

Targeting Tumor Microenvironment by Small-Molecule Inhibitors



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Abstract

The tumor microenvironment (TME) is a hypoxic, acidic, and immune/inflammatory cell-enriched milieu that plays crucial roles in tumor development, growth, progression, and therapy resistance. Targeting TME is an attractive strategy for the treatment of solid tumors. Conventional cancer chemotherapies are mostly designed to directly kill cancer cells, and the effectiveness is always compromised by their penetration and accessibility to cancer cells. Small-molecule inhibitors, which exhibit good penetration and accessibility, are widely studied, and many of them have been successfully applied in clinics for cancer treatment. As TME is more penetrable and accessible than tumor cells, a lot of efforts have recently been made to generate small-molecule inhibitors that specifically target TME or the components of TME or develop special drug-delivery systems that release the cytotoxic drugs specifically in TME. In this review, we briefly summarize the recent advances of small-molecule inhibitors that target TME for the tumor treatment.

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Introduction

The tumor microenvironment (TME) is a hypoxic and acidic milieu constituted of cellular and noncellular components. The cellular component is composed of various stromal cells, including endothelial cells (ECs), cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), tumor-infiltrating lymphocytes (TILs), and tumor-associated macrophages (TAMs). The noncellular component includes nonsoluble or semisoluble substances, such as the extracellular matrix (ECM), and soluble substances, such as interstitial fluids, various cytokines and chemokines, growth factors, and metabolites [1–5]. TME is not only intrinsically immunosuppressive to protect tumor cells from

immune surveillance but also dynamically adaptive to accommodate rapid tumor growth and progression and to counter any stress and insult conditions, such as chemotherapy [6,7]. TME is an essential part of the tumor mass, which is important for tumor growth, progression, metastasis, and therapy resistance [4,6,8]. Therefore, targeting TME would be an efficient way for the treatment of cancer. Indeed, many strategies have been developed to target the TME. As small molecules can easily access TME than can penetrate into tumor cells, development of small-molecule inhibitors that specifically target TME is one of the rapidly growing areas in this field.

Small-molecule inhibitors are compounds with a small size (≤ 500 Da). Compared with macromolecule agents, small-molecule inhibitors are more penetrative to the targets and usually can be engineered to be suitable for oral administration [9–12]. Many small-molecule inhibitors have been successfully applied to treat a wide range of cancers, and much more are currently in either clinical trials or ongoing development. For example, sunitinib (Sutent), a multiple-tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGFR), oncogene *c-KIT* (*KIT*), receptor tyrosine kinase and platelet-derived growth factor receptor (PDGFR), has been approved as a potent antiangiogenesis drug and is applied to treat various tumors [9,13].

Recently, many small-molecule inhibitors have been developed to specifically or mainly target TME. These small molecules are designed

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to interrupt the specific features of TME, including the hypoxic, acidic, inflammatory milieu, as well as the abnormal ECM network in TME. Here, we briefly review the recent advances in the development of therapeutic small-molecule inhibitors that target TME.

Targeting Hypoxia in the TME

Hypoxia is one of the prominent features of TME. The rapid proliferation of cancer cells speeds up the consumption of oxygen, resulting in reduced oxygen level in solid tumor areas [14]. The disorganized vascular networks in tumor site that induce diffusion distance of oxygen also contribute to low oxygen level in TME [6,14,15]. In addition, tumor-associated and/or therapy-induced anemia causes a decreased O_2 transport capacity of the blood, leading to hypoxia in tumor sites [16]. Hypoxia is associated with tumor metastasis, radiotherapy/chemotherapy resistance, and poor prognosis [15,17]. In hypoxic environment, tumor cells can use many mechanisms to survive, including shifting from aerobic to anaerobic

metabolism, erythropoietin (EPO) production, deregulating DNA repair systems, recruiting the stromal components, as well as upregulating protooncogenes and hypoxia-inducible factor (HIF) 1α and HIF 2α [18,19]. For a detailed review of targeting hypoxia in cancer therapy, please refer to a recent publication by Wilson and Hay [20]. To exploit the unique feature of hypoxia in TME, the therapeutic agents are often designed as low-toxicity prodrugs in normoxia environment while selectively activated in hypoxic tumor areas (Figure 1). Papadopoulos et al. [21] designed the hypoxia-activated prodrug AQ4N (banoxantrone) that is converted into AQ4, a potent inhibitor of topoisomerase II, in hypoxic areas. This prodrug is applied to treat advanced solid tumors such as bronchoalveolar lung cancer and ovarian cancer. Weiss et al. [22] designed a hypoxia-activated prodrug TH-302 that is consisted of 2-nitroimidazole, a hypoxia trigger, and a brominated version of isophosphoramidate mustard (Br-IPM). This prodrug remains intact in normal oxygen conditions and can be activated in severe hypoxic conditions ($<0.5\%$

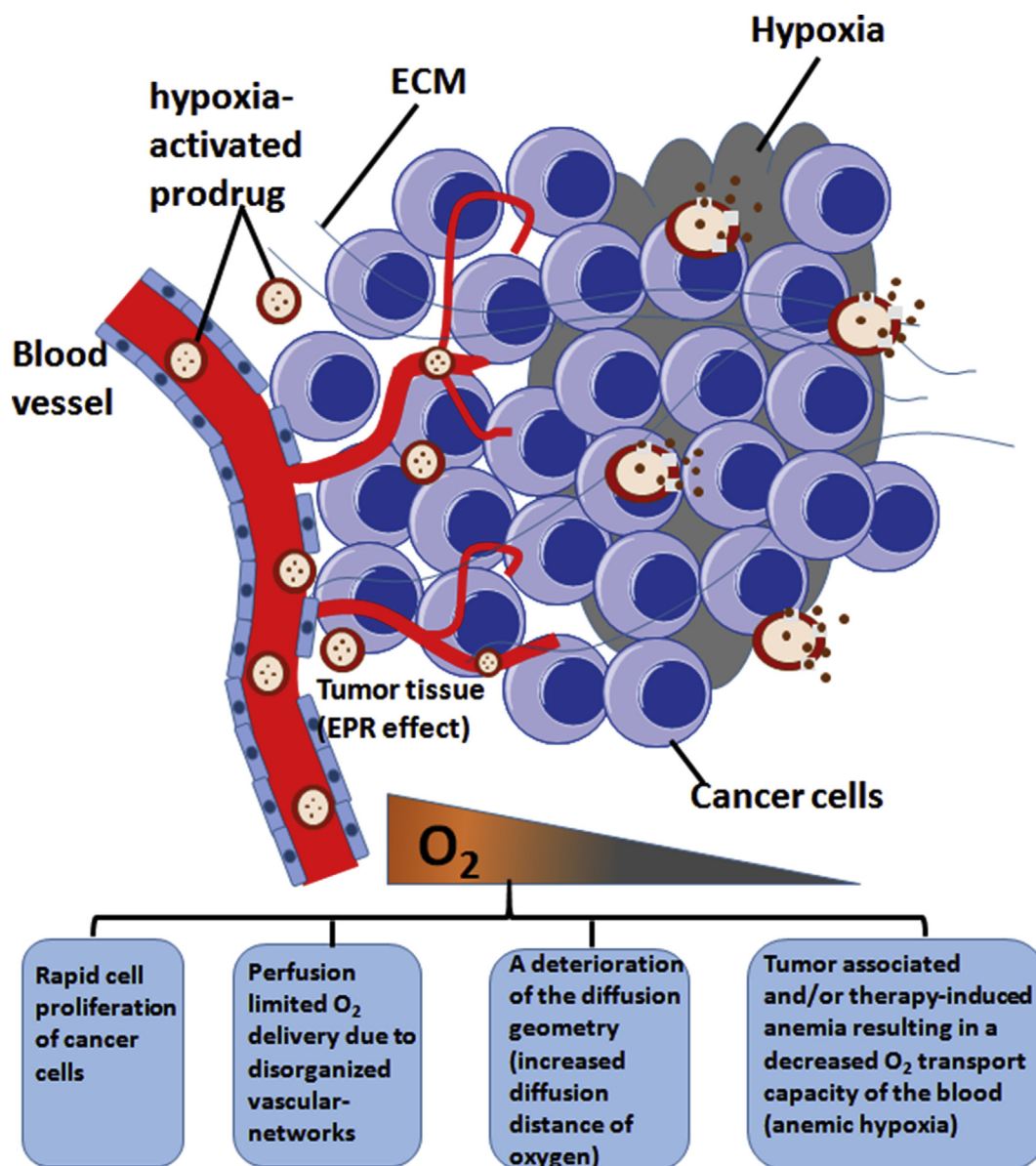


Figure 1. Hypoxia-targeted therapy. The hypoxia in TME is resulted from several factors. Some hypoxia-activated prodrugs or hypoxia-targeting nanoparticle drug-delivery system are developed to inhibit the growth of cancer cells. TME, tumor microenvironment; ECM, extracellular matrix; EPR, enhanced permeability and retention effect.

O₂) to release Br-IPM, a DNA cross-linking agent. TH-302 shows antitumor activities in metastatic melanoma and small cell lung cancer (SCLC). Another hypoxic cell toxin is tirapazamine (TPZ), which preferentially shows cytotoxic activity to hypoxic cancer cells. The underlying mechanism is that TPZ forms a radical by adding an electron under the catalytic action of various intracellular reductases. This TPZ radical is highly reactive and can lead to DNA single- or double-strand breaks in hypoxic environment. However, under aerobic conditions, the TPZ radical is back-oxidized into its nontoxic parent, and its cytotoxicity is rapidly reduced [15,23]. Another strategy is to design a delivery system that releases the carried-on drug preferentially in hypoxic microenvironment. For instance, Huo et al. [24] reported a size-tunable nanocluster bomb with an initial size of approximately 33 nm featuring a long half-life during blood circulation and destructed to release small hypoxia microenvironment-targeting nanoparticles (NPs) to achieve deep tumor penetration. The small-molecule inhibitors that target hypoxic TME are summarized in Table 1 [21–23,25].

Targeting the Acidic TME

The extracellular pH in normal tissues is ~7.4, while the pH value in TME is much lower (~6.7–7.1) [26]. There are many mechanisms for the formation of acidic pH in tumors. Tumor cells use aerobic glycolysis as a major energy metabolism pathway in hypoxic environment, leading to increased production of lactic acid and H⁺ which are subsequently released in TME through passive diffusion and active membrane-based ion transport [27]. The H⁺-ATPases, Na⁺-H⁺ exchanger NHE1, as well as monocarboxylate-H⁺ efflux cotransporter MCT1 and MCT4 are highly increased or/and activated in tumor cells, which drive H⁺ efflux [26,28–30]. In addition, the carbonic anhydrase 9 (CA9), which is overexpressed in many types of cancer, also participates in the maintenance of low pH in TME [31,32]. In addition, tumor cells can induce oxidative stress to their neighboring stromal cells such as CAFs and TAMs by producing reactive oxygen species (ROS), which lead to mitochondrial dysfunction in CAFs and TAMs, resulting in accumulation of lactate in TME [33,34] (Figure 2). In addition, several mechanisms including the adaptation to hypoxia, oncogene activation, uncontrolled cell growth, and deficiencies in tumor perfusion due to the disorganized vascular networks also contribute to the tumor acidic microenvironment [35].

The dysregulated pH in TME contributes to tumor progression, invasion, metastasis, and chemoresistance, and therefore, targeting acidic TME is a desirable tumor therapeutic strategy [26,35–39]. Some small-molecule inhibitors targeting acidic TME are developed (Table 1) (Figure 2) [40–52]. In addition, efforts have recently been made to develop pH-responsive drug-release systems that deliver cytotoxic chemotherapy drugs specifically to acidic microenvironment (Figure 2). Zhang et al. [53] established a drug delivery system for targeting tumor acidic microenvironment via modifying pH (low) insertion peptide (pHLIP) on mesoporous organosilica nanoparticles (MONs), in which the doxorubicin (DOX) is loaded and can be released in response to glutathione and low pH in TME. Chen et al. developed another pH-responsive delivery system using polyethylene glycol (PEG)–DOX-encapsulated aza-BODIPY nanotheranostic agent. They linked DOX with PEG-benzaldehyde (PEG–CHO) via –HC=N– bond to form a Schiff's base, and then a near-infrared photosensitizer aza-BODIPY (AB) was encapsulated to form hydrophilic nanoparticles (DAB NPs). The –HC=N– bond can

be broken in acidic TME, resulting in the release of DOX specifically in the tumor site [54].

Targeting Immune and Inflammatory Signaling in TME

The immune system is implicated in both tumor initiation and progression, and immune cells are enriched in TME in some solid tumor such as prostate cancer [57,58]. Some immune cells in TME, for instance TAMs and myeloid-derived suppressor cells (MDSCs), are tumor-promotive, while the immune activity of other cells, for instance CD8⁺ cells of TILs, is suppressed in TME [5,59,60]. Many therapeutic strategies have been tested for the treatment of cancer through inhibiting the tumor-promotive cells and their signaling or reversing/reconstituting the function of TILs. The small-molecule inhibitors that target immune cells or/and the inflammatory signaling are developed and summarized in Table 2 [61–76].

TAMs are one of the most abundant and crucial cell components in TME. A high presence of TAMs in TME is significantly associated with poor prognosis of patients [77,78]. The phenotype of TAMs is diverse and plastic. There are 17 TAM phenotypes being identified based on single-cell analysis [79], and these subsets are potential targets for therapy. The strategies that suppress M2-type TAM recruitment, survival, and the relevant signaling cascades or repolarize M2-type TAMs to an M1 phenotype have been proposed for the treatment of cancer [3,80–82]. Some small-molecule inhibitors that target TAMs or TAM-associated signals have been developed (Table 2) [61–67].

MDSCs are a heterogeneous group of myeloid cells with an immature phenotype that expand in response to various tumor-derived cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin (IL)-6 [83–86]. MDSCs are associated with tumor progression, metastasis, and poor clinical prognosis [87–89]. MDSCs play important roles in the maintenance of the immunosuppressive TME through affecting the interactions between cancer cells and immune effectors [90]. MDSCs can release high levels of Arginase-1 in TME, leading to L-arginine depletion (a crucial nutrient for lymphocytes) that inhibits T-cell function. MDSCs also suppress dendritic cells (DCs)–mediated activation of T cells [91–93]. DCs act as a key cellular sensor to capture danger events such as invading microbes in the environment and provide necessary signals for T-cell activation, thereby shaping immune responses [94,95]. Targeting MDSC expansion or inhibiting their protumorigenic functions is a promising strategy to inhibit tumor progression. Some small-molecule inhibitors that target MDSCs or/and their associated signals have been developed and are summarized in Table 2 [68–72].

TILs are a complex group of T lymphocytes infiltrated in TME [96]. TILs have different subpopulations with different even opposite roles in immune responses. For instance, the subset of CD4⁺CD25⁺FOXP3⁺ regulatory T (Treg) cells suppress tumor-specific T-cell immunity and are associated with poor prognosis in ovarian carcinoma [97], and tumor-infiltrating CD4⁺CD25⁺FOXP3⁺ Treg cells showed prometastatic function in receptor activator of nuclear factor-κB (RANK)-expressing breast/mammary cancer cells [98]. However, the CD8⁺ TILs are positively correlated with patients' overall survival in many cancer types, including cutaneous angiosarcoma, esophageal carcinomas, and non-small cell lung cancers (NSCLCs) [99–101]. Some small-molecule inhibitors that either enhance the function of CD8⁺ T cells or inhibit Treg cell proliferation and cytokine production have been developed (Table 2) [73–76].

Table 1. Small-Molecule Inhibitors Target Hypoxia and Acidic Microenvironment

Target	Small-molecular Inhibitor	Target Strategy	Mechanism of Action	Cancer Target	References
Hypoxia	Hypoxia-activated prodrug AQ4N (banoxantrone)	Inhibit tumor growth and progression	Be converted into AQ4, a potent inhibitor of topoisomerase II, in hypoxic areas	Bronchoalveolar lung cancer and ovarian cancer	[21]
	Hypoxia-activated prodrug TH-302	Inhibit tumor growth	Release brominated version of isophosphoramidate mustard (Br-IPM) in hypoxic areas	Small cell lung cancer (SCLC) and melanoma	[22]
	Tirapazamine (TPZ)	Show preferentially cytotoxic activity to hypoxic cells	Form a reactive radical under the catalytic action of various intracellular reductases	Squamous cell carcinoma	[23]
	PR-104 [2-((2-bromoethyl)-2-((2-hydroxyethyl) amino)carbonyl-4,6-dinitroanilino)ethyl methanesulfonatephosphateester]	Be converted into cytotoxic drug, hydroxylaminePR-104H, selectively under hypoxia, resulting in suppression of growth of hypoxic and aerobic cells	DNA cross-linking	Pancreatic and prostate tumors	[25]
Acidic microenvironment	Esomeprazole (ESOM)	pH neutralization	Alter tumor pH by inhibiting proton extrusion	Melanoma	[40]
	Omeprazole	pH neutralization	Inhibit V-H ⁺ -ATPase activity and alter extracellular pH	Colon, breast, ovarian cancer, melanoma	[41]
	Bicarbonate	pH neutralization	Increase tumor extracellular pH and reduce the formation of spontaneous metastases	Breast and prostate cancer	[42]
	4,4'-Diisothiocyanatostilbene-2,2'-disulfonic acid (DIDS)	Induce cell growth arrest and cell apoptosis	Inhibit anion exchangers (AEs)	Hepatocellular carcinoma	[55]
	α -Cyano-4-hydroxycinnamate (CHC) (combined with radiotherapy)	Retard tumor growth and render the remaining cancer cells sensitive to irradiation	Inhibit monocarboxylate transporter 1 (MCT1)	Lung carcinoma and colorectal adenocarcinoma	[56]
	Sulfonamide-based CAIX inhibitors (CAI17 and U-104)	Inhibit tumor growth, metastasis formation and deplete cancer stem cells	Inhibit CAIX activity	Breast cancer	[43–45]
	Glycosylcoumarins(GC-204 and GC-205)	Inhibit tumor growth and metastasis formation	Inhibit CAIX activity	Breast cancer	[43]
	Small organic ligands (such as AAZ)	Retard tumor growth, reduce metastasis and tumor stem cell expansion	Inhibit CAIX activity	Renal cell carcinoma	[50]
	Acetazolamide (combined with rapamycin)	Inhibit tumor growth and potentiate the anticancer activity of rapamycin	Inhibit CAIX activity	Colorectal adenocarcinoma	[51]
	SLC-0111 (combined with dacarbazine, temozolomide, doxorubicin, and 5-fluorouracil)	Potentiate the cytotoxic effects of conventional chemotherapeutic drugs	Inhibit CAIX activity	Melanoma, breast and colon cancer	[52]
2-Aminophenoxazine-3-one (Phx-3)	Disturb intracellular pH homeostasis, leading to apoptotic and cytotoxic events	Inhibit NHE1 activity	Gastric cancer	[46]	
Cariporide	Regulate intracellular pH reduce proliferation and induce apoptosis	Inhibit NHE1 activity	Cholangiocarcinoma, breast cancer	[47–49]	
S3705	Regulate intracellular pH, reduce proliferation, and induce apoptosis	Inhibit the Na ⁺ -dependent Cl ⁻ /HCO ₃ ⁻ exchanger activity	Cholangiocarcinoma	[48]	

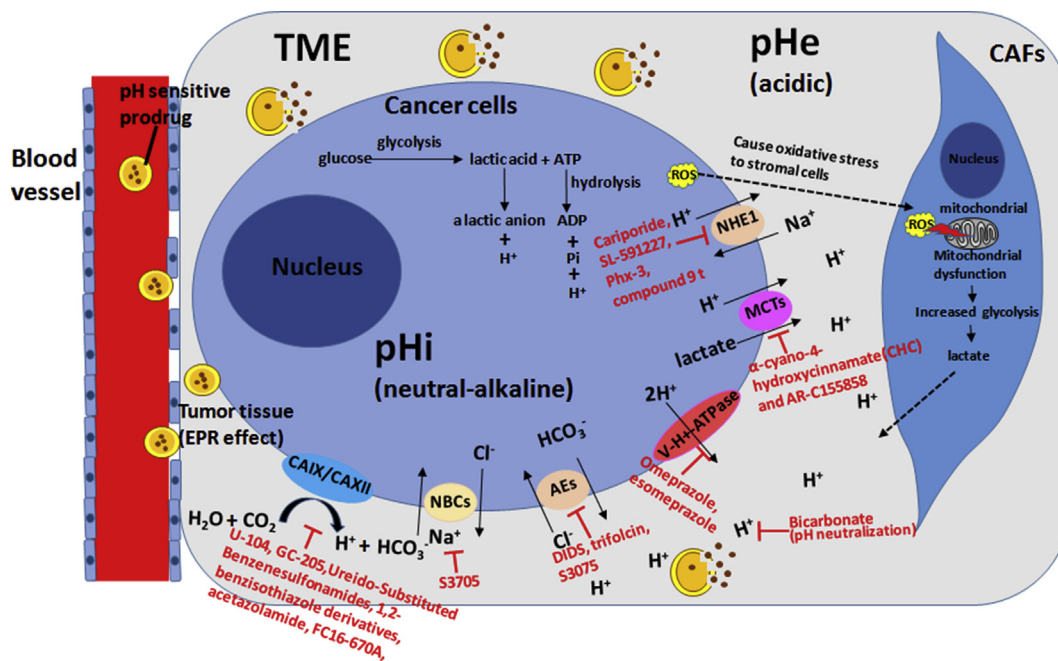


Figure 2. Schematic diagram for the acidic-targeted therapy. When acid is produced due to the anaerobic glycolysis in tumor cells, several membrane transporters or exchangers, including NHE1, MCTs, V-H⁺-ATPase, AEs, and NBCs, transport the acid to extracellular microenvironment. In addition, the oxidative stress from tumor cells impairs the mitochondrial function of CAFs, resulting in the production and secretion of lactate. Some small-molecule inhibitors are designed to target these proton membrane transporters or exchangers to suppress tumor progression. And some pH-responsive prodrugs or pH-sensitive drug delivery systems are developed to specifically release drug in acidic TME. Abbreviation: pHi: intracellular pH; pHe: extracellular pH; NHE1: Na⁺/H⁺ exchanger 1; MCTs: monocarboxylate-H⁺ efflux cotransporters; V-H⁺-ATPase: vacuolar-type H⁺-ATPase; AEs: anion exchangers; NBCs: Na⁺-HCO₃⁻ co-transporters; CAIX: carbonic anhydrase IX; CA XII: carbonic anhydrase XII; ROS: reactive oxygen species; TME, tumor microenvironment; CAFs, cancer-associated fibroblasts; EPR, enhanced permeability and retention effect.

Targeting immune checkpoint, for instance, antibodies binding to programmed death 1 (PD-1) or programmed cell death 1 ligand 1 (PD-L1), has shown remarkable efficacy for cancer therapy. However, most immune checkpoint inhibitors currently used in clinic or in clinical trials are antibody drugs, which have some disadvantages such as immunogenicity. Immune checkpoint small-molecule inhibitors could offer inherent advantages in terms of pharmacokinetics and druggability. Many efforts have been made to develop immune checkpoint small-molecule inhibitors. The small-molecule inhibitors targeting PD-1 or PD-L1 have been well summarized by Li and Tian [102] in a recent review.

Targeting CAFs and ECs

CAFs are heterogeneous with various origins, including resident fibroblasts, mesenchymal cells, epithelia, and endothelia cells via epithelial/endothelial–mesenchymal transition [104,105]. CAFs are an essential component of TME and play an indispensable role in tumor development [105,106]. CAFs secrete various cytokines, chemokines, growth factors, and other factors such as WNT16B, which promote tumorigenesis, metastasis, chemoresistance, angiogenesis, and cancer stem cell self-renewal [105,107]. CAFs express several specific markers, such as fibroblast activation protein (FAP), alpha smooth muscle actin (α -SMA), vimentin, S100A4 protein, fibroblast-specific protein-1 (FSP-1), insulin-like growth factor-binding protein 7 (IGFBP7), and Thy-1 [108–112]. These CAF markers not only make CAFs identifiable from normal counterparts but also can be used as specific therapeutic targets for tumor treatment. Some small-molecule inhibitors that target CAFs

have been developed (Table 3) [113–120]. In addition, the CAFs markers can be exploited as a drug delivery tool. For example, an FAP-specific peptide is coupled to a potent cytotoxic natural plant product thapsigargin (TG), which can be cleaved by the membrane-bound post-prolyl endopeptidase FAP in TME, resulting in TG release specifically in TME [121].

Endothelial cells (ECs) are mostly quiescent and slowly proliferated in normal tissues of adults [122,123], while ECs in tumors are activated and possess high proangiogenic properties [124]. As a result, the morphologies and gene expression of tumor-associated ECs are very different compared with those in normal ECs. The tumor-associated ECs upregulate several angiogenesis-related genes and markers, such as aminopeptidase N (APN) and tumor endothelial marker 8 (TEM8) [125]. The tumor vessels are disorganized, irregular, fragile, and leaky, resulting in abnormal blood flow in tumor [126]. The disorganized tumor vessels hinder the delivery of drugs to some tumor sites and impair the efficacy of chemotherapy. Therefore, some therapeutic strategies are designed to normalize tumor vasculature, which can alleviate hypoxia in tumor and increase the efficacy of therapies [127]. Because the tumor endothelium dysfunction helps to sculpt the microenvironment and establish an immunosuppressed TME necessary for tumor progression and metastasis [128], targeting tumor-associated ECs is a very promising strategy for the tumor treatment. It has been reported that some naturally occurring endogenous angiogenesis inhibitors act as tumor suppressor proteins or peptides that block the angiogenic switch in tumors [129]. Small-molecule inhibitors designed to specifically target tumor-associated ECs are summarized in Table 3 [130–138].

Table 2. Small-Molecule Inhibitors Target Immune Cells and Inflammatory Signaling in TME

Target	Small-molecular Inhibitor	Target Strategy	Mechanism of Action	Cancer Target	References
TAMs	Bindarit	Decrease infiltration of TAMs and impair inflammatory cell responses	Inhibit the synthesis of MCP-1/CCL2	The prostate and breast cancer	[61]
	AS1517499	Inhibit the differentiation of mouse macrophages into the M2-type	Target Stat6 pathway and reduce expression of Arg-1 and Mrc-1 expression and arginase activity	Breast cancer	[62]
	Tasquinimod	Inhibit MDSCs and TAMs of the M2-polarized phenotype	Target the inflammatory protein S100A9	Prostate cancer and melanoma	[63]
	Trabectedin	Selective cytotoxicity to TAMs and circulating monocytes, resulting in TAMs depletion	Activates extrinsic TRAIL apoptotic pathway and inhibits production of cytokines such as CCL2 and IL-6	Fibrosarcoma, ovarian and lung carcinoma	[64,65]
	BLZ-945 Sorafenib	TAMs depletion Reverse the immunosuppressive cytokine profile of TAMs	Inhibit CSF-1R (colony-stimulating factor 1 receptor) Restore secretion of IL-12, suppress IL-10 production	Breast and colon cancer Breast tumor	[66] [67]
MDSCs	GW2580	Reduce MDSC infiltration to tumors	Inhibit CSF1/CSF1R signaling	Prostate cancer	[68]
	Sunitinib	Reduce MDSCs and tumor T regulatory cells and inhibit angiogenesis	Inhibit Stat3 in MDSCs and downregulate angiogenic gene expression	Metastatic renal cell carcinoma and pancreatic neuroendocrine tumor	[69,103]
	Axitinib	Decrease in the number of MDSCs in the spleens and tumor site	Downregulate STAT3 expression and reverse MDSC-mediated tumor-induced immunosuppression	Metastatic renal cell carcinoma (RCC)	[70]
	Sildenafil	Reduce MDSC function and enhance intratumoral T-cell infiltration and activation	Inhibit phosphodiesterase-5 and downregulate arginase 1 and nitric oxide synthase-2 expression	Multiple myeloma and head and neck cancer	[71]
DCs	Paclitaxel (nontoxic dose)	Attenuate the propagation of regDC	Target Rho GTPase signaling	Lung cancer	[72]
TILs	SB415286	Enhance the function of CD8+ T cells	Downregulate PD-1 expression through targeting GSK-3 α/β	Melanoma and lymphoma	[73]
	Trametinib	Inhibit CD4+ T-cell proliferation and cytokine production	Inhibit MEK	Colon cancer	[74]
	Cyclophosphamide (CTX) (combined with an agonist antibody OX40)	Induce Treg cell depletion	Induce Treg cell-specific apoptosis and enhance effector CD8+ T cells	Melanoma	[75]
	IC87114	Inhibit activation and proliferation of Tregs and enhance CD8+ responses	Inhibit the PI3K-Akt pathway	Colon cancer and melanoma	[76]

TAMs, tumor-associated macrophages; TILs, tumor-infiltrating lymphocytes; DCs, dendritic cells; CSF, cerebrospinal fluid; MDSCs, myeloid-derived suppressor cells; IL, interleukin.

Targeting the Abnormal ECM Network of TME

The ECM contains more than one hundred proteins, which are organized into a structural framework and act as a scaffold [144,145]. The major components of the ECM are fibrous proteins and proteoglycans including fibronectin, collagen, and hyaluronan (HA). The ECM also contains various growth factors, cytokines, and chemokines secreted by tumor cells and stromal cells. For example, vascular endothelial growth factor (VEGF) in TME, secreted by tumor cells, CAFs, and inflammatory cells, plays important roles in remodeling the ECM [6,146]. Some small-molecule inhibitors have been developed to target ECM components (Table 4) [147–154].

Hyaluronan

HA, a major ECM component, is synthesized by HA synthases (HAS) and degraded by hyaluronidase (HYAL). HA is elevated in many solid tumors, which leads to increased interstitial fluid pressure and reduced elasticity of tumor tissue [155,156]. Based on its function in ion exchange, HA level may act as a molecular sieve, which blocks perfusion of anticancer drugs and contributes to chemoresistance. High HA levels are correlated with poor prognosis in breast, gastric, colorectal, and bladder cancer [157,158]. Targeting HA has been used to manipulate tumor stroma remodeling and to facilitate drug delivery. For instance, initial reports demonstrated that the addition of corticosteroids to chemotherapeutic regimens, which rapidly decreases HA via inhibiting its synthesis, could significantly improve therapeutic efficacy [156]. Pegvorhyaluronidase alfa (PEGPH20), an enzymatic agent that can ablate stromal HA level and remodel TME, facilitates drug delivery by overcoming physical barriers in the ECM. The combination of chemotherapeutic regimen gemcitabine with PEGPH20 for the treatment of pancreatic ductal adenocarcinoma has shown objective tumor responses and nearly

doubled overall survival [159,160]. HYAL, an enzyme that catalyzes the degradation of HA, promotes DOX penetration and its cell killing effect [161]. In addition, HA is an anionic cell surface-associated polysaccharide, which facilitates HA binding to the CD44 receptor overexpressed in most of cancer cells. Thus, HA has been exploited as a part of delivery tool to transport drug to tumor cells [162–164].

Matrix Metalloproteinase Protein

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases. MMPs are synthesized as inactive zymogens, which are subsequently activated by serine proteinases or other MMPs in the microenvironment [165]. Because MMPs can cleave almost all components of the ECM, they play important roles in ECM remodeling. Accumulated evidence has shown that increased expression or/and activation of MMPs is involved in the processes of carcinogenesis, invasion, and metastasis [166]. Several small-molecule inhibitors selectively targeting MMPs have been developed (Table 4) [150,151]. In addition to being a direct target for cancer therapy, MMPs have also been used as part of drug delivery tools that release the cytotoxic drugs specifically in TME. Sun et al. integrated the chemotherapy drug paclitaxel into nanoparticles that is modified with an MMP-cleavable linker and a cell-penetrating peptide. This functionalized nanoparticle showed a high affinity to both tumor cells and TAMs, and the integrated paclitaxel was effectively delivered and released into the tumor site owing to high levels of MMPs in TME [167].

Lysophosphatidic Acid

Lysophosphatidic acid (LPA) is a crucial component of TME. LPA is mainly produced from lysophosphatidylcholine (LPC) by a secreted enzyme, autotaxin (ATX). LPA activates six G protein-coupled

Table 3. Small-Molecule Inhibitors Target Cancer-associated Fibroblasts and Endothelial Cells in TME

Target	Small-molecular Inhibitor	Target Strategy	Mechanism of Action	Cancer Target	References
CAFs	PT-100 (combined with oxaliplatin)	Inhibit CAFs and reduce chemoresistance	Target fibroblast activation protein	Colon cancer	[113]
CAFs	RKN5755	Inhibit CAF migration	Bind to β -arrestin 1 and interfere with β -arrestin 1-mediated cofilin signaling pathways.	Breast cancer	[114]
CAFs	mPGES-1 inhibitor compound III (CIII)	Reduce tumor growth, impair angiogenesis, inhibit CAFs migration and infiltration, and favor shift in the M1/M2 macrophage ratio	Block CAF-derived prostaglandin E2 (PGE2) production	Neuroblastoma tumor	[115]
CAFs	Scriptaid	Repress TGF β -mediated CAF differentiation and inhibit ECM secretion	Alter the cellular epigenetic regulatory machinery via HDAC inhibition	Melanoma	[116]
CAFs	LE135 and bicalutamide (combined with cisplatin)	Suppress CAF-facilitated oncogenesis and reduce chemoresistance	Retinoic acid receptor β and androgen receptor antagonists	Squamous cell carcinoma	[117]
CAFs	AC1MMYR2 (combined with taxol)	Reprogram CAFs, suppress tumor migration and invasion ability	Reprogram CAFs via the NF-kB/miR-21/VHL axis	Breast cancer	[118]
CAFs	SOM230 (combined with gemcitabine)	Reprogram CAFs and reduce chemoresistance	Activate the sst1 receptor and inhibit the mTOR/4E-BP1 pathway and the resultant synthesis of secreted CAF proteins	Pancreatic cancer	[139]
CAFs	Navitoclax	Trigger CAF apoptosis and suppress tumor outgrowth	Upregulate the proapoptotic protein Bax and diminish expression of the desmoplastic extracellular matrix protein tenascin C	Cholangiocarcinoma	[119]
CAFs	WRG-28	Inhibit tumor invasion and migration	Inhibit receptor–ligand interactions via allosteric modulation of the collagen receptor discoidin domain receptor 2 (DDR2)	Breast cancer	[140]
CAFs and ECs	PD173074	Reduce proliferation of CAFs and ECs suppress fibroblast-enhanced tumor cell growth and inhibit tumor growth	Inhibit fibroblast growth factor receptor (FGFR)	Head and neck squamous cell carcinoma (HNSCC)	[120]
ECs	DIMP53-1	Induce cancer cell apoptosis, inhibit the migration and tube formation of ECs and inhibit angiogenesis	Bind to p53 inhibiting its interaction with MDM2 and MDMX	Colon cancer	[130]
ECs	BEZ235 (combined with verteporfin)	Enhance vascular-targeted photodynamic therapy inhibit endothelial cell proliferation and suppress tumor regrowth	Inhibit PI3K pathway activation	Prostate cancer	[141]
ECs	Biochanin A	Inhibit ECs functions such as cell viability, migration, invasion, and tumor progression	Inhibit activation of proangiogenic proteins (ERK/AKT/mTOR), inhibit chemical hypoxia-inducible factor-1 α and vascular endothelial growth factor	Angiogenic gliomas	[131]
ECs	LLL12	Reduce proliferation/migration of ECs and inhibit VEGF-induced tube formation, suppress tumor growth	Inhibit VEGF-stimulated STAT3 phosphorylation in ECs	Osteosarcoma	[132]
ECs	TW-37 (combined with radiotherapy)	Abrogate new endothelial cell sprouting, inhibit tumor growth	Inhibit Bcl-2	Head and neck cancer	[133]
ECs	CX-4945	Inhibit EC migration, tube formation, cause cell-cycle arrest and selectively induce apoptosis in cancer cells	Attenuate PI3K/Akt signaling and block CK2-dependent HIF-1 α transcription	Breast and pancreatic cancer	[134]
ECs	CC-5079	Inhibit ECs, fibroblast, cancer cell proliferation and migration, inhibit microvessel formation	Stimulate MKP1 expression in ECs and fibroblast	Colon cancer	[135]
ECs	Dasatinib	Inhibit motility and other functions of ECs and myeloid cells, suppress tumor growth associated with increased tumor cell apoptosis, decreased microvessel density	Inhibit phosphorylation of SFKs and downstream signaling, reduce matrix metalloproteinase (MMP)-9 levels in TME	Prostate cancer and colon cancer	[136]
ECs	Pazopanib (GW786034B)	Block cancer cell growth, survival, and migration, and inhibit VEGF-induced up-regulation of adhesion molecules on ECs and tumor cells and decrease angiogenesis	Inhibit VEGF-triggered signaling pathways	Multiple myeloma and metastatic renal-cell cancer	[137,142]
ECs	TNP-470	Inhibit vascular hyperpermeability of tumor blood vessels	Inhibit VPF/VEGF-induced phosphorylation of vascular endothelial growth factor receptor-2, calcium influx, and RhoA activation in ECs	Melanoma, glioblastoma and breast cancer	[138]
ECs	Sunitinib(SU11248)	Cause regression, growth arrest, or substantially reduced growth of cancer cells	Target the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), KIT, and FLT3 receptor tyrosine kinases	Epidermoid carcinoma, colon carcinoma and metastatic renal-cell cancer	[142,143]

CAFs, cancer-associated fibroblasts; ECs, endothelial cells; TME, tumor microenvironment.

Table 4. Small-Molecule Inhibitors Target Extracellular Matrix Components

Target	Small-molecule Inhibitor	Target Strategy	Mechanism of Action	Cancer Target	References
Hyaluronan (HA)	4-methylumbelliferone (MU)	Lower HA levels	Inhibit HAS to synthesize HA	Prostate, breast, pancreatic cancer	[147–149]
Matrix metalloproteinases (MMPs)	cis-ACCP N-[4-(difluoromethoxy)phenyl]-2-[(4-oxo-6-propyl-1H-pyrimidin-2-yl)sulfanyl]-acetamide ONO-8430506 PF-8380	Inhibit MMPs and show antimetastatic activity Abrogate MMP-9 homodimerization and block MMP-9-mediated cell migration related signaling pathway	Sustain and prolong absorption occurred via paracellular Target hemopexin (PEX) domain of matrix metalloproteinase-9	Prostate and melanoma cancer Breast cancer	[150] [151]
Lysophosphatidic acid (LPA)	ONO-8430506 PF-8380	Decrease lysophosphatidate signaling Abrogate radiation-induced tumor neovascularization and delay tumor growth	Inhibit activity of secreted enzyme, autotaxin (ATX) Inhibit activity of secreted enzyme, autotaxin (ATX)	Breast cancer Glioblastoma multiforme	[152] [153]
Collagen	3-[4'-methoxy-3,2'-dimethyl-(1,1'; 4',1'')terphenyl-2''-yl]propionic acid (T12)	Impair the formation of mesh collagen IV and impede tumor EMT	Target mesenchymal goodpasture antigen-binding protein (GPBP) and disturb its multimerization	Non-small cell lung carcinoma (NSCLC)	[154]

receptors to regulate cell division, survival, and migration; LPA signaling is essential for vasculogenesis in embryonic development [168]. LPA acts as a profibrotic and prooncogenic factor and plays important roles in tumor progression, metastasis, angiogenesis, and therapy resistance [2,169–173]. Targeting LPA signaling has been reported to be a promising method to inhibit tumor growth and to improve the efficacies of chemotherapy and radiotherapy (Table 4) [152,153].

Collagen

Collagen is an indispensable component of the ECM. Collagen is composed of 3 polypeptide α chains that form a triple helical structure. In vertebrates, 46 distinct collagen chains assemble to form 28 collagen types that are categorized into fibril-forming collagens, network-forming collagens, fibril-associated collagens with interruptions in their triple helices (FACITs), and others [145,174,175]. Multiple reports have shown that collagen is associated with tumor initiation and progression. Collagen level and cross-linking are strongly correlated with tumor stiffness. Increased stiffness is associated with poor prognosis of breast tumor [176–179]. Targeting collagen is a promising strategy to inhibit tumor growth (Table 4) [154].

Conclusions and Perspectives

Conventional cancer chemotherapies are mostly designed to directly kill cancer cells, and the effectiveness is always compromised by their penetration and accessibility to cancer cells. Small-molecule inhibitors, which exhibit good penetration and accessibility as compared with other large molecules, are widely studied, and most of them are designed to attack cancer cells directly. TME is a complicated and dynamic system, which is an indispensable part of tumor as a whole. As TME is more penetrable and accessible than tumor cells, many efforts have been made to develop therapeutic strategies that target TME. A large number of small-molecule inhibitors that target TME have been developed, many of which are still at the early stages in preclinical and clinical trials. These small-molecule inhibitors are designed to specifically target TME or the components of TME or to be delivered and released specifically in TME.

As there are rapid advances in understanding the underlying mechanisms of the interaction between tumor cells and TME, more and more specific targets in TME will be emerged as druggable targets for cancer therapy. New small-molecule inhibitors that specifically interrupt these new targets will be highly appreciable. To improve the tumor-killing potency and reduce side toxicity effect of the TME-oriented small-molecule inhibitors, we should also consider combining the "three specifics" for the same inhibitor (namely, targeted specifically, delivered specifically, and released specifically in TME). For instance, modifying a small-molecule inhibitor with tumor-selective ligands (such as folate, transferrin, peptides) and PEGylation will improve target specificity, while integrating this inhibitor into nanoparticle delivery systems will increase the delivery efficiency. In addition, exploiting environmental stimuli-responsive delivery systems will enhance inhibitors' target selectivity.

Inhibition of immune regulatory checkpoints, such as CTLA-4 and the PD-1–PD-L1 axis, is currently at the forefront of immunotherapy for cancers of various histological types. However, the CTLA-4 and PD-1/PD-L1 antibodies currently available for tumor immunotherapy are only effective for 20–30% of patients with solid tumor [180–182]. The complexity and heterogeneity of

the TME suggest that there would be other unknown important mechanisms leading to inhibition of T-cell killing and immune suppression. For the immune system to mount an adequate response to cancer, it must overcome a slew of obstacles. First, T cells that recognize tumor antigens must be sufficiently activated by antigen-presenting cells, and they need to (leave lymphoid system and reside beyond the lymphoid system) migrate and amass within specific solid tumors to destroy tumor cells. However, numerous factors from tumors and TME can dampen and suppress antitumor T-cell responses by preventing T cells from amassing into tumors [183]. Second, signals present within the harsh TME undermine the ability of the tumor-infiltrating lymphocytes (TILs), the CD8+ T cells, to fight cancer. Therefore, any strategies, particularly small-molecule inhibitors (or activators) that target TME to promote CD8+ T-cell infiltration in tumors and to prevent the development of a dysfunctional or "exhausted" T-cell state or reverse the function of "exhausted" T cells, would be highly desirable.

Conflicts of interests

The authors declare no conflicts of interests.

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