death ligand; PTN, pleiotropin; RSG5, regulator of protein signaling 5; SDF, stromal-derived factor; TIMP, tissue inhibitor of metalloproteinase; TGF, transforming growth factor; TLR, toll-like receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor and receptor.