Role of the tumor microenvironment in cancer hallmarks and targeted therapy (Review)

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Abstract. Genetic alterations drive tumor onset and progression. However, the cross-talk between tumor cells and the benign components of the surrounding stroma can also promote the initiation, progression and metastasis of solid tumors. These cellular and non-cellular stromal components form the tumor microenvironment (TME), which co-evolves with tumor cells. Their dynamic and mutualistic interactions are currently considered to be among the distinctive hallmarks of cancer. Biochemical and physical cues from the TME serve an essential role in regulating tumor onset and progression. They are also associated with resistance to treatment and poor prognosis in patients with cancer. Therefore, a deep understanding of the TME is vital for developing potent anticancer therapeutics and improving patient outcomes. The present review aims to review the biology of both cellular and non-cellular constituents of the TME and novel findings regarding their contribution to core as well as emerging cancer hallmarks. The present review also describes key TME markers that are either targeted in interventional clinical trials or serve as promising potential anticancer therapies. Understanding TME components and their intercellular interactions is key toward identifying the mechanisms of progression and treatment resistance. Such understanding is of utmost significance for personalized and effective cancer therapy strategies.

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Abbreviations: ACT, adoptive cell therapy; αSMA, α-smooth muscle actin; APCs, antigen-presenting cells; AVCs, angiogenic vascular cells; CAFs, cancer-associated fibroblasts; CAR, chimeric antigen receptor; CCL, C-C motif chemokine ligand; circRNA, circular RNA; CRC, colorectal cancer; CSF-1, colony-stimulating factor-1; CSF-1R, colony-stimulating factor-1 receptor; CTLs, cytotoxic T lymphocytes; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CXCL, CXC-chemokine ligand; DCs, dendritic cells; ECs, endothelial cells; ECM, extracellular matrix; EGF, epithelial growth factors; EMT, epithelial-to-mesenchymal transition; EVs, extracellular vesicles; FAK, focal adhesion kinase; FAP, fibroblast activation protein; FGF, fibroblast growth factors; GM-CSF, granulocyte-macrophage colony-stimulating factor; HA, hyaluronic acid; HEVs, high endothelial venules; HGF, hepatocyte growth factor; HOTAIR, HOX transcript antisense RNA; ICIs, immune checkpoint inhibitors; IFN, interferon; IGF, insulin-like growth factor; IICs, infiltrating immune cells; IMCs, immature myeloid cells; LINC, long intergenic non-coding RNA; lncRNA, long non-coding RNA; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility complex; MIP, macrophage inflammatory protein; miRNA, microRNA; MSCs, mesenchymal stem cells; NKs, natural killer cells; NSCLC, non-small cell lung cancer; OXPHOS, oxidative phosphorylation; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1; PDAC, pancreatic ductal adenocarcinoma; PDGFR, platelet-derived growth factor receptor; PFS, progression-free survival; PGs, proteoglycans; RCC, renal cell carcinoma; SDF, stromal cell-derived factor; TAMs, tumor-associated macrophages; TCA, tricarboxylic acid; TME, tumor microenvironment; VCAM1, secreted vascular cell adhesion molecule 1

Key words: TME, therapy, solid tumors, ECM, CAFs

Contents

1. Introduction

Cancer develops from genetically altered cells with a high proliferation rate and the ability to disseminate from a primary location to invade distant sites (1). In the past, scientists assumed that cancer progression and invasiveness were solely determined by factors within tumor cells (1,2). However, focus is now put on cancer-supporting components, which have been demonstrated to aid tumor cells in manifesting the disease (3,4). It is now widely established that the tumor microenvironment (TME) components contribute to different cancer hallmarks and are thus recognized as possible cancer therapy targets (2,5-7). These components include cells of the stroma [cancer-associated fibroblasts (CAFs), endothelial cells (ECs), pericytes and immune cells] in addition to non-cellular

components, such as the extracellular matrix (ECM), extracellular vesicles (EVs) or exosomes, and the microbiome, collectively forming the TME (5,8,9).

Oxygen levels, metabolites, nutrients and pH have also been acknowledged as factors that may be controlled by the TME (10,11). The immunosuppressive and metabolically stressed nature of the TME serves an instrumental role in exacerbating the aggressiveness of cancer cells (11). For instance, interactions between tumor and stromal components may result in additional modifications of the TME cells, ECM remodeling and angiogenesis, thus leading to metastasis (12).

Cross-talk between cancer cells and TME components may also decrease the efficacy of antitumor treatments, contributing to drug resistance (13). Accordingly, an improved understanding of the biological and chemical nature of the TME paves the way for the development of therapeutic strategies for more efficient targeted cancer therapy. The present review aims to discuss TME components and their molecular features, and how they modulate cancer hallmarks. It also reviews key factors of the TME for targeted cancer treatment, with a focus on current TME pathways and mediators targeted in interventional clinical trials.

2. Composition of the TME

TME refers to all non-cancer cellular components surrounding tumor cells, and non-cellular components exerting tumor-supporting roles (2,6). Stromal cells of the TME include CAFs, ECs lining the blood vessels and immune cells (Fig. 1) that are recruited by cancer cells from neighboring tissue stroma (5). Interactions of TME stromal cells with cancer cells create a protective environment that promotes tumor growth in both cases (2,5). Tumor-associated stromal cells not only physically support cancer cells but also secrete growth factors, cytokines, chemokines and ECM proteins with tumor-promoting properties (14,15). In addition to stromal cells, scientists have identified the ECM, the microbiome and cell messengers referred to as EVs as non-cancerous constituents of the TME (10,16-18).

Stromal cells

CAFs. Fibroblasts are the prevalent cell type in connective tissue stroma and the primary source for ECM and basement membrane proteins (15,19). Most fibroblasts within tumors differentiate into CAFs (15,20). CAF activation is driven by different stimuli, such as inflammation (Fig. 1), ECM stiffness and other physiological stresses (19,21). CAFs are a highly heterogeneous cell population and, to the best of our knowledge, their origin remains unclear (15). While it was earlier hypothesized that most CAFs originate from local fibroblasts that are activated and reprogrammed to support tumor growth (22), some groups have demonstrated that CAFs originate from mesenchymal stem cells, specifically bone marrow-derived stem cells located in the bones (23-25). Others attribute their origin to the human adipose tissue-derived stem cells found in the adipose tissues (26-28). This emphasizes the remarkable plasticity of cancer, enabling it to employ different sources to promote growth and progression (27).

CAFs differ from normal fibroblasts both functionally and phenotypically (15). Generally, CAFs express an array of different proteins, such as vimentin, α-smooth muscle actin (αSMA), platelet-derived growth factor receptor α/β (PDGFR α/β) and fibroblast activation protein (FAP) (15). However, studies have identified CAF subtypes lacking the expression of these markers (29,30). Accordingly, stromal cells that are negative for epithelial, endothelial and leukocyte markers having elongated morphology might be considered to be CAFs (19). Using transcriptomic analysis, a number of groups have identified different subpopulations of CAFs (28,31). For instance, in pancreatic ductal adenocarcinoma (PDAC), three CAF subtypes have been identified: i) Myofibrotic CAFs showing myofibroblastic features with high expression of αSMA and other contractile proteins and low IL-6 expression; ii) inflammatory CAFs (iCAFs) with low αSMA expression and high expression of cytokines involved in inflammation (such as IL-6); and iii) antigen-presenting CAFs highly expressing major histocompatibility complex II (MHC II) family genes (30-33). Tumor-supporting CAFs secrete MMPs, cytokines, chemokines and angiogenic factors that can stimulate the proliferation of tumor cells and enhance angiogenesis (34). CAFs also alter ECM signaling and stiffness by upregulating ECM components, such as collagen type I and III, and fibronectin (30). Accumulation of fibrous connective tissues is referred to as desmoplasia and is associated with increased hypoxia, neoangiogenesis and drug resistance (30,35).

ECs. Given their role in angiogenesis, ECs form the inner lining of the blood vessels and remain the most extensively studied cells of the TME (36). Typically, blood vessels enable the exchange of oxygen, nutrients, wastes and immune cells between the circulatory system and body tissues (36). Due to the increased metabolic and nutritional requirements of tumor cells, ECs branch from pre-existing vasculature to form new blood vessels (37). Newly formed vessels are structurally and functionally abnormal because of their leaky nature and dissimilar chaotic branching that increase the interstitial fluid pressure rendering a hypoxic and acidic environment (38). Tumor vascularization, caused by hypoxia, involves vascular ECs and other TME cell types, including pericytes and bone marrow-derived precursor cells (39,40). The pro- and anti-angiogenic molecules secreted by cells determine the transformation of normal angiogenic processes to tumor angiogenesis (37,41). While thrombospondin-1 and Endostatin are major anti-angiogenic factors (42), VEGF-A secreted by cancer cells can stimulate the formation of new vasculature that, in turn, supplies tumor cells (Fig. 1) (37). In addition, platelet-derived growth factor β (PDGFβ) recruits pericytes to the tumor vasculature aiding blood vessel formation and maturation (43).

Infiltrating immune cells (IICs). Tumor cells and CAFs secrete chemoattractant factors that recruit various immune cells to their niche (6). TME IICs include immunosuppressive and antitumor immune cells of myeloid lineages, such as macrophages, myeloid-derived suppressor cells (MDSCs), neutrophils, mast cells and dendritic cells (DCs), and lymphoid lineages, such as B and T lymphocytes, and natural killer cells (NKs) (14,44).

Activated macrophages can be polarized into two main subtypes: Pro-inflammatory M1 and anti-inflammatory M2 (45). Tumor-recruited macrophages infiltrating the TME constitute the tumor-associated macrophages (TAMs), the

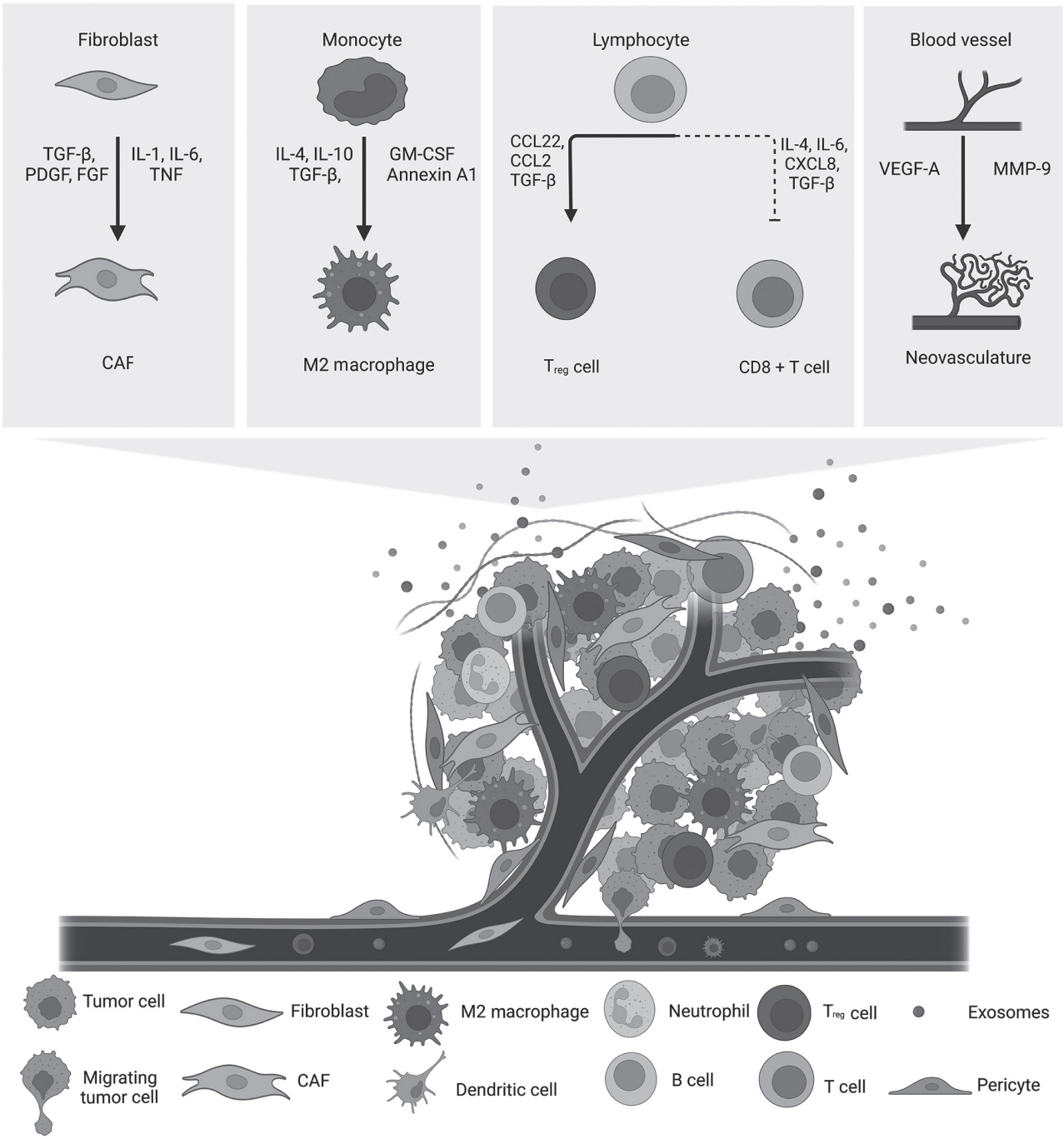

Figure 1. Mechanisms of TME stromal cell activation and the complexity of the TME organization. This schematic highlights the multiple mechanisms that can contribute to the activation of TME CAFs, macrophages and T_{reg} cells, and to the increased neovasculature in tumors. Adapted from 'Tumor Microenvironment 2', by BioRender.com (2022). Retrieved from https://app.biorender.com/biorender-templates/t-5f63a4bebecfd300b1f68c0c-tumor-microenvironment-2. CAF, cancer-associated fibroblast; CCL, CC-chemokine ligand; CXCL, CXC-chemokine ligand; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony stimulating factor; PDGF, platelet-derived growth factor; TME, tumor microenvironment; T_{reg}, regulatory T.

most abundant immune cells of the TME (46,47). Data indicate that TAMs are mainly of the M2 subtype, and thus, are tumor-promoting (45,48). TAMs secrete cytokines and soluble factors that contribute to tumor progression by influencing angiogenesis, cell migration, invasion and metastasis (2). The presence of TAMs is associated with poor prognosis in most cancer types (49).

MDSCs represent a unique category of immunosuppressive myeloid cells that are abundant in the TME (50,51). Chronic inflammation in cancer disturbs normal myelopoiesis, and thus, differentiation and maturation of immature myeloid cells (IMCs) are impaired (52). This disturbance drives the generation of MDSCs from IMCs (52). MDSC are subdivided in two main subsets according to their origin and phenotypical and morphological characteristics. These subsets are the granulocytic polymorphonuclear neutrophils-MDSCs and monocytic MDSCs (53).

Neutrophils, also referred to as tumor-associated neutrophils, possess immunosuppressive activity (54). Neutrophils are also polarized into two subsets: Antitumor N1 and

tumor-promoting N2 (54). IICs include mast cells capable of releasing soluble factors that enhance EC proliferation and promote tumor angiogenesis (50). DCs are antigen-presenting cells (APCs) capable of producing pro-inflammatory cytokines and chemokines and promoting T cell stimulation (50,55). However, DCs in the tumor exhibit abnormal antigen-presenting capabilities, and thus, are dysfunctional (56).

Among the lymphoid lineage of IICs, different types of T cell populations infiltrate the TME (44). Cytotoxic T cells can eliminate malignant cells, and thus, are associated with a good cancer prognosis (44,57). This is the case of the antigen recognizing cytotoxic memory T cells that are positive for CD8 and produce IL-2 and IFNγ (2). $CD4^+$ T helper (Th) cells are divided into different subtypes: The pro-inflammatory Th1 lineage, anti-inflammatory Th2 cells and the immunosuppressive regulatory T (T_{reg}) cells (2). The ratio of Th1 to Th2 cells in cancer is associated with tumor stage and grade (50,58,59). B cells are also present at the invasive borders of tumors and in the lymph nodes and lymphoid structures neighboring the TME (2). In breast and ovarian cancer, the presence of B cells is associated with a good prognosis (60). On the other hand, the presence of immunosuppressive regulatory B cells is associated with skin cancer and may promote lung metastasis, suggesting a type-specific effect of B cells on cancer (61). Finally, NKs are cytotoxic lymphocytes capable of killing tumor cells without antigen presentation (50). NKs control tumor growth by providing innate immunity to the sites of transformed tumor cells and inducing cytotoxicity (62,63).

Overall, TME stromal cells, namely CAFs, ECs and IICs, and their secretome contribute to the growth and development of tumors (14,15). Notably, the complexity of interactions between cancer and TME cells demonstrates remarkable tumor mass heterogeneity (64). In their review, Koppensteiner *et al* (65) discussed how negative anticancer immune responses may result from the interactions between CAFs and T cells. On the other hand, Mun *et al* (66) reviewed the positive and negative relationships between immune and stromal cells of the TME. Despite the advancement in technologies capable of studying the TME at the single-cell level (67), a detailed understanding of all tumor-TME connections remains largely lacking. Therefore, anticancer strategies that only target one cell population are inadequate, and need to be fully updated in line with such rapid discoveries in TME biology.

ECM. The ECM is a dynamic network of interconnected macromolecules in which the cells reside (10,68). It comprises minerals, an array of extracellular proteins, glycosaminoglycans, and other proteoglycans (PGs) and polysaccharides (10,68). The main components include collagens, elastins, fibronectins, laminins, hyaluronic acid (HA), heparan sulfate, chondroitin sulfate and keratan sulfate (10,68). This intricately organized structure forms a supportive substrate that serves as a biological scaffold for surrounding cells and as an anchor for cell attachment to the ECM (at focal adhesions and hemidesmosomes) (69-71). The ECM also regulates cell-cell and cell-matrix bidirectional signal transduction, including transport and mechano-transduction (16,72). This is partly due to the ECM being a reservoir for EVs and soluble bioactive effectors, such as cytokines, growth factors, chemokines and enzymes (73-75). ECM components and ECM-associated factors collectively make up the ECM 'matrisome', which is responsible for regulating transport, proliferation, motility, survival, homeostasis and other fundamental cellular mechanisms (76-79).

The ECM is present in all tissues and organs in the body, including tumors and the TME (68). Its organization is both cell-specific and tissue-specific (80). The ECM composition within tumors is heterogeneous and accounts for up to 60% of the tumor mass (10). Both cancer cells and stromal cells contribute to the production of the tumor ECM (77,81). However, CAFs remain the primary source of ECM in the TME (10,20,74,82). Cancer ECM differs from normal tissue ECM in composition, organization, density, and physical and biochemical properties (68). These differences are also noted across tumors of different metastatic potentials (83,84). For instance, primary and pre-metastatic cancers increase ECM production (74,85-88). This TME fibrotic response, clinically termed desmoplasia, results in a substantial accumulation of collagens, fibronectins and PGs in benign and malignant tumors (89,90). Collagen and collagen-processing enzymes, laminins, integrins, MMPs and HA are among the most enriched ECM proteins in tumors (10,62,78,81,91,92).

On the other hand, the shift between low and high molecular weight PGs in different solid tumors illustrates the association between the composition of the ECM and cancer grade (93). Similarly, the tumor environment favors the increase in collagen type I, III or V at the expense of collagen type IV in breast, ovarian, lung and ductal carcinoma (94-96).

Finally, the crosslinking of collagen, and other fibrillary proteins, such as elastins, renders the ECM denser and stiffer (10,74,91,97-99). Changes in the ECM may be induced by proteases (MMPs and cathepsins) or nonproteolytic enzymes (heparanases and hyaluronidases) secreted by tumor and stromal cells, by oxygen free radicals produced by IICs, or as a response to hypoxia and acidosis (16,77,100).

The upsurge in the production of ECM components with altered properties, in turn, reduces the diffusion of nutrients and metabolites, and modulates cytokine secretion (79,83,101). This creates a hypoxic tumor-promoting environment capable of stimulating proliferation, tumor growth, epithelial-to-mesenchymal transition (EMT), aggressiveness, resistance to cell death, evasion from the immune system, and invasion and tumor dissemination, among others (10,97,102). Overall, this highlights the need for potent ECM-targeting therapies.

EVs. EVs are cell messengers, which mediate the signaling cross-talk between a cell and its environment (103-105). Cancerous and non-cancerous cellular constituents of the TME, including the microbiome, communicate with one another by secreting soluble factors and/or releasing EVs (75,103,105-110). Therefore, EVs are an integral and functional non-cellular component of the TME (75,103,111,112). Briefly, EVs are membrane-enclosed particles subdivided into exosomes, microvesicles and oncosomes depending on their size, biogenesis, function, etc. (105,113). Exosomes are intraluminal vesicles destined for exocytosis (105). They exhibit a classic dish or saucer-like morphology with diameters ranging between 30 and 100 nm (17,114,115). As the name suggests, intraluminal vesicles are formed by the

inward budding of endosomal membranes inside the lumen of endosomes (17,114-116). Unlike exosomes, microvesicles are the products of the outward budding and fission of the plasma membrane (105,117,118). Their diameters range between 100 and 1,000 nm (105). By contrast, oncosomes are cancer-specific large EVs with diameters ranging between 1 and 10 μm (105,118,119). They shed off the 'non-apoptotic membrane blebs' of amoeboid cancer cells (105,120). All aforementioned biogenesis processes simultaneously result in the packaging of various cytosolic materials inside the EVs (105). Therefore, the cargo of EVs can comprise lipids, proteins and nucleic acids, such as DNA, mRNA, microRNA (miRNA), long non-coding RNA (lncRNA) and circular RNA (circRNA) (17,114-116,121,122).

Studies have demonstrated that all types of cells secrete EVs (75,103-106,117,123). However, the data suggest that cancer cells secrete more EVs than normal cells and that the load of EVs can increase with cancer grade and aggressiveness (124-126). For instance, hypoxic solid tumors secrete more EVs than non-hypoxic tumors and control the composition of the released EVs (126). The differential expression of wild-type or mutant p53 also impacts the secretion, size, and RNA and protein load of cancer-derived EVs (127,128). This is in line with reports demonstrating that the molecular composition of EVs and their effect on cancer hallmarks and response to chemotherapy depends primarily on the origin of the secretory cells (104,110,121,126,129-133). Furthermore, emerging evidence has revealed that EVs derived from different cell types exhibit distinct content profiles (131). Researchers could even differentiate between EVs originating from various subtypes of the same lineage, namely between the exosomes of lymph node metastasis-derived LNCaP (lymph node carcinoma) and VCaP (vertebral) prostate cancer cell lines (134).

EV cargo commonly includes type-specific and or stage-specific cancer biomarkers (117). For instance, EVs isolated from patients with ovarian cancer express distinct protein and miRNA sets compared with those found in cancer-free individuals (114). Similarly, specific RNA classes are particularly abundant in EVs of patients with triple-negative breast cancer compared with those with hormone receptor-positive breast cancer (124,135). Several other non-coding RNAs have been demonstrated to serve a role in tumor development (136). The long non-coding lymph enhancer-binding factor 1-antisense RNA1 has been found to act as a tumor promoter in a number of malignant tumors; however, it acts as a tumor suppressor in myeloid cancer (137). Furthermore, circ0021205 is a non-coding circRNA that promotes cancer progression in cholangiocarcinoma and non-small cell lung cancer (NSCLC) (138). In patients with colorectal cancer (CRC), upregulated miRNA-7062-5p inhibits G protein-coupled receptor 65, thus promoting osteoclast genesis during bone metastasis (139). Long intergenic non-coding RNA (LINC)02257 is a survival-associated enhancer RNA serving important immunotherapy roles in a number of cancer types (140). In lung adenocarcinoma, the LINC00987/A2M axis acts as an effective tumor suppressor, as well as a biomarker for the evaluation of the tumor immune microenvironment or the prognostic and therapeutic potential (141).

Further observations have revealed that the expression of the polymerase I and the transcript release factor glioma biomarker in EVs is positively associated with tumor grade (142). The clinical expression of programmed cell death ligand-1 (PD-L1) in EVs is associated with diverse cancer types, including melanoma and colon cancer (143-145). Finally, researchers have reported that both surgery and radiation treatments change the composition of EVs, thus demonstrating the close association between tumors and their TME (132,142). These data collectively highlight the growing interest in EVs as promising targets cancer for diagnosis, prognosis and treatment.

Microbiome. The microbiome is a component of the TME, which has become a subject of interest in cancer research recently (18,146). By definition, the microbiome represents 'the characteristic microbial community occupying a reasonably well-defined habitat, which has distinct physico-chemical properties' (146). In principle, only the microbial community present in or around the tumor tissues can strictly be labeled as the microbiome of the TME (18). However, microbes at distant sites from tumors (such as the gut) have also emerged as critical modulators of cancer onset and progression (147-153). Therefore, this section reviews the composition and role of all microbes with direct or indirect effects on cancer to overcome the shortcomings of the TME-centric view and highlight the importance of the different layers of cancer environment beyond the immediate spatial boundaries of tumors (i.e., at the level of what is now known as the tumor organismal environment) (154). The microbiome is: i) A fingerprint for tumors; ii) a major factor in the pathology of the disease; and iii) a diagnostic tool to predict the response to treatment of patients (150,151,155-164). Researchers have reported substantial differences in the microbiome composition of normal tissues compared with tumor tissues (162,163,165-173). These observations have revealed tumor-type specific, tumor subtype-specific and grade-specific bacteria spanning several major phyla (162,163,165-173). Furthermore, the data suggest that the majority of bacteria of the tumor microbiome of different solid tumors are intracellular (165).

The hypoxic nature of tumors contributes to the abundance of anaerobic bacteria, which are unable to survive in an oxygen-rich environment (174). The anaerobic *Fusobacterium* genus is particularly abundant in various carcinomas, including oral, colorectal and bladder cancer (168,171,173-175). For instance, several species of *Fusobacterium*, namely, *F. nucleatum*, *F. mortiferum* and *F. necrophorum*, have been identified in metastatic colon cancer tissues, while *F. nucleatum* and *F. periodonticum* are a signature of oral cancers (174,175). Further highlighting the tumor-specificity, the *Bacteroides* depleted in colon cancers were, by contrast, profuse in rectal tumors (175,176). In addition, rectal tissue sample analysis revealed a distinct microbiome in cancer tissues compared with normal tissues (176,177). *Phascolarctobacterium*, *Parabacteroides*, *Desulfovibrio* and *Odoribacter* species are abundant in tumors, whereas *Pseudomonas*, *Escherichia*, *Acinetobacter*, *Lactobacillus* and *Bacillus* species are primarily found in healthy tissues (176). Similarly, the microbiome of the breast cancer TME indicated the enrichment in specific microbes (*Actinobacteria*, *Listeria*

spp, *Haemophilus influenzae*, *Anaerococcus*, *Caulobacter* and *Streptococcus*) and the depletion of others (*Propionibacterium* and *Staphylococcus*) (164,177). Interestingly, in lung cancer, the genera *Streptococcus* and *Staphylococcus* exhibit the same expression trend as that observed in breast cancer (163). Specifically, *Streptococcus* and *Neisseria* genera thrive in cancer, unlike *Staphylococcus* and *Dialister*, which favor normal tissues (163). Different microbes, including *Fusobacterium*, *Streptococcus* and *Bacteroides*, are also differentially expressed in bladder cancer, prostate cancer and other cancer types (171,172,178).

Finally, mycoplasma species, such as the *Mycoplasma hyorhinis*, also exhibit disparate manifestation in tumor tissues compared with normal tissues, and are associated with tumor-promoting properties, resistance to treatment and poor prognosis (179-186). These reports emphasize the importance of identifying and characterizing the different genera of the tumor microbiome to determine potential biomarkers and therapeutic targets (146,154,163,176,177).

3. Cancer hallmark capabilities of TME stromal cells

In 2000, Hanahan and Weinberg (187) proposed a conceptual categorization to organize the distinctive key traits of cancer. They noticed that all cancer cells acquire six fundamental functional capabilities, which they named 'The Hallmarks of Cancer' (187). These fundamental hallmarks are: Sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis (Fig. 2). Due to the remarkable progress in cancer research, Hanahan and Weinberg (187) incorporated additional 'emerging cancer hallmarks', which are: Evading immune destruction and reprogramming energy metabolism (Fig. 3). In addition, 'enabling characteristics' that facilitate acquisition of fundamental and emerging hallmarks, were also introduced. These are: Genome instability and mutation and tumor-promoting inflammation (Fig. 3) (4,188). TME stroma markedly contribute to cancer hallmarks (6). The reciprocal communications between TME components and cancerous cells mediate cancer development (5). This section reviews the various mechanisms by which TME stromal cells influence cancer hallmarks and highlights the complexity of cancer targeting.

Sustained proliferative signaling. The mutational capabilities of cancer cells have been recognized as the core factor for sustaining cancer proliferative signaling (187). Stromal cells serve an important role in augmenting oncogenic mutations, and thus, the hyperproliferation of cancer cells by driving mitogenic signals (Fig. 2) (6,7,187).

Different CAF subtypes exhibit diverse functions and affect multiple cancer hallmark capabilities (30). CAFs secrete mitogenic epithelial growth factors (EGF), fibroblast growth factors (FGF), hepatocyte growth factors (HGF) and other signaling proteins that drive cancer cell proliferation (189-191). HGF secretion results in the activation of mesenchymal epithelial transition factor (a HGF receptor), and thus, the activation of the MAPK and PI3K/AKT survival signaling pathways (192). These pathways are also activated by CAF-secreted vascular cell adhesion molecule 1 (VCAM1) and promote the proliferation of lung cancer cells (193). Furthermore, leptin, a cytokine secreted by CAFs, binds to its receptor, activates MAPK/ERK1/2 and PI3K/AKT signaling pathways, and promotes proliferation of cancer cells in NSCLC (194).

Angiogenic vascular cells (AVCs) also directly support cancer hyperproliferation. Experimentally stimulating angiogenesis results in increased proliferation of cancer cells (195,196). These ECs secrete growth-promoting factors that influence multiple hallmarks, including proliferation, invasion and metastasis (further described subsequently) (197). Similarly, IICs stimulate neoplastic cell proliferation by secreting mitogenic growth factors, such as TNF-α, ILs, chemokines, heparins and histamine, in addition to EGF, FGF and TGF-β [reviewed in (198)]. Additionally, IICs secrete metallo- and serine proteases that cleave and modify the ECM leading to chronic paracrine and juxtacrine mitogenic activity sustaining cell proliferation (199).

Evading growth suppressors. Adhesion molecules at cell-cell and cell-ECM connections transmit extrinsic growth-suppressing signals to cancer cell cycle machinery (5,187). As aforementioned, disruption of adhesion molecules is induced by IIC-secreted metallo- and serine proteases and heparinase, which cleave and modify the ECM (10). ECM modifications disrupt the transmission of antigrowth signals and the formation of growth-suppressing adhesion complexes (200-202).

Notably, fibroblasts naturally exhibit extrinsic growth-suppressing capabilities to maintain epithelial homeostasis (15). In the TME, CAFs secrete high amounts TGF-β and ECM components [reviewed in (203)], thus stimulating mechanical remodeling of the ECM. Therefore, it was hypothesized that CAFs may acquire a 'loss-of-function' phenotype as they are reprogrammed to sustain cancer hallmarks (5). TME components can also affect tumor growth-suppressing signals by regulating cell cycle check points (204). The TME of renal cell carcinoma (RCC) exhibits FGF-dependent degradation of p27Kip1, a cyclin-dependent kinase inhibitor (204). This leads to enhanced tumor cell proliferation (Fig. 2) (204).

Resisting cell death. Cancer cells foster an intrinsic ability to resist cell death programs, mainly apoptosis (187). Stromal cells of the TME confer an additional protective mechanism for cancer cells to resist cell death and targeted cytotoxic therapy (Fig. 2) (6). CAFs mediate cancer cell survival by secreting survival factors [insulin-like growth factor 1 (IGF-1) and insulin-like growth factor 2 (IGF-2)] (15). CAFs also form neoplastic ECM that selectively transmits survival signals and promotes epithelial cell migration (199).

The prominent role of CAFs in resisting cell death is demonstrated by the contribution of CAFs to chemoresistance (15). CAFs co-cultured with NSCLC cell lines have been demonstrated to resist apoptosis and enhance chemoresistance (205,206). This is achieved by the secretion of stromal cell-derived factor-1 (SDF-1) and the expression of exosomal miRNA-103a-3p, which lead to Bcl-xL upregulation and BCL2 antagonist/killer 1 downregulation, respectively (205,206). In a separate study, Sun and Chen (207) demonstrated that CAF-secreted C-C motif chemokine ligand (CCL)5 upregulated HOX transcript antisense RNA (HOTAIR)

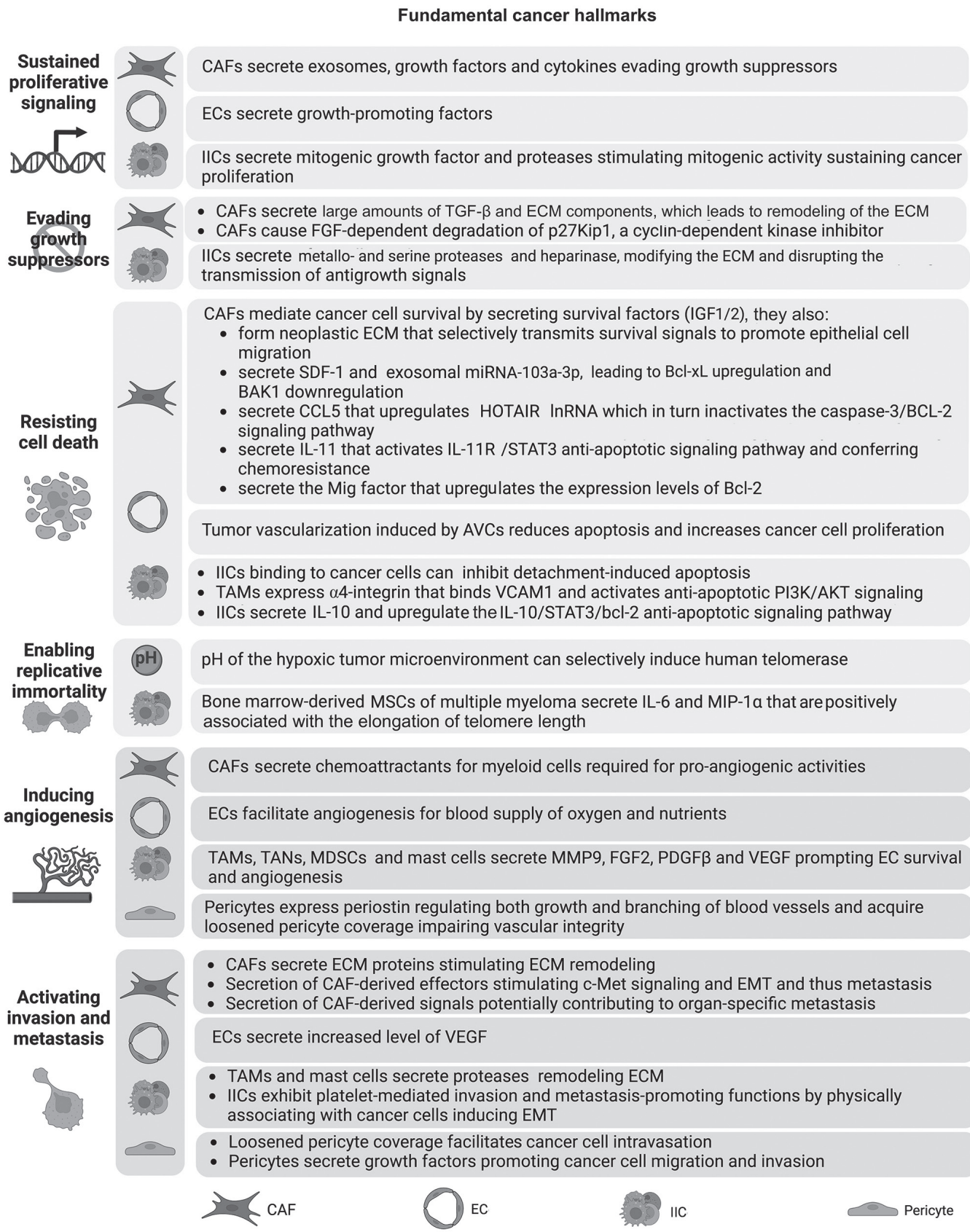

Figure 2. Contributions of TME components to fundamental hallmarks of cancer. This schematic illustrates the contribution of TME cell types to: i) Sustained proliferative signaling; ii) evading growth suppressors; iii) resisting cell death; iv) enabling replicative immortality; v) inducing angiogenesis; and vi) activating invasion and metastasis. Created with BioRender.com. APCs, antigen presenting cells; AVCs, angiogenic vascular cells; BAK1, BCL2 antagonist/killer 1; CAFs, cancer-associated fibroblasts; CCL, CC-chemokine ligand; ECs, endothelial cells; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; FGF, fibroblast growth factor; HOTAIR, HOX transcript antisense RNA; IGF, insulin growth factor; IICs, infiltrating immune cells; lncRNA, long non-coding RNA; MDSCs, myeloid-derived suppressor cells; Mig, monokine induced by IFN-γ; MIP, macrophage inflammatory protein; miRNA, microRNA; MDSC, myeloid-derived suppressor cells; MSC, mesenchymal stem cells; PDGF, platelet-derived growth factor; SDF, stromal cell-derived factor; TAMs, tumor-activated macrophages; TANs, tumor-activated neutrophils; TME, tumor microenvironment; VCAM1, secreted vascular cell adhesion molecule 1.

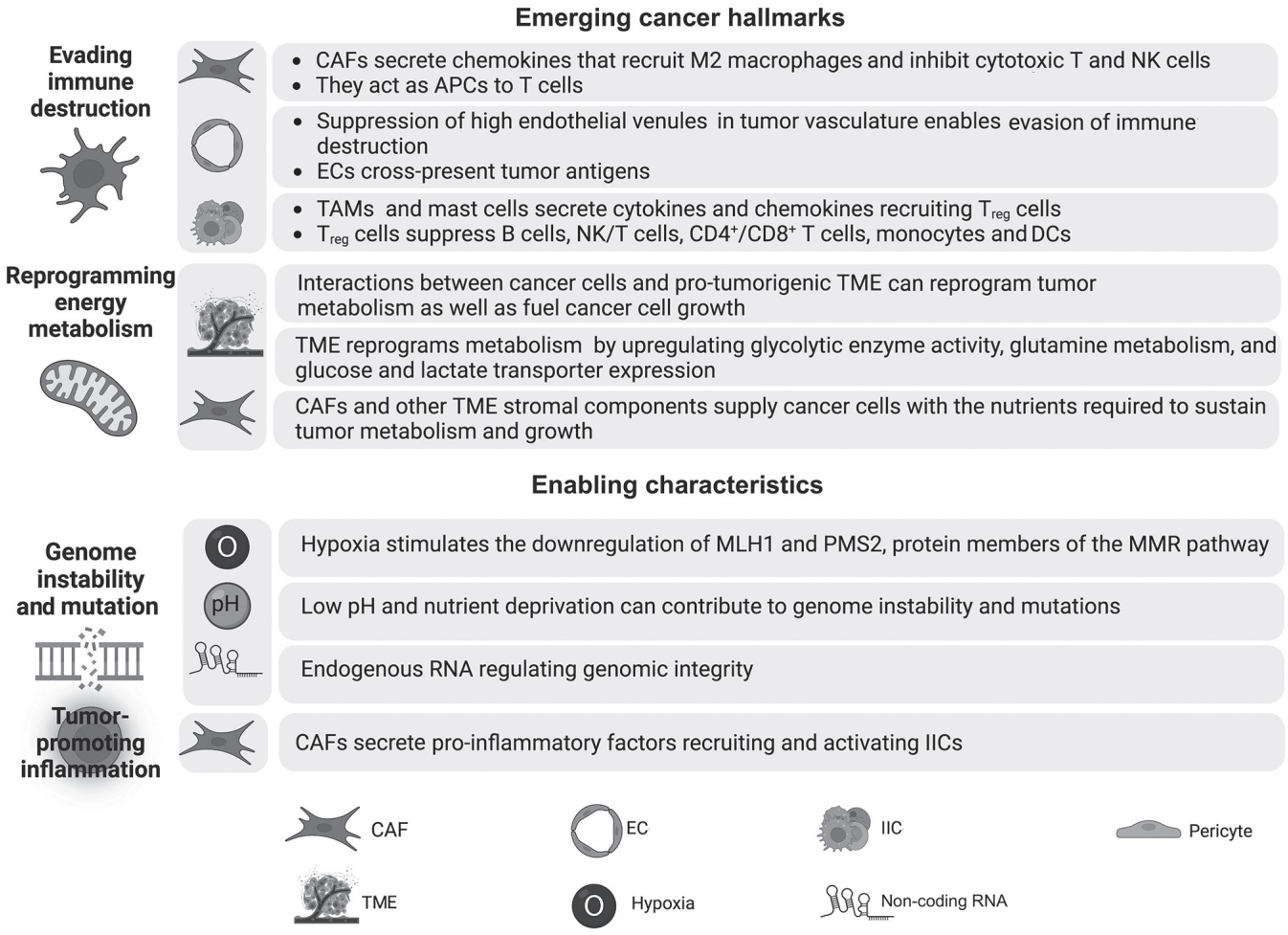

Figure 3. Contributions of TME components to emerging hallmarks of cancer and enabling characteristics. This schematics illustrates the contribution of TME components to: i) Evading immune destruction; ii) reprogramming energy metabolism; iii) genome instability and mutation; and iv) tumor-promoting inflammation. Created with BioRender.com. APCs, antigen presenting cells; CAFs, cancer-associated fibroblasts; DCs, dendritic cells; ECs, endothelial cells; HEVs, high endothelial venules; IICs, infiltrating immune cells; MLH1, mutL homolog 1; MMR, mismatch repair; NK, natural killer cell; PMS2, PMS1 homolog 2, mismatch repair system component; TAMs, tumor-activated macrophages; TME, tumor microenvironment; T_{reg}, regulatory T.

lncRNA expression. HOTAIR, in turn, inactivated the caspase-3/BCL-2 signaling pathway in these cells conferring chemotherapy resistance in NSCLC cells (207). Additionally, the chemotherapeutic drug, cisplatin, induces CAF-secreted IL-11 in lung adenocarcinoma (208). IL-11 activates the IL-11 receptor/STAT3 anti-apoptotic signaling pathway (208). The monokine induced by IFN-γ factor is a CAFs-secreted chemokine that has also been demonstrated to upregulate the expression levels of Bcl-2 and protect Tca8113tongue squamous cell carcinoma cells from heat-induced apoptosis (209).

Tumor vascularization induced by AVCs reduces apoptosis, thus increasing cancer cell proliferation (5). This phenotype is altered by the administration of vascular disrupting agents that increase cell death in treated cancer (210). Binding of IICs to cancer cells can also inhibit detachment-induced apoptosis (5). TAMs, on the other hand, express α4-integrin that binds VCAM1 expressed on breast cancer cells (211). This interaction initiates a signaling pathway that activates anti-apoptotic PI3K/AKT signaling and resists apoptosis (211). In addition, IICs secrete cytokines, leading to cell death resistance (212). For instance, TAM-secreted IL-10 is associated with elevated Bcl-2 expression via upregulation of the IL-10/STAT3/bcl-2 anti-apoptotic signaling pathway (212). This leads to increased proliferation and is associated with drug resistance of breast cancer (212).

Enabling replicative immortality. Shortening of telomeric DNA obstructs cellular replication and triggers senescence or apoptosis (5). Cancer cells, however, need to insure limitless replication as a defense mechanisms to overcome normal senescence caused by telomere shortening (4,5). Therefore, cancer cells activate telomerases that stabilize telomere length and confer replicative immortality (4,213). This critical trait occurs in >90% of cancers (213). Telomerase activation is enhanced by the upregulation of the human telomerase reverse transcription (*hTERT*) gene (214). The pH of the hypoxic TME can selectively induce human telomerase (215). At present, there is little evidence for the contribution of TME stromal cells to stabilizing telomeres in cancer cells (5). For instance, bone marrow-derived mesenchymal stem cells (MSCs) of multiple myeloma secrete IL-6 and macrophage inflammatory protein (MIP)-1α (216). Li *et al* (216) provided evidence of a positive association between IL-6 and MIP-1α secretion and the elongation of telomere length. MSCs may thus facilitate

multiple myeloma development (216). Further research is required to investigate whether other TME cellular components can regulate telomerase activity and enable replicative immortality.

Inducing angiogenesis. Angiogenesis in chronic inflammation is illustrated by constitutive activation of pro-angiogenic factors (37). In tumors, it is regulated by different components of the TME, such as CAFs, ECs, different IICs and pericytes, which secrete angiogenesis-inducing factors (Fig. 2) (2,5,6,37). Myeloid cells secrete soluble mediators that impact EC survival and new vessel remodeling (50). For instance, TAMs control tumor angiogenesis by producing VEGF-A (50,217), the bioavailability of which depends on TAM-secreted MMP-9 (218). Mast cells, on the other hand, secrete VEGF, histamine and heparin, thus regulating tumor angiogenesis (50). Mast cells also secrete proteases, such as MMP-9 and tryptase, which in turn activate pro-angiogenic signaling pathways (218-220). In addition to the secretion of pro-angiogenic factors, CAFs synthesize ECM proteins that sequester angiogenic growth factors and ECM-degrading enzymes (15). For example, in hepatocellular carcinoma, CAFs secrete VEGF, regulating the enhancer of zeste homolog-2/vasohibin 1 pathway, thus promoting angiogenesis (221). CAFs also regulate tumor angiogenesis by secreting chemoattractants for myeloid cells (5,222). Additionally, pericytes promote angiogenesis in glioma by expressing periostin, which regulates both growth and branching of blood vessels (223).

Activating invasion and metastasis. A key feature of cancer cells is the ability to spread throughout the body by invasion and metastasis (187). Cancer cells and tumor stromal cells can mediate local invasive growth or seeding metastases at distant sites (2,6,7). Tumor vasculature upregulation of VEGF loosens tight junctions between ECs and reduces pericyte coverage (62,224). This impairs vascular integrity and facilitates cancer cell intravasation into circulation (62). Hypoxia, induced by hypoxia-inducible factors, then triggers tumor dissemination and metastasis (224,225). Furthermore, pericytes in the TME activate TGF-β receptors (226). The subsequent TGF-β response initiates an autocrine activation loop (226). Analysis of the secretome of these activated pericytes has revealed upregulation of IGF-binding protein-3, a key paracrine factor that has been demonstrated to promote cancer cell migration and invasion (226). Additionally, proteases secreted by TAMs and mast cells remodel ECM components, promoting tissue invasion and dissemination (227,228). Soluble factors secreted by IICs also contribute to this hallmark. For instance, TNF-α, secreted by IICs, activates downstream JNK and NF-κB signaling cascades, ultimately enhancing MMP-2 and MMP-9 activity (229). Equally importantly, IICs mediate cancer metastasis by inhibiting the expression of metastasis suppressor genes. For example, IICs inhibit maspin, a serine protease inhibitor, which normally acts as a tumor suppressor by increasing cell adhesion to extracellular matrix. Thus, maspin inhibition negatively regulates tumor migration and invasion (230,231).

Platelets also exhibit invasion and metastasis-promoting functions by physically associating with cancer cells, inducing EMT, enabling extravasation and forming secondary tumors at metastatic sites (232). Different components within the ECM might also initiate or enhance EMT-like processes (10). Collagen reorganization, PG expression and protease-mediated ECM macromolecule degradation affect cell invasion and metastasis (16). Finally, CAFs are also implicated in activating invasion and metastasis (15). CAF-derived effectors, such as HGF and TGF-β, trigger/activate c-Met signaling and EMT, respectively, mediating tumor invasion and metastasis (233). In breast cancer cells, IGF-1 and CXCL12 secreted by CAFs stimulate cancer metastasis to the bone (234). ECM proteins and remodeling enzymes produced by CAFs are also considered to support cancer invasion by modifying the structure and function of the ECM (7). One study revealed that cancer cells circulate in the blood alongside CAFs derived from the primary tumor (235). It has also been suggested that CAF-derived signals may control organ-specific metastasis of breast tumors (236). Therefore, CAFs are promising targets in pre-clinical therapeutic strategies in patients with breast cancer (236).

Evading immune destruction. Effective destruction of cancer cells necessitates an influx of immune cells, including T_{reg} cells, NKs and NK T cells (5,187). However, tumor vasculature is considered to attenuate the influx of immune cells, rendering them incapable of killing cancer cells (5). This is partly mediated by high endothelial venules (HEVs), which typically support the homeostatic trafficking of immune cells during routine immune surveillance (43). Absence of HEVs in tumor vasculature allows cancer cells to evade immune destruction (237-239).

In the TME stroma, ECs cross-present tumor antigens and stimulate the development of a tolerizing, hence immunosuppressive, environment (240). CAFs are also essential factors that allow the tumor to evade immune destruction (Fig. 3). CAF-derived interleukins (IL-4 and IL-6) and chemokines (TGF-β and CXCL8) recruit M2 macrophages and inhibit cytotoxic T lymphocytes (CTLs) and NK cells (240,241). Among the intricate tumor-promoting roles of CAFs is the ability to act as APCs to T cells (20). In addition to ECs and CAFs, IICs serve an important role in enabling cancer to avoid immune destruction (44). IICs prompt immunosuppressive activity that blocks the antitumor effect of CTLs and NK cells (14). Among these IICs are TAMs, which lack cytotoxic activity, and release immunosuppressive factors and suppress $CD8^+$ T cell proliferation (242-244). CCL22 secreted by TAMs recruits T_{reg} cells, which enable cancer cells to evade immune destruction (245). T_{reg} cells can also be recruited by other cytokines, such as CCL2 and TGF-β, secreted by mast cells and other immunosuppressive IICs (50,246). T_{reg} cells can suppress B cells, NK/T cells, $CD4^+$/$CD8^+$ T cells, monocytes and DCs (247). T_{reg} cells suppression can be direct through cell contact or immunosuppressive soluble mediators or indirect by suppressing APCs (14). In particular, T_{reg}-induced inhibition of $CD4^+$ T cells is mediated by inhibition of receptor-induced calcium, nuclear factor of activated T-cells and NFκB signaling (50,247). Tumors expressing high levels of immunosuppressive cytokines are often associated with decreased $CD8^+$ T cell populations and poor survival (242). Reciprocal communication occurs between IICs and other TME stromal cells where M2 macrophages secrete EGF, FGF and TGF-β

to support CAF survival and activation (240). Finally, TAM, MDSC and mast cell secretion of MMP9, FGF2, PDGFβ and VEGF prompts EC survival and angiogenesis (240).

Reprogramming energy metabolism. Metabolic differences between normal and cancer cells have long been observed (4,248). However, scientists have revealed that tumors are metabolically heterogeneous and can be grouped into different metabolic phenotypes (249-251). This heterogeneity is likely to stem from differences in glycolytic and mitochondrial reprogramming (249-253).

Advancements in physiologic magnetic resonance imaging of tumors have demonstrated that metabolic phenotypes remain flexible and can switch depending on the surrounding TME conditions and the nature of the exchanged signaling molecules (254). Therefore, the plasticity is contingent on the availability of nutrients and anaplerotic molecules (255). Consequently, interactions between cancer cells and pro-tumorigenic TMEs can reprogram tumor metabolism and fuel cancer cell proliferation (Fig. 3) (255).

Substantial evidence indicates that tumors can reshape TME metabolism and even the patients' organismal metabolism and homeostasis (256-258). For instance, cancer cells can induce aerobic glycolysis in TME CAFs and stromal cells through the reverse Warburg effect (259). Tumor-derived metabolites can also exert immunosuppressive effects that block the activation and differentiation of various immune cells of the TME (260,261). In return, CAFs and other TME stromal components supply cancer cells with the nutrients required to sustain tumor metabolism and growth (260).

In summary, most findings highlight the ability of the metabolism to reshape the TME, whereby cancer cells turn the normal TME into a permissive tumor-promoting environment and a nutrient factory to be used for efficient energy production (259,262). Therefore, it is crucial to review the metabolic features of TME components and to identify critical factors behind metabolic reprogramming.

Cancer cell metabolism. Cell metabolism refers to the set of chemical reactions that sustain the normal functions of cells, including: i) Production of macromolecule building blocks; ii) energy harvesting; and iii) the elimination of metabolic wastes (248,263). Cells rely on nutrient uptake and degradation to generate ATP, the energy currency of cells (248,263). Cancer cells are fast replicating cells with high anabolic and catabolic energy requirements (4). These cells can rewire their metabolism to maintain sufficient ATP production and ensure proliferation and survival (264-266). Metabolism reprogramming is achieved by a complex interplay of various signaling pathways, which can be intrinsically triggered by oncogenes or extrinsically influenced by the inhospitable TME (264,267-269). One such mechanism is the significant increase in glucose uptake, typically observed in positron emission tomography scans of patients (270). Another major metabolic difference between normal and cancer cells is the fate of glucose. Normal cells harvest glucose energy through aerobic respiration, a four-stage process that combines glycolysis, pyruvate oxidation, the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) (248,263). In this route, glucose is oxidized into carbon dioxide and water.

On the other hand, cancer cells switch to aerobic glycolysis, which converts glucose into pyruvate and then lactate via the lactate dehydrogenase enzyme (248,265). This phenomenon, also known as the Warburg effect or the Warburg phenotype, is commonly stimulated by energy demands of rapid proliferation and/or hypoxia (251,270,271). To the best of our knowledge, it is still unclear whether the Warburg effect is a cause or consequence of carcinogenesis (272). However, this phenotype allows faster ATP production than OXPHOS and may provide a selective advantage for cells, specifically in the hypoxic TME (273,274).

Another important benefit of aerobic glycolysis is that the generated glycolytic metabolites facilitate the biosynthesis of sugars, amino acids, nucleotides and fatty acids critical for rapid cell proliferation (248). These advantages explain why high amounts of aerobic glycolysis have been detected in proliferating cells and progressive cancer types (270,275). The TCA cycle is also active in these cells, with the resulting substrates rerouted for use in *de novo* synthesis pathways, particularly lipogenesis (276).

Cancer cells heavily rely on the uptake and metabolism of glutamine as an alternative carbon source to glucose (276). Glutamine, the amide derivative of glutamate, is one of the most abundant nutrients in the plasma (255,276). Glutaminolysis converts glutamine to lactate and NADPH (255,276). In normal cells, glutamine is used as a nitrogen source to synthesize nucleotides and other non-essential amino acids (264). However, in cancer cells, glutamine metabolism exceeds the needs of cells for *de novo* proteins and nucleotides production (276). Instead, the data suggest that glutamine metabolism allows the cells to use glucose-derived carbon and TCA cycle intermediates as precursors for fatty acid synthesis (276). This is achieved by continuous replenishment of the TCA cycle intermediates (mainly oxaloacetate) through a set of five chemical reactions, which combined, form the anaplerosis process (276).

Drivers of metabolic reprogramming. Metabolic reprogramming in the TME is driven by oncogenic alterations in cancer cells, as well as by changes in the signaling of normal cells (269). Typically, these modifications impact the dynamics underlying nutrient uptake and bioenergetic gene expression (269). For instance, constitutive activation of the PI3K-AKT-mTOR signaling pathway has been directly linked to glycolysis stimulation in cancer cells and in CAFs (269,277,278).

Similarly, there is a clear association between Myc transcription factor and the expression of various metabolic genes, glycolytic enzymes, and glucose and glutamine transporters (279). Specifically, Myc activates glucose and glutamine metabolism, as well as purine, pyrimidine, fatty acid and cholesterol synthesis (269,280-282). Oncogenic KRAS also triggers TME metabolic reprogramming by upregulating glycolytic enzyme activity, glutamine metabolism, and glucose and lactate transporter expression (283-285). In addition, KRAS stimulates nucleotide biosynthesis by channeling glycolytic metabolite intermediates to the pentose phosphate pathway (284-286). Furthermore, KRAS sustains autocrine and paracrine signaling by inducing the expression of cell surface receptors responsible for upregulating type I cytokine receptors (269,287,288). KRAS promotes micropinocytosis

and autophagy processes for nutrient scavenging by cancer cells (289,290). On the other hand, loss of p53 function in cancer cells increases glycolysis, glucose transporters and lipid metabolism, among others (291-294). Overall, cells of the TME have several distinct metabolic signatures that are directly associated with tumor growth and represent promising targets for cancer therapy.

Genome instability and mutation. Genome maintenance in normal cells results in a low rate of spontaneous mutations (4). Compromised check points and sensitivity to mutagenic agents increase the rate of mutation (4). The TME is characterized by hypoxia, low pH and nutrient deprivation (295). These conditions contribute to genome instability and mutations (Fig. 3) (295). For instance, hypoxia stimulates the downregulation of mutL homolog 1 and PMS1 homolog 2, mismatch repair system component, which are protein members of the mismatch repair pathway and required to rectify DNA mismatch errors (296,297). Therefore, hypoxia is a major factor inducing substantial DNA damage leading to genetic instability of solid tumors (295).

In addition to hypoxia, it has been recently shown that a novel competing network of competing endogenous RNA can regulate genomic integrity (298). Therefore, these genome instability-related lncRNAs may act as biomarkers for genetic instability, immunetherapy prognosis and therapeutic sensitivity in colon adenocarcinoma and colon cancer (298,299).

Tumor-promoting inflammation. Chronic inflammation is a major contributor to cancer, and the inflammatory response can be triggered by various factors, including pathogens, carcinogen exposure and imbalanced immune regulation (Fig. 3) (300). Immune cells can either exert an antitumor or protumor activity depending on the polarization state. For example, Th1 cells act as antitumor agents, whereas Th17 subsets of $CD4^+$ T cells act as tumor-promoters (300,301). On the other hand, anti-inflammatory M2 macrophages and N2 neutrophils are both tumor-promoting cells that secrete cytokines, proteases and growth factors, contributing to tissue remodeling and angiogenesis, eventually leading to the conversion of cells into malignant cells and cancer formation (300,301). TAMs, an M2 subtype, produce VEGF-C and VEGF-D, which leads to peritumoral inflammation and lymphangiogenesis in human cervical cancer (302).

CAFs exert pleiotropic functions in immunomodulation mainly by secreting a range of pro-inflammatory factors, which recruit and activate IICs (191,303,304). In 2010, Erez *et al* (191) revealed that the CAF secretome causes tumor-promoting inflammation in a NF-κB-dependent manner. iCAFs secrete various chemokines and cytokines, such as CXC-chemokine ligand (CXCL)1, cyclooxygenase-2, IL-1, IL-6 and SDF-1, and receptors, such as IL 6 receptor α and IL-6 cytokine family signal transducer, which add to the tumor-promoting inflammatory milieu of the TME (305-308). In addition to TGF-β production, CAFs secrete thymic stromal lymphopoietin, favoring Th2 cell polarization, which is associated with poor prognosis (309). Overall, TME-mediated inflammation influences tumor development, invasion, angiogenesis, metastasis and immunosuppression (191,305,306). Therefore, targeting inflammation may be a promising tool for cancer treatment.

Therefore, cancer development is mediated by TME components that contribute to major cancer hallmarks, including tumor proliferation, survival, angiogenesis, invasion and metastasis (2,66,240). Overall, these findings have prompted researchers to target TME cells for cancer treatment alone or in combination with conventional therapeutic modalities (9,67,310).

4. Targeting the TME for cancer therapy

Clinical anticancer therapeutic efficiency is limited due to several factors, including tumor heterogeneity and the ability of cancer cells to develop multidrug resistance (11). Another reason for this observation is that cancer cells exhibit different responses when moving from bench to bedside translational medicine (311). The cross-talk among tumor cells, stromal cells and other TME components adds to the complexity of efficient treatment (8). Increasing awareness of the role of the TME in tumor development brought about novel cancer therapy strategies targeting TME components (310). Additionally, combined therapies targeting more than one cell type or signaling pathway are also being investigated (11). The present review highlights the TME cells, signaling pathways and soluble factors that are targeted for cancer treatment. It also reviews anticancer drugs that are currently in clinical trials or show promising results for drug development.

Targeting CAFs. Membrane-bound serine protease FAP expression distinguishes tumor tissues from healthy tissues (30). Inhibitors selectively targeting FAP (FAPi) are currently in phase I and II clinical trials (http://clinicaltrials.gov). For instance, ^{68}Ga-DOTA-FAPI is being studied for FAP-based imaging and therapy using gallium-68 (312,313). FAP is also targeted by CD40 agonist (RO7300490) or 4-1BB agonist (RO7122290; phase I/II; NCT04826003; Table I). The latter resulted in activation of T and NK cells in the first-in-human phase I study, suggesting potential antitumor activity (314). An early phase I clinical trial is investigating the effect of combining FAPi with anti-neoplastic monoclonal antibodies (NCT01722149). More studies are warranted to determine the efficiency of targeting FAP-positive CAFs and tumor cells.

Targeting ECs. One main mechanism for inhibiting angiogenesis is targeting VEGF or VEGFR, alone or in combination with chemotherapeutic drugs (315). More than 400 interventional clinical trials are investigating the anticancer potential of VEGF targeting (based on http://clinicaltrials.gov; accessed, January 6, 2022). Promising results have been reported with the administration of the U.S. Food and Drug Administration (FDA)-approved bevacizumab (Avastin), an anti-angiogenic antibody that targets VEGF, and Bevacizumab-IRDye800CW, its fluorescent form (316,317). Combined administration with chemotherapeutic agents resulted in increased overall survival or progression-free survival (PFS) in CRC, NSCLC and breast cancer (315). Additionally, therapeutic strategies are currently considering the administration of two anti-angiogenic agents. For instance, a phase III trial carried out on patients with NSCLC is comparing the efficacy of two anti-VEGF antibodies, LY1008 and bevacizumab (Avastin), combined with the chemotherapeutic drugs paclitaxel and carboplatin (NCT03533127). In

Table I. Therapeutic agents targeting cancer-associated fibroblasts and vascular endothelial cells in interventional clinical trials.

Targeting strategy	Therapeutic agent	Therapeutic target	Therapeutic strategy	Cancer type	Phase	Clinical trial
Targeting fibroblasts	RO7122290	FAP targeted 4-1BB ligand	RO7122290 in combination with immunotherapeutic cibisatamab after pretreatment with chemotherapeutic obinutuzumab	Metastatic colorectal cancer	Phase I/II	NCT04826003
	^{68}Ga-DOTA-FAPI	FAP	Exploring the application value of positron emission tomography molecular imaging targeting FAP	Oral squamous cell carcinoma	Early recruiting	NCT05030597
	FAP-specific re-directed T cells	FAP	Transferred FAP-specific re-directed T cells are given directly in the pleural effusion	Malignant pleural mesothelioma	Early phase 1	NCT01722149
Targeting vascular endothelial cells	Cabozantinib	VEGFR2, RET and MET	Cabozantinib vs. placebo	Differentiated thyroid cancer	Phase III	NCT03690388
	Bevacizumab	VEGFA	Apatinib vs. placebo	Advanced/metastatic gastric cancer	Phase III	NCT01512745/ NCT00970138
			Oxaliplatin chemotherapy associated or not associated with the targeted therapies (anti-EGFR panitumumab and bevacizumab)	Metastatic colorectal cancer restricted to the liver (OSCAR)	Phase III	NCT02885753
			Tamoxifen citrate or letrozole with or without bevacizumab	Stage IIIB or stage IV breast cancer	Phase III	NCT00601900
			Bevacizumab in combination with paclitaxel compared with paclitaxel plus placebo	Her2-negative metastatic breast cancer	Phase III	NCT01663727
			Bevacizumab, pemetrexed, or a combination of bevacizumab and pemetrexed following carboplatin, paclitaxel chemotherapy and bevacizumab	Non-squamous non-small cell lung cancer	Phase III	NCT01107626
			Chemotherapeutic paclitaxel, nab-paclitaxel, or ixabepilone with or without bevacizumab	Stage IIIC or stage IV breast cancer	Phase III	NCT00785291
			Chemotherapeutic imatinib mesylate with or without bevacizumab	Gastrointestinal stromal tumor	Phase III	NCT00324987

Table I. Continued

Targeting strategy	Therapeutic agent	Therapeutic target	Therapeutic strategy	Cancer type	Phase	Clinical trial
	Bevacizumab, everolimus (also referred to as RAD001) and lapatinib	VEGFA, mTOR, and Her-1 and Her-2 receptor tyrosine kinase, respectively	Bevacizumab, everolimus (RAD001) and lapatinib as neoadjuvant docetaxel chemotherapy	Primary breast cancer	Phase III	NCT00567554
	QL1101 and Avastin® (also referred to as bevacizumab)	VEGF	QL1101 and Avastin, respectively, combined with paclitaxel and carboplatin	Non-squamous non-small cell lung cancer	Phase III	NCT03169335
	Bevacizumab and LY01008	VEGF	Bevacizumab and LY01008 combined with paclitaxel and carboplatin	Non-small cell lung cancer	Phase III	NCT03533127
	Everolimus (RAD001)	mTOR, HIF and VEGF	Alone	Metastatic renal cell carcinoma	Phase IV	NCT01266837/ NCT01206764
			Everolimus vs. placebo	Neuroendocrine tumors	Phase III	NCT00510068
			Belzutifan (anti-HIF-2α) vs. everolimus	Advanced renal cell carcinoma	Phase III	NCT04195750
	Sorafenib	VEGFR, Raf, PDGFR and Kit	Dovitinib (inhibitor of FGFRs) vs. sorafenib	Metastatic renal cell carcinoma	Phase III	NCT01223027
	Vandetanib (also referred to as ZACTIMA)	VEGFR, PDGFR and EGFR	ZACTIMA combined with docetaxel chemotherapy compared with docetaxel	Non-small cell lung cancer	Phase III	NCT00312377
	Cediranib	VEGFRs	Olaparib (PARP inhibitor) with cediranib or olaparib alone	Ovarian cancer	Phase III	NCT03278717
	BD0801	VEGF	BD0801 combined with paclitaxel chemotherapy vs. placebo combined with chemotherapy	Epithelial ovarian cancer	Phase III	NCT04908787
	Endostatin	VEGFR2	Endostatin combined with vinorelbine and cisplatin (NP) as neoadjuvant therapy	Non-small cell lung cancer	Phase IV	NCT02497118

Only interventional phase III and IV clinical trials are listed here for therapeutic agents targeting vascular endothelial cells. Data were acquired from the U.S. National Library of Medicine (http://clinicaltrials.gov; date accessed, January 6, 2022). FAP, fibroblast activation protein; FGFR, fibroblast growth factor receptor; HIF, hypoxia-inducible factor; MET, mesenchymal-epithelial transition factor; nab-paclitaxel, paclitaxel albumin-stabilized nanoparticle formulation; NP, vinorelbine and cisplatin; OSCAR, OlmeSartan and Calcium Antagonists Randomized; PARP, poly (ADP-ribose) polymerase; PDGFR, platelet-derived growth factor receptor; RET, rearranged during transfection.

addition to VEGF or VEGFR targeting, anti-angiogenic strategies include using multi-receptor tyrosine kinase inhibitors that stimulate the inhibition of VEGF, VGEFR, PDGFR or c-Kit (NCT03533127). The FDA-approved pazopanib (Votrient) is one example that inhibits VEGFR1/2/3 and c-Kit for the treatment of patients with soft tissue sarcoma and RCC (318,319). There are currently three phase IV clinical trials that target the VEGF pathway. Two of these trials studied the effect of everolimus (RAD001), an mTOR inhibitor, for the treatment of patients with advanced or metastatic RCC and (NCT01206764 and NCT01266837). Another study assessed endostatin, an inhibitor of tyrosine phosphorylation of VEGFR2 (320) in combination with the anti-mitotic vinorelbine and cisplatin for the treatment of patients with NSCLC (NCT02497118). Therapeutic agents targeting vascular ECs in interventional clinical trials (in phases III and IV) are listed in Table I.

Targeting IICs. Given the pivotal role of the immune system in cancer, several anti-inflammatory drugs have been designed to inhibit tumor-promoting inflammation (50). TME immune cells within the tumor are targets of several clinical phase trials (8,51,315). One approach is the inhibition of macrophage recruitment and activation in tumors (9). This involves targeting and inhibiting colony-stimulating factor-1 (CSF-1), a macrophage-recruiting mediator, and its receptor (CSF-1R) (51). This approach is associated with reduced infiltration of TAMs and MDSCs, and inhibiting tumor progression and metastasis (51). At present, there are >50 clinical trials targeting CSF-1 and 16 clinical trials targeting CSF-1R, according to https://clinicaltrials.gov (date accessed, January 6, 2022). One promising drug, vimseltinib, a CSF-1R inhibitor also referred to as DCC-3014, has reached a phase III clinical trial and is being assessed for its efficacy in treating patients with tenosynovial giant cell tumor (NCT05059262). TAMs are characterized by the high expression of CD204 (macrophage scavenger receptor class A) and folate receptor β (FRβ) on their surface (321). TAMs were successfully eliminated using an anti-CD204 antibody and a targeted FRβ-immunotoxin in mice and rat models, respectively (322,323).

Secondly, a promising approach is to target pro-tumorigenic factors secreted by IICs (310). The use of TGF-β inhibitors and immune checkpoint inhibitors (ICIs), such as PD-L1 antibodies, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies has been reported in a number of clinical phase trials (310,324). These strategies increase the infiltration of T cells into the tumor vicinity and the inhibition of T_{reg} cells (8,51,325,326). Furthermore, signal transducers and transcription factors that mediate tumor growth and survival, such as STAT3 and NF-κB, are targeted (50,51). Prolonged inhibition of NFκB may lead to immune deficiency and enhanced acute inflammation (315). Consequently, the progress of NF-κB inhibitor development is obstructed in clinical trials (315,327). Pro-inflammatory chemokines and cytokines are also targeted. In *in vivo* studies, receptor antagonists are used to inhibit C-C chemokine receptor 2 and CXC chemokine receptor 4 (229). Clinical trials are also evaluating inhibitors targeting other cytokines, such as IL-1, IL-6 and TNFα (51,315). One important example is the FDA-approved anakinra, an IL-1 receptor antagonist used to treat patients with pancreatic cancer and metastatic breast, colon and prostate cancer (NCT02550327/NCT03233776).

Enhancing the antitumor activity by increasing the infiltration of pro-inflammatory cells is also a promising approach (51). For instance, embelin, a small-molecule inhibitor of X-linked inhibitor of apoptosis protein, induces apoptosis and suppresses gastric carcinoma and pancreatic cancer *in vivo* (328,329). Mechanistically, this is achieved by increasing the infiltration of pro-inflammatory immune cells, such as Th1 cells, NKs and NK T cells, while decreasing the infiltration of immunosuppressive MDSCs and IL-8- and IL-6-positive immune cells (8,328,329). Therefore, it would be interesting to move this research forward in clinical trials.

Another approach is the use of pro-inflammatory cytokines for tumor treatment. One example is the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), which stimulates antigen presentation on macrophages and DCs, thus enhancing antibody-dependent cellular cytotoxicity (330). GM-CSF has been evaluated in a number of clinical trials, both as a monotherapy or adjuvant (NCT02451488 and NCT03686683 for example). A phase IV clinical study is testing the neoadjuvant effect of GM-CSF in cutaneous stage L-III melanoma (NCT02451488; Table III). In addition, one active non-recruiting phase III clinical trial is investigating the therapeutic potential of sipuleucel-T in patients with prostate adenocarcinoma (NCT03686683). Sipuleucel-T is an autologous cell product comprising APCs loaded with a recombinant fusion protein, PA2024, composed of prostatic acid phosphatase linked to GM-CSF (NCT03686683). Drugs targeting CSFs in phase III and IV clinical trials are presented in Table II.

In addition to cytokine therapies and ICIs, immunity of the TME can be also triggered by adoptive cell therapy (ACT) and cancer vaccines (50). During ACT, autologous T lymphocytes with antitumor activity are isolated from a patient, expanded *ex vivo*, and then amplified tumor-resident or engineered T cells are transferred back to patients (331,332). One promising ACT approach is the chimeric antigen receptor (CAR) gene therapy where CAR modified T cells recognize various types of antigens regardless of their presentation on MHC molecules (333). T cells then mediate tumor killing via: i) The perforin and granzyme axis; ii) cytokine secretion; or iii) Fas-Fas ligand axis (334). Currently, there are 48 completed clinical trials that used CAR-T cell therapy on different malignancies (based on http://clinicaltrials.gov; accessed, January 6, 2022). One study evaluated CAR-engineered autologous primary human $CD8^+$ T lymphocytes against IL13 receptor α2 in 3 patients with recurrent glioblastoma (NCT00730613), and reported promising anti-glioma activity (335). CAR-T cell immunotherapy has shown promise in terms of efficacy, while causing minimal toxicity (334,336). However, limitations such as tumor heterogeneity and antigen heterogeneous expression, as well as the function of T lymphocytes at tumor sites, make tumor eradication difficult (336).

In addition to ACT, cancer vaccines are currently intensively studied as a promising therapeutic approach that activates the humoral and cellular immunity of patients with cancer (337-339). An efficient cancer vaccine design depends on a good antigen selection, where an ideal antigen should be specifically expressed and presented on all cancer cells but not normal cells, highly immunogenic and essential for the survival of cancer cells (340). After antigen delivery, DCs will uptake

Table II. Therapeutic agents targeting colony stimulating factors in interventional clinical trials.

Therapeutic agent	Therapeutic agent description	Therapeutic strategy	Cancer type	Phase	Clinical trial
Pexidartinib (PLX3397)	CSF-1R inhibitor	Pexidartinib vs. placebo	Giant cell tumor of the tendon sheath	Phase III	NCT02371369
Durvalumab and pexidartinib	Anti-PD-L1 antibody and CSF-1R inhibitor	Durvalumab combined with pexidartinib	Pancreatic or colorectal cancer	Phase I	NCT02777710
LY3022855 (IMC-CS4)	CSF-1R inhibitor	LY3022855 in combination with durvalumab (checkpoint inhibitor, targeting PD-L1/PD-1 interaction) or tremelimumab (anti-CTLA-4)	Advanced solid tumors	Phase I	NCT02718911
		Combining cyclophosphamide, pembrolizumab (an antibody that blocks negative signals to T cells), GVAX (GM-CSF pancreatic cancer vaccine) and LY3022855	Pancreatic adenocarcinoma	Early phase I	NCT03153410
PDR001 and MCS110	Anti-PD-1 and CSF-1 antibody, respectively	PDR001 in combination with MCS110	Gastric cancer	Phase II	NCT03694977
DCC-3014 (vimseltinib)	CSF-1R inhibitor	Alone	Tenosynovial giant cell tumor	Phase I/II	NCT03069469
		Vimseltinib vs. placebo	Tenosynovial giant cell tumor	Phase III	NCT05059262
		DCC-3014 administered concurrently with avelumab (anti-PD-L1 antibody)	Sarcomas	Phase I	NCT04242238
SNDX-6352 (UCB6352)	CSF-1R antibody	SNDX-6352 alone or in combination with durvalumab	Solid tumors/intrahepatic cholangiocarcinoma	Phase I and phase II	NCT03238027 and NCT04301778
TPX-0022	MET/CSF-1R/SRC inhibitor	Alone	Solid tumors	Phase I	NCT03993873
NMS-03592088	FLT3, KIT and CSF-1R inhibitor	Alone	Acute myeloid leukemia or chronic myelomonocytic leukemia	Phase I/II	NCT03922100
Q702	Axl/Mer/CSF-1R selective tyrosine kinase inhibitor	Alone	Solid tumor	Phase I	NCT04648254
Chiauranib	Tyrosine kinase inhibitor	Chiauranib vs. placebo	Small cell lung cancer	Phase III	NCT04830813

Data were acquired from the U.S. National Library of Medicine (http://clinicaltrials.gov; date accessed, January 6, 2022). CSF-1, colony-stimulating factor-1; CSF-1R, colony-stimulating factor-1 receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FLT3, ms-like tyrosine kinase 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; GVAX, GM-CSF pancreatic cancer vaccine; MET, mesenchymal-epithelial transition factor; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1.

Table III. Molecularly cloned myeloid growth factors used in interventional clinical trials.

Therapeutic agent	Therapeutic strategy	Cancer type	Phase	Clinical trial
GM-CSF	Alone	Acute myeloid leukemia	Phase III	NCT00880243
	Neoadjuvant GM-CSF treatment	Cutaneous stage L-III melanoma	Phase IV	NCT02451488
	Administration of Sipuleucel-T (an autologous cell product consisting of APCs loaded with PA2024, a recombinant fusion protein composed of prostatic acid phosphatase, linked to GM-CSF.	Adenocarcinoma of the Prostate	Phase III	NCT03686683
PEG-G-CSF	Combination of cabazitaxel (microtubule inhibitor) with prednisolone (corticosteroid hormone) with primary prophylaxis with PEG-G-CSF	Prostate cancer	Phase IV	NCT02441894
PEG-rhG-CSF	PEG-rhG-CSF for preventing neutropenia after intensive chemotherapy	Breast cancer	Phase IV	NCT04009941 and NCT02944604
Lenograstim (G-CSF)	G-CSF as primary prophylaxis for chemotherapy-induced neutropenia	Solid tumors	Phase IV	NCT01107756
Neupogen (G-CSF)	Neupogen vs. ciprofloxacin antibiotic	Breast cancer	Phase IV	NCT02816112
Filgrastim (G-CSF)	Weight-based plerixafor (antagonist of CXCR4) compared with a fixed dose of plerixafor in combination with filgrastim	Non-Hodgkin's lymphoma	Phase IV	NCT01164475

Data were acquired from the U.S. National Library of Medicine (http://clinicaltrials.gov; date accessed, January 6, 2022). APC, antigen presenting cell; CXCR4, C-X-C chemokine receptor type 4; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; PEG-G-CSF, PEGylated human granulocyte colony-stimulating factor; PEG-rhG-CSF, pegylated recombinant human granulocyte colony stimulating factor.

these antigens and present relevant antigens on MHC I and MHC II to $CD8^+$ and $CD4^+$ T cells, respectively (337). Effector T cells then migrate to the TME, recognize and kill cancer cells by releasing cytotoxic particles, including perforin, granzymes, IFN-γ or TNF-α, or by directly inducing apoptosis (341). In addition to T cells, B lymphocytes, NK cells and macrophages promote tumor eradication (341). Personalized vaccines are also gaining interest. There are currently three clinical trials that evaluated personalized cancer vaccination in patients with glioblastoma (active, not recruiting, NCT00045968; and completed, NCT01280552 and NCT00643097) (324). These studies reported increased numbers of infiltrating T cells with improved PFS (338,339,342). These studies show that immunization with vaccines has a promising effect in patients with cancer.

Targeting the ECM and exosomes. In addition to targeting of the cellular components of the TME and their soluble factors, TME non-cellular features are also targeted and evaluated in clinical trials. ECM remodeling and increased stiffness (desmoplasia), for instance, are targeted to reduce mortality in different cancer types (310). FDA-approved angiotensin II receptor antagonists, such as losartan and candesartan, increased the survival of patients with gastro-esophageal cancer by inhibiting the TGF-β signaling pathway and consequently reducing collagen I secretion and desmoplasia (343). Losartan has also shown clinical benefits in pancreatic cancer phase II trials (NCT01821729) when combined with FOLFIRINOX and chemoradiation with fluorouracil or capecitabine (344). The ECM may be alternatively modified by targeting integrins or focal adhesion kinase (FAK) proteins using the FAK inhibitor defactinib (NCT01870609) (345). MMP inhibitors target MMPs. However, trials failed clinically mainly because these inhibitors exhibit a broad-spectrum activity that may result in secondary side effects (346), and ECM degradation may boost cancer progression instead of inhibiting it (310,347,348).

Exosomes are: i) Targeted for reducing vesicle trafficking in cancer cells; ii) used as biomarkers for cancer diagnosis; or iii) used as vehicles of small interfering RNA for targeted therapy (51). Furthermore, the association between non-coding RNA and the TME is gaining interest, especially with respect to the TME immune environment (136,349). In this regard, Huang *et al* (350) developed a novel TME-related lncRNA risk model that could be used as a predictor of ICIs and a prognostic biomarker in patients with hepatocellular carcinoma.

Targeting the microbiome. Published research has linked the gut and intratumoral microbiota to response and toxicity in a variety of treatments, including chemotherapy (351). For instance, commensal microbes interact with chemotherapeutics primarily by modulating drug metabolism and host immunity (351,352). Drug activity can either be directly driven by microbes or indirectly driven by microbe-derived metabolites (352). Therefore, targeting the microbiome may hold promise for improving chemotherapeutic efficacy and lowering toxicity (18). Retrospective clinical studies on patients with PDAC demonstrated that administration of antibiotics to target bacteria that produce a long isoform of cytidine deaminase resulted in improved gemcitabine response, and thus, overcame the intratumoral bacterial-induced chemoresistance (353-355).

The microbiome has also been recognized for its intricate interaction with host immunity, and thus, is considered a potential therapeutic target to optimize immunotherapy responses (310). Gut microbiota, in particular, serve a role in modulating immune checkpoint blockade responses in multiple cancer types (356-359). A recent recruiting observational study aims to evaluate the effect of the microbiome in terms of efficacy and toxicity of ICIs in patients with advanced cancer (NCT04107168). The search for biomarkers in the gut microbiome has resulted in the identification of microbiome signatures that aid in determining when ICIs are effective (360,361). According to a study that looked at phase II neoadjuvant trials of anti-programmed cell death 1 (PD-1)/anti-CTLA-4 antibodies for melanoma, NSCLC and sarcoma, patients with high abundance of *Ruminococcus* were reported as responders with a marked increase in B cell signatures (362). Given that the favorable microbiota signatures result in enhanced intratumoral immune infiltrates (357-359), creating an ideal combination of bacteria is a potential therapeutic approach to be administered in combination with checkpoint blockade.

In addition to targeting the gut microbiome, efforts are now being made to target the tumor microbiome in order to slow cancer progression and improve the response to cancer therapy. For instance, targeting the tumoral microbiome with antibiotics results in enhanced response to both chemotherapy and ICIs in CRC and pancreatic cancer (181,363,364). The intratumoral microbiome can also be targeted by bioengineered bacteria that can either kill tumor cells directly, or create an immune microenvironment that encourages antitumor immune responses (18). In mice for example, attenuated *Salmonella* strains expressing Vibrio-derived toll-like receptor 5 ligand flagellin elicited an immune response that recruited an antitumor immune responses against orthotopic human CRC87 lines (365).

A growing body of evidence suggests that the microbiome serves a role in determining cancer therapeutic efficacy and toxicity (18,351). Laboratory research and clinical trials have also shown that microbiota modulation can help with cancer treatment (18,366-368). Therefore, understanding the microbiome and its interactions with cancer is critical in personalized medicine. Manipulation of the gut microbiota may yield novel cancer treatment insights for enhanced cancer therapeutic responses. Since the microbiome exhibits complex interactions with both the host immunity and cancer cells, it would be challenging to identify an optimal bacterial consortia and metabolites to affect the TME, as well as to introduce it for cancer treatment (18).

In addition to the aforementioned targeted therapeutic strategies, combination therapies have gained popularity as they result in enhanced efficacy, reduced drug resistance and lowered toxicity compared with monotherapy (369). Studies are investigating combination regimens that simultaneously affect several targets, thus achieving cooperative and synergistic effects (369,370). In this context, therapeutic agents targeting multiple stromal cells of the TME have been evaluated in interventional clinical trials (Table IV) (51,371). For example, the PD-1/PD-L1 signaling pathway is targeted with anti-angiogenic interventions targeting VEGFR1/2/3, PDGFR or c-Kit (235), or with tyrosine kinase

Table IV. Therapeutic agents for combinatorial therapy targeting multiple stromal cells of the tumor microenvironment.

Therapeutic strategy	Cancer type	Status	Clinical trial
Simlukafusp alfa (IL-2 variant targeting FAP-A) in combination with atezolizumab (anti-PD-L1)	Head and neck, oesophageal, and cervical Cancer	Phase II	NCT03386721
RO7300490 (4-1BB agonist targeting FAP) and atezolizumab (anti-PD-L1 antibody)	Solid tumors	Phase I	NCT04857138
Sintilimab (anti-PD-1) with IBI305 (anti-VEGF) with chemotherapeutic pemetrexed and cisplatin	Non-squamous non-small cell lung cancer	Phase III	NCT03802240
Chemotherapeutic PLD with atezolizumab (PD-L1 inhibitor) vs. PLD with bevacizumab (anti-VEGF) and atezolizumab vs. PLD with bevacizumab	Ovarian, fallopian tube and peritoneal carcinoma	Phase II/III	NCT02839707
Bevacizumab (anti-VEGF) with chemotherapeutic carboplatin and pemetrexed vs. bevacizumab with atezolizumab (anti-PD-1), carboplatin and pemetrexed	Malignant pleural mesothelioma	Phase III	NCT03762018

Data were acquired from the U.S. National Library of Medicine (http://clinicaltrials.gov; date accessed, January 6, 2022). FAP, fibroblast activation protein; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1; PLD, pegylated liposomal doxorubicin.

inhibitors (372-374). Additionally, anti-stromal interventions are also combined with chemotherapeutics and radiation agents (51,315,369,370). Furthermore, to better decide on a combination therapy, researchers should fully understand the stage of the tumor, as well as the specific state of the TME and its immune markers.

5. Discussion

Cancer is a complex disease caused by malignant cells and a supporting TME. The cross-talk between these two main entities embodied by bidirectional mediators governs tumor progression. Low levels of both oxygen and pH create local stress within the TME, triggering a response from, thereby activated, stromal cells and the infiltration of more immune cells (136). Such communications are not only governed by cytokines, chemokines and metabolic products secreted by TME stromal cells but other factors such as epigenetic factors (such as miRNA), methylation DNA and histone modification are also critical (375). Furthermore, an increasing number of studies have highlighted the important effects of metabolism on the activities of immune cells, and thus, their effect on cancer progression (257,260,376). The orchestration of autocrine and paracrine communications within the tumor environment may expedite ECM stiffness, inflammation and angiogenesis, and possibly cancer cell dissemination and metastasis (4). These results warrant examining the effect of TME components on the outcome of the disease. Such findings urged research to investigate the relevance of TME targeting for more efficient therapeutic methods. While most studies focus mainly on the stromal composition of the TME (64,66), the present review provides a comprehensive examination of not only the stromal components but also the non-cellular TME components, including the ECM, exosomes and microbiome. The present discusses the contribution of cellular and non-cellular TME components to fundamental cancer hallmarks as well as emerging hallmarks and enabling characteristics. The present review also provides a detailed report on TME cells, signaling pathways and soluble factors that can be targeted for cancer therapy, highlighting TME components that are currently targeted in interventional clinical trials.

TME targeting provides promising strategies to overcome the chemotherapeutic resistance of tumor cells. Research efforts have resulted in the development of FDA-approved or newly developed TME-targeted drugs, including anti-angiogenic and anti-inflammatory agents. Clinical implementation of these drugs also shows promising successful clinical results (9,51,315). In addition, and with the help of large-scale data mining and bioinformatics analysis, several immune-related gene signatures serving as predictors for therapeutic outcomes or biomarkers for prognosis in several cancer types have been constructed (136,377-380).

TME-targeted strategies may soon become mainstream for cancer therapy and can be used in combination with conventional antitumor methods. However, further research is required to address the time of TME-targeted drug administration and the treatment strategies, since certain studies have indicated that TME components may augment tumor resistance to cancer therapy (97,181,200,381). For instance, CAFs promote resistance to chemotherapy primarily by mediating EMT, maintaining the stemness of cancer stem cells and promoting metabolic reprogramming (382). The augmented ECM deposition and increased cytokine secretions mediated by CAFs may aid tumor cells in resisting cancer-therapies and, in particular, chemotherapy (383). Furthermore, a growing body of evidence suggests that hypoxia-driven residual VEGF and other pro-angiogenic factors cause resistance to VEGF receptor inhibition (381,384). Therefore, combinations of medicines targeting these factors may enhance treatment outcomes compared with single VEGF pathway blocking alone (385).

In addition to the aforementioned concerns, the pharmacokinetics and biodistribution of TME-targeted drugs is not yet well investigated due to the difficulty of detecting the exact

state of the TME (386). One way to overcome this limitation is using 3D cell culture systems to recapitulate the complexity of tumor architecture and simulate the TME (387). Another method is using animal models that facilitate the recreation of a developed tumor in an improved pathophysiologic environment (324,388-390). Tumor tissues obtained from a patient are processed into patient-derived organoids or patient-derived xenografts, which are then functionally and quantitively analyzed after treatment [reviewed in (391)]. These methods may help identify clinically relevant immune checkpoints and predict treatment efficacy (391). Such efforts allow for an enhanced pre-clinical validation of novel cancer methodologies towards full integration of immunotherapeutic prediction tools (391,392). In addition to combination therapy, nanotechnology also promises good therapeutic prospects (324,393). Regarding all discussed interventions and their limitations, and arriving at the era of the comprehensive cancer model treatment, it is important to treat tumors as a multifactorial disease in a stage, tissue/organ and patient-specific manner.

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The authors declare that they have no competing interests.

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