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Tumor microenvironment as a therapeutic target in cancer

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Abstract

Tumor microenvironment denotes the non-cancerous cells and components presented in the tumor, including molecules produced and released by them. The constant interactions between tumor cells and the tumor microenvironment play decisive roles in tumor initiation, progression, metastasis, and response to therapies. The tumor microenvironment as a therapeutic target in cancer has attracted great research and clinical interest. Here we summarize the current progress in targeting the tumor microenvironment in both drug development and clinical trials; highlight challenges in targeting the tumor microenvironment to achieve therapeutic efficacy; explore new technologies and approaches to better decipher the tumor microenvironment; and discuss strategies to intervene in the pro-tumor microenvironment and maximize therapeutic benefits.

Keywords

Tumor microenvironment; target; therapy; drug; resistance

1. Introduction

Cancer is a genetic disease driven by the accumulation of mutations in cancer cells. Even though non-cancerous cells in tumors, such as stromal cells and immune cells, have been known for quite some time to play critical roles in tumor progression and therapeutic responses, attention has been predominantly focused on cancer cells. However, only 5–10% of cancer cases can be attributed to genetic defects, with 90–95% of all cancer cases having their roots in the environment and lifestyle[1]. Over time, cancer has been recognized as an evolutionary and ecological process[2], involving constant, dynamic, and reciprocal interactions between cancer cells and the tumor microenvironment (TME). The TME comprises all the non-cancerous host cells in the tumor, including fibroblasts, endothelial cells, neurons, adipocytes, adaptive, and innate immune cells, as well as its non-cellular

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components, including the extracellular matrix (ECM) and soluble products such as chemokines, cytokines, growth factors, and extracellular vesicles.

The acquisition and maintenance of the hallmarks of cancer—such as sustaining proliferative signaling, resisting cell death, inducing angiogenesis, activating invasion and metastasis, triggering tumor-promoting inflammation, and avoiding immune destruction—depend, to various degrees, on the contributions from the TME. This reliance on the TME offers an opportunity for therapeutic intervention by targeting TME elements or its signaling pathways. Given the increased understanding of the crucial roles of the TME in tumor development and therapeutic resistance, many efforts have been devoted to targeting components of the TME to achieve therapeutic benefits in cancer patients. There is a significant therapeutic advantage in targeting the TME compared with directly targeting cancer cells, because cancer cells are prone to drug resistance due to their genomic instability, whereas non-tumor cells in the TME have a genetically more stable nature and are more vulnerable. On the other hand, therapies targeting the TME must be specifically directed to cancer-related phenotypic changes in the non-tumor cells to avoid potential adverse effects caused by targeting normal healthy cells in other tissues. To achieve this requires an in-depth understanding of the differences between the pro-tumor host cells in the TME and normal host cells at the molecular and cellular levels. However, many non-tumor host cells present in the TME have a broad spectrum functional status, which brings challenges to deciphering the mechanisms and identifying targets for intervention in the pro-tumor TME.

In this review, we summarize current progress in targeting the TME in both drug development and clinical trials, highlight the challenges and opportunities, and discuss new technologies and strategies that can be adapted to exploring the roles of TME and developing drugs for therapeutic targeting of the TME.

2. Targeting tumor microenvironment: from bench to bedside

2.1 Targeting tumor-infiltrating T-cells

Because targeting immune checkpoints on tumor-infiltrating T-cells to booster anti-tumor immunity and the functions of T-cells have been discussed extensively in many reviews[3–8], we will not reassess these here.

2.2 Targeting cancer-associated fibroblasts and the extracellular matrix

Among the stromal cells present in the TME, cancer-associated fibroblasts (CAFs) are the most abundant[9]. CAFs are critically involved in tumorigenesis, metastasis, angiogenesis, immune evasion, and drug resistance via cell-cell contact, secretion of abundant regulatory molecules and extracellular vesicles, and particularly, synthesizing and remodeling the extracellular matrix (ECM)[10]. Due to their abundance and well-established pro-tumor roles in many tumor types, CAFs have been promising therapeutic targets for cancer intervention, and numerous drugs targeting CAFs have been developed and tested in preclinical studies.

2.2.1 The roles of CAFs and ECM in tumor progression and therapeutic resistance—

CAFs constitute a complex population of cells with wide varieties of cells-of-

origin, heterogeneous phenotypes, and diverse functions[10], all of which are also shared by many other non-cancerous host cells in the TME. Pro-tumor activities of CAFs have been reported in prostate cancer[11], breast cancer[12,13], pancreatic cancer[14], and colorectal cancer[15]. As an example, CAF-derived CXC-chemokine ligand 12 (CXCL12; also known as stromal cell-derived factor 1, SDF-1) promoted breast cancer cell proliferation and rapid tumor growth via binding to CXC-chemokine receptor 4 (CXCR4) expressed on breast cancer cells[12]. A recent study found that activated pancreatic stellate cells (PSCs, resident pancreatic fibroblasts) released a key paracrine factor, leukemia inhibitory factor (LIF), which facilitated pancreatic cancer progression by inhibition of cancer cell differentiation[16]. In addition to secreted factors, CAFs also enhance cancer cell invasion and metastasis through remodeling ECM or cell adhesions. Many ECM components, such as certain types of collagens[17] and matrix metalloproteinases (MMPs)[18], stimulate invasion and metastasis by promoting cancer cell epithelia-mesenchymal transition (EMT)[19] or collective invasion of cancer cells[20]. Mechanically, active adhesion between N-cadherin on CAFs and E-cadherin on cancer cells drives cooperative tumor invasion[21]. Recent in-depth studies of the heterogeneous subsets of CAFs revealed some previous unappreciated functions of CAFs, including antigen presenting[22], depletion of tumor antigen-specific cytotoxic T lymphocytes (CTLs)[23], and tumor suppression[9], suggesting the multiplex functions of CAFs.

Numerous studies have also shown that CAFs, in addition to their extensive influences on tumor development, confer cancer chemotherapy resistance[24] (Fig.1, left). One of the most well-known examples is pancreatic ductal adenocarcinoma (PDAC), which manifests a unique fibrotic TME and is quite resistant to chemotherapy[25]. Some of the CAF-mediated resistant mechanisms include delivery of exosomes stimulating cancer cell survival[26]; promoting cancer cell EMT, which decreases expression of transporters responsible for drug uptake[27]; and scavenging chemo drug to reduce the amount of intra-tumoral chemotherapy drug[28]. CAFs also contribute to targeted therapy resistance. For example, CAF-derived hepatocyte growth factor (HGF) elicits innate resistance of BRAF-mutant cancer cells to RAF inhibitors[29]. Evidence also indicates that CAFs are involved in immune evasion and resistance to immunotherapies. For example, fibroblast activation protein (FAP)-positive CAFs secrete CXCL12, which protected PDAC cancer cells from anti-tumor T-cells and caused unresponsiveness to immune checkpoint blockade (ICB) therapies in mouse PDAC models[30]. Interestingly, a recent study also found that a distinct ECM gene signature is correlated with immune evasion and immunotherapy failure[31], suggesting critical roles of CAFs in responses to immunotherapy.

2.2.2 Developing drugs targeting CAFs and ECM—Various drugs targeting CAFs or ECMs are under preclinical and/or clinical studies (Table 1). Among the potential targets identified in CAFs, FAP is the most extensively studied. FAP is a serine protease expressed on activated CAFs in greater than 90% of human cancers[32]. FAP-targeting immunotoxin successfully depleted FAP^+ CAFs *in vivo* and showed potent tumor inhibitory activities in multiple cancer models[33,34]. Other approaches to target FAP also have been developed, including DNA vaccine[35] and chimeric antigen receptor (CAR) T cells[36]. However, contradictory results generated from different groups raised cautions in the targeting of FAP. For example, the multipotent bone marrow stromal cells also express FAP and can be killed

by immunotoxin, leading to potential toxicity and cachexia[37]. In addition, FAP-targeting immunotoxin failed in an early phase II trial (NCT02198274) in patients with advanced colorectal cancer due to limited therapeutic response[38]. Another potential surface target of CAF is GPR77, which is specifically expressed in a subset CAF population with pro-tumor and chemo-resistance activities[39]. Similar to FAP, GPR77$^+$ CAFs can be selectively targeted by specific antibodies for deletion, which led to a significantly improved response to chemotherapy[39]. Other surface targets of CAF include vitamin D receptor (VDR)[40] and platelet-derived growth factor receptor (PDGFR)[41], both of which can be targeted by small molecules to enhance responses to chemotherapy. VDR has been identified as a crucial suppressor of CAF activation and vitamin D analogs induced notable stromal remodeling in preclinical PDAC models[40]. Several Phase I/II clinical trials are conducted to investigate if paricalcitol, an analog of vitamin D2, will improve response to chemotherapies or immunotherapies in PDAC patients (Table 1) and most results are still pending. Platelet-derived growth factors (PDGF) facilitate the formation of a prominent tumor stroma via recruiting/ activating CAFs and blockade of stromal PDGFR may benefit cancer treatment[42]. However, PDGFR inhibitor Imatinib failed to show therapeutic benefit in patients with advanced stage PDAC in a multi-institutional Phase 2 clinical trial (NCT00161213)[43]. In addition to surface targets, CAF-derived cytokines (IL6[44]), chemokines (CXCL12[12]), and growth factors (LIF[16]) that support tumor cells or the pro-tumor TME also can be blocked to achieve therapeutic benefit. For example, CXCL12 derived from CAFs plays a critical role in local immunosuppression by excluding T-cells from infiltration. The CXCR4 inhibitor AMD3100, which blocks CXCL12 and CXCR4 interaction, restored anti-tumor immunity by enhancing infiltration of CD8$^+$ T-cells into tumor[30]. A recent phase IIa COMBAT clinical trial (NCT02826486) indicated that the combination of pembrolizumab (anti-PD1) and BL-8040 (motixafortide), a CXCR4 antagonist, expanded the benefit of chemotherapy in PDAC[45]. Importantly, BL-8040 treatment effectively reprogramed TME, characterized by increased CD8$^+$ effector T-cell infiltration and decreased immunosuppressive cell populations, including myeloid-derived suppressor cells (MDSCs) and circulating regulatory T-cells[45]. Given their critical roles in promoting tumor progression, ECM molecules such as tenascin C[46], hyaluronan[47], and MMPs[48] have also attracted much attention in drug development. In several phase I and II clinical trials[47,49,50], recombinant human hyaluronidase (PEGPH20), which depleted hyaluronan in tumors, showed promising clinical activities in pancreatic cancer and non-small cell lung cancer, especially hyaluronan high tumors. However, a recent phase III HALO-301 trial of PEGPH20 (NCT02715804) missed it's primary endpoint in patients with metastatic pancreas cancer and further development of PEHPH20 was halted[51]. This failure suggests that targeting desmoplasia alone in PDAC treatment may not be sufficient. Other clinical trials targeting LOXL2[52] and MMPs[53] are also mostly disappointing. Nevertheless, although many potential targets of CAFs have been identified and drugs targeting them have shown some promising results in preclinical tests, only a few such drugs have moved into the clinic in the end (Table 1)[32].

2.3 Targeting tumor-associated macrophages

Tumor-associated macrophages (TAMs), which are abundant in the TME of most cancer types, are generally associated with poor clinical outcome in cancer patients[54,55]. The established pro-tumoral roles of TAMs include stimulating pro-tumor inflammation,

facilitating cancer cell immune evasion, promoting angiogenic switch, and accelerating tumor cell invasion/metastasis. Because TAMs are one of the dominant innate immune cell populations in tumors, the reciprocal interactions between cancer cells and TAMs shape the tumor immune landscape. TAMs are emerging as a key target in immunotherapy.

2.3.1 The roles of TAMs in tumor progression and therapeutic resistance—As an important source of cytokines/chemokines, TAMs are critically involved in the initiation and maintenance of chronic inflammation, which is associated with tumorigenesis and tumor progression[56]. For example, TAM-derived pro-inflammatory cytokines such as IL-1β[57], IL-6[58], and IL-23[59,60] promoted tumor growth and progression in colorectal cancer and other cancer types. The chronic inflammation is induced and maintained by the feed-forward networks formed between cancer cells and TAMs, which may be also involved with mucosal barrier defects and complex interactions with the microbiome[54,61]. In addition to pro-tumor inflammation, TAMs also play a central role in suppression of adaptive antitumor immunity[55]. For example, TAMs express elevated levels of immune checkpoint ligands, such as PD-L1, PD-L2[62], and VISTA[63], which can suppress T-cell activities directly. Furthermore, TAMs can recruit regulatory T-cells (T-reg) and facilitate expansion of T-reg in the TME, ultimately resulting in suppression of T-cell immunity[64]. Angiogenic switch, which refers to the induction of a tumor vasculature, is required for tumor growth and expansion[65]. TAMs promote angiogenic switch by delivering critical pro-angiogenic factors[66], including vascular endothelial growth factors (VEGF)[67], IL-8[68], and MMP9 [69], which reinforce the recruitment and activation of endothelial cells and other cells supporting the generation of the vascular networks. In addition, a subset of TAMs, which express the angiopoietin-1 receptor TIE2 ($TIE2^+$) and cluster around tumor blood vessels, regulates angiogenesis in various mouse tumor models and is correlated with micro-vessel density in human tumors[70]. Given the essential roles of TAMs in stimulating the pro-tumor TME, it is anticipated that metastatic cancer cells will attract bone marrow-derived monocytes, which differentiate into TAMs once extravasated from blood vessels. Indeed, highly invasive cancer cells secrete elevated levels of CCL2 and/or CSF1 to recruit and expand TAMs, which then engage in vicious cycles with cancer cells and promote cancer cell migration[71], intravasation[72], and outgrowth in the metastatic sites[73]. Our team has found that PTEN loss in brain metastases leads to an increased secretion of CCL2, which attracted $CCR2^+$ (CCL2 receptor) microglial cells into the brain; CCL2-knowkdown MDA-MB-231 cells significantly prolonged survival of mice bearing brain metastases[74].

Accumulation of TAMs has been frequently observed in tumors that have received various therapeutic treatments[75], including radiotherapy[76], chemotherapy[77], and anti-VEGF therapy[78]. The protective role of TAMs in response to therapeutic treatment was confirmed by enhanced therapeutic efficacy when recruitment or polarization of TAMs was blocked[79]. Distinct mechanisms may be involved in TAM-mediated therapeutic resistance, including but not limited to restoration of vascularization and suppression of cytotoxic T-lymphocytes. A recent study found that the metabolites released by TAMs in PDAC, particularly the pyrimidines, inhibited gemcitabine through molecular competition and resulted in chemotherapy resistance[80]. TAMs also contribute to adaptive resistance to targeted therapy in cancer. As an example, treatment of melanoma patients with MAPK pathway inhibitor

increased TAMs in the tumor; consequently, TAMs-derived TNFα as a crucial melanoma growth factor caused resistance to MAPK pathway inhibitors[81]. As one of the dominant immunosuppressive cell populations in the TME, TAMs are an important determinant of response to immunotherapy[55]. TAMs prevented cytotoxic CD8+ T-cells from reaching the tumors and led to unresponsiveness to anti-PD1 immunotherapy[82].

2.3.2 Developing drugs targeting TAMs—Drugs targeting monocytes/macrophages with ongoing clinical trials are summarized in Table 2. CSF1R signaling has attracted the most attention so far because CSF1/CSF1R plays a central role in the production, differentiation, and function of macrophages. Inhibitors (PLX3397, JNJ-40346527, PLX7486, and ARRY-382) and neutralizing antibodies (RG7155, IMC-CS4, and FPA008) targeting CSF1R successfully depleted TAMs and microglia in preclinical animal models and cancer patients[54,83]. Some of the inhibitors and antibodies under clinical evaluation induced anti-tumor responses in patients with glioma, lymphoma, or other advanced-stage solid tumors. Among the CSF1R inhibitors, PLX3397 is currently under investigation in multiple clinical trials. PLX3397 was well tolerated but showed no efficacy in glioblastomas (NCT01349036) [84]. Another clinical study of PLX3397 and Pembrolizumab (anti-PD1) (NCT02452424) to treat advanced melanoma and other solid tumors also terminated early due to lack of clinical efficacy (https://clinicaltrials.gov/). Similarly, CSF1R neutralizing antibody FPA008 did not meet its primary end point of progression-free survival in a phase II clinical trial in patients with advanced pancreatic cancer (NCT03336216, https://bwnews.pr/391gi3X). In addition, the potential risk and toxicity caused by depletion of all the macrophages, including normal resident macrophages, need to be carefully evaluated[54]. The CCL2-CCR2 axis is another focus of developing drugs targeting TAMs. CCL2 has been identified as a potent chemoattractant for monocytes/macrophages. Despite the fact that anti-CCL2 monoclonal antibody (mAb) was able to significantly reduce TAMs in the tumor during treatment, withdrawal of the antibody accelerated lung metastasis in several breast cancer mouse models due to fast rebound of monocyte recruitment[82]. Additionally, compensatory and redundant mechanisms leading to the failure of CCL2-CCR2 axis blockade were uncovered in preclinical models[54], suggesting that a better understanding of monocyte recruitment/retention is necessary before performing clinical trials. A phase 1b study of PF-04136309, a small molecule antagonist of human CCR2, in combination with chemotherapies (NCT02732938) raised concern for synergistic pulmonary toxicity and did not show extra benefit over chemotherapies in treatment of metastatic PDAC[85]. On the other hand, an anti-CCR2 antibody (MLN1202) tested in a phase II clinical trial (NCT01015560) for metastatic cancer showed therapeutic effects in 14 out of 43 patients with bone metastases[85]. In addition to depletion of TAMs or blocking recruitment of monocytes, there have also been attempts to develop drugs that can reprogram TAMs, such as agonistic anti-CD40 antibodies[86], histone deacetylase inhibitors[87], and PI3Kγ inhibitors[88,89]. The goal is to convert TAMs from a pro-tumor phenotype to an anti-tumor phenotype, which includes releasing TAM-mediated immunosuppression of adaptive immunity, abolishing pro-angiogenic function, and interrupting the bad cycle between TAMs and tumor cells. Despite that the antitumor effects of targeting CD40 for monotherapy or combination therapy have been observed in some tumors, the therapeutic efficacy has been moderate and heterogeneous[90]. Macrophage PI3Kγ controls an important switch between immune

stimulation and suppression during inflammation and cancer[89]. Initial clinical results from IPI-549, a PI3Kγ inhibitors, combined with nivolumab (anti-PD1) in advanced solid tumors (NCT02637531) demonstrated favorable tolerability, evidence of immune stimulation, and early signs of clinical activity[91]. CD47-mediated "do not eat me" signaling is another potential target to invigorate anti-tumor activities of macrophages. CD47, which is highly expressed on tumor cells, interacts with thrombospondin 1 and signal regulatory protein-α (SIRPα) expressed by macrophages, activating the "do not eat me" signal and protecting tumor cells from phagocytosis by macrophages[92]. Blockade of the CD47-SIRPα axis by anti-CD47 antibodies[93] or recombinant SIRPα-crystallizable fragment (Fc) fusion protein[94] increased tumoricidal activity of macrophages in preclinical studies and early clinical trials. Gilead's Magrolimab (Hu5F9-G4), a first-in-class investigational anti-CD47 mAb, is tested in multiple clinical trials. A phase Ib/II clinical study of magrolimab in combination with cetuximab (anti-EGFR) showed encouraging responses in colorectal cancer patients[95].

2.4 Targeting tumor-associated neutrophils

Neutrophils, which originate from myeloid precursors, are the most abundant population of white blood cells in peripheral blood and the first responders of innate immunity[96,97]. Tumor-associated neutrophils (TANs) constitute an important part of the TME and are actively involved in tumor progression and metastasis. Many preclinical studies have demonstrated the pro-tumor roles of TANs, which are achieved partially by stimulating the ECM and inflammation of the TME. Neutrophil-released granules consist of various proteases, including matrix metalloprotease 9 (MMP-9)[98], neutrophil elastase[99], and cathepsin G[100], which can remodel ECM and promote tumor invasion[101]. Besides proinflammatory cytokines/chemokines, TANs also produce immunosuppressive factors, such as arginase 1 and TGFβ, which suppress adaptive immunity[102], and release growth factors, including HGF[103], which support tumor progression. Recent studies found that not only TANs in the TME but also neutrophils in the peripheral blood facilitate tumor progression and metastasis[104]. Interactions between circulating tumor cells (CTC) and neutrophils in the bloodstream drive tumor cell cycle progression[104], stimulate tumor cell extravasation[105], and significantly enhance metastatic potential of CTC. Consistent with these findings, a high circulating neutrophil-to-lymphocyte ratio (NLR) in patients represented a poor prognostic factor in breast, colon, liver, and many other types of cancer[96,102]. Targeting of neutrophils has emerged as a potential therapeutic approach for cancer patients[106]. One of the most promising targets is CXCR2, a critical regulator for neutrophil mobilization[107]. Small inhibitors or antibodies blocking interactions between CXCR2 and its ligand (CXCL8), which showed anti-tumor activities and enhanced responses to chemotherapies in preclinical studies, are under clinical evaluation[106]. Several clinical trials of SX-682, a potent inhibitor of CXCR1/2, are proposed to test whether SX-682 can block cancers from attracting MDSCs and enhance therapeutic efficacy in combination with immunotherapies[108]. Recently, our team revealed that EZH2 can be phosphorylated at tyrosine (Y) 696 by Src, and p-696-EZH2 works as a transcription factor to upregulate G-CSF, which recruits immunosuppressive neutrophils into brain metastases lesions; G-CSF antibodies, and combinatorial immune checkpoint blockade plus Src inhibitors can block neutrophil infiltration to inhibit brain metastasis[109].

2.5 Targeting tumor-promoting chronic inflammation

Inflammation is a fundamental innate immune response to disturbed tissue homeostasis[110]. Chronic inflammation is recognized as one of the hallmarks of cancer[111], which fuels tumorigenesis and promotes cancer progression. Anti-inflammatory drugs, including aspirin, significantly reduced cancer risks in large population studies[112,113], suggesting that inflammation is a promising target for cancer therapy. Macrophages, which are the prime source of inflammation, and tumor cells both can produce proinflammatory cytokines and inflammatory mediators, which sustain tumor cell proliferation and survival[58], immune evasion[114], angiogenesis[115], ECM remodeling[116], metastasis[56], chemoresistance[117], and radioresistance[118]. Targeting either the key mediators involved in proinflammatory pathways, such as primary inflammatory cytokines (e.g., IL-1, TNF, IL-6), or the master regulators of the inflammatory response, such as transcription factors NF-κB and STAT3, may inhibit cancer-promoting inflammation[119]. TGFβ is also an attractive target since it is a master regulator of chronic inflammation. Different classes of TGFβ inhibitors, including neutralizing, and bifunctional antibodies, receptor kinase inhibitors, antisense oligonucleotides, and TGFβ-related vaccines have been developed and tested in multiple clinical trials.[120] However, despite extensive efforts in > 15 years since the first clinical trial was engaged, the translation of TGFβ inhibitors from bench to bedside has been slow and challenging. For example, the antitumor activity of PF-03446962, a fully human IgG2 monoclonal antibody that blocks TβRI, has been investigated and failed in hepatocellular carcinoma[121], urothelial cancer[122], malignant pleural mesothelioma[123], and metastatic colorectal cancer[124]. Galunisertib (LY2157299), a first-in-class small inhibitor of TGFβRI, didn't show clinical benefit in patients with malignant glioma in two separate studies[125,126]. With ongoing clinical trials of next generation TGβRI inhibitors and bifunctional antibodies combining TGFβ and immune checkpoint inhibition[120], TGFβ is now considered an appealing therapeutic target in the era of immunotherapy. Another option is targeting macrophages, because they are the major source of inflammatory factors[127]. Currently, some antibodies/inhibitors have shown anti-tumor activities in preclinical studies and a few of them have been explored in early-stage clinical trials[54]. A challenge of targeting inflammation is how to achieve selective inhibition of pro-tumor chronic inflammation without ruining anti-tumor immunity.

2.6 Targeting tumor angiogenesis

Angiogenesis is considered essential for tumor development and progression. Many antiangiogenic drugs have been developed and tested in the clinic to treat various human malignancies. However, antiangiogenic therapy provides only transitory improvements in a small subset of cancer patients[128]. One major reason for failure of the therapy is that the hypoxia TME, which is prompted by disruption of tumor vessels, drives tumor neovascularization and regrowth. On the other hand, more in-depth studies found that antiangiogenic therapies, such as inhibition of VEGF and the VEGF receptor (VEGFR), create a more mature and functional vasculature, which will enhance drug delivery and efficacy[129]. Therefore, targeting tumor angiogenesis may have potential in combinatory therapies.

2.7 Targeting other components of the tumor microenvironment

Other components in the TME, including B-lymphocytes[130,131], Treg[132], adipocytes[133–135], mesenchymal stem cells[136], and exosomes[137,138], also influence tumor progression and therapeutic responses. For example, adipocytes can promote ovarian cancer metastasis and chemoresistance via adipokine release and lipid transfer[133,134]. However, the functions and mechanisms of these components underlying their relationships with cancer cells are much less appreciated compared with those discussed above, and how to maneuver them to achieve therapeutic effects remains unclear.

3. Challenges of targeting the tumor microenvironment

3.1 Paradox: friends or foes?

To develop effective therapies targeting the TME, it is critical to determine the roles of non-cancerous host cells and non-cellular components in the TME. Host cells or non-cellular components with pro-tumor roles need to be restrained by antagonists to block their activities or reduce their amounts, while cells or components with anti-tumor functions could be targeted by agonists to enhance their activities or increase their amounts. One of the greatest challenges to targeting the TME is that various host cells or non-cellular components within the TME may have contradictory relationships with cancer cells. In addition to the conventional pro-tumor roles of CAFs and TANs, recent studies found some populations of CAFs and TANs have tumor-suppressive activities. Depletion of alpha smooth muscle actin positive (α-SMA+) CAFs in PDAC mouse models increased cancer stem cells (CSC) and induced more aggressive tumors that ultimately diminished survival[139]. Similarly, targeting tumor-derived sonic hedgehog signaling, which drove the desmoplasia in PDAC, accelerated tumor progression despite reduced fibrotic contents[140]. These data suggest that at least some CAFs may restrain PDAC growth. Studies on TANs also resulted in controversy regarding the role of neutrophils in cancer[141–143]. In fact, TANs with a pro-tumor phenotype (N2) would switch to an anti-tumor phenotype (N1) upon blockade of TGFβ signaling, suggesting multifaceted and dynamic roles of TANs[144]. Although it is still not clear whether certain subtypes of macrophages can restrain tumor growth, the anti-tumor efficacy of anti-CD47 in preclinical studies indicates potential tumoricidal activity of TAMs[94]. In sum, the paradoxical roles of TME components discovered in recent years indicate important knowledge gaps in our understanding of the fundamental components of the TME. This may be a reason why attempts to eliminate CAFs or TAMs largely failed to show efficacy in cancer clinical trials as monotherapies. How to distinguish the contradictory functions of TME components and precisely target subsets with desired functionality remains a huge challenge.

3.2 Complexity: heterogeneous and dynamic phenotypes

One major barrier to deciphering and targeting the TME is its complexity. The TME comprises numerous cell types, each of which consists of heterogeneous subsets with various phenotypes and diverse functions. Recent studies have found that the immune cells in the TME show significantly increased heterogeneity of cell states and marked phenotypic expansions compared with those in blood and normal tissues[145]. For example, 14 unique myeloid and 17 unique T-cell clusters were found in human breast tumor tissues, double the

number of observed clusters in normal breast tissue[145]. The heterogeneity of non-cancerous cells likely derives from a wide variety of cells-of-origin and the exposure of cells to diverse local microenvironments, which differ in the extent of hypoxia, inflammation, nutrient supply, growth factors, and other inputs.

Conventional classification, which separates non-cancerous cells into a few mutually exclusive categories marked by discrete activation or differentiation status (polarization), has been widely adopted to analyze $CD4^+$ T helper cells (Th1 vs. Th2), macrophages (M1 vs. M2), and neutrophils (N1 vs. N2). However, the latest evidence from CyTOF and single-cell sequencing indicated that the conventional classification, based mostly on markers generated in *in vitro* experiments, may utterly oversimplify the phenotypic complexity of non-cancerous cell populations in the TME[146,147]. Recent analysis of T-cells in the TME revealed that T-cells reside along a broad continuum of activation status[145]. The phenotypic heterogeneity of T-cells in the TME is likely shaped by a combination of antigen TCR stimulation and local microenvironmental stimuli, which together may lead to more discrete states of T-cells despite the fact that many of the responses individually (e.g., inflammation, hypoxia) represent phenotypic continuums. The myeloid cells in the TME are even more complicated in their heterogeneity[148], and their effect on tumor progression remains poorly characterized. Analysis of TAMs in human breast cancer at single-cell resolution challenged not only the traditional macrophage polarization model (M1 vs. M2) but also the refined model in which TAMs reside along a spectrum between the M1 and M2 states[145]. Instead, this analysis suggested the co-existence of M1 and M2 states in TAMs[145].

The TME is not static but undergoes massive dynamic changes during tumor development. However, little is known about these changes of TME components in human cancer. Additionally, cancer therapies, including radiotherapy, chemotherapy, targeted therapy, and immunotherapy, have enormous impact on the TME. For example, chemotherapies can eliminate most neutrophils in the TME[149]. On the other hand, chemotherapeutic agents can influence multiple aspects of TAMs[150], such as recruitment of monocytes/macrophages to the tumor sites, depletion of monocyte/macrophage linages, and regulation of macrophage phenotypes. Immunotherapy also has broad impacts on the TME, including myeloid cells[151]. Whether and how these impacts on TME will affect patient responses to treatment is still largely unknown.

The complexity of the TME imposes vast challenges to a full understanding of the TME components and structure, and to development of effective drugs to target them. However, recent technological advances, including single-cell omics and artificial intelligence (AI), provide unprecedented opportunities to unbiasedly decipher the complexities of the TME at the single-cell level on a genome scale.

4. Profiling and deciphering the tumor microenvironment

4.1 Profiling the tumor microenvironment

Attempts to dissect the complexity of the TME have motivated development of computational approaches, such as deconvolution methods, to integrate the estimation of type-specific expression profiles of tumor cells, immune cells, and the tumor stroma.

However, small subsets of TME components are either invisible or only partially characterized when interrogated using standard analyses that average data across a bulk population of cells. The ongoing revolution in single-cell omics, with single-cell RNA sequencing (scRNA-seq) leading the way, addresses the problem and provides novel and important insights into highly complex and dynamic biological systems, such as the TME.

Characterization of single-cell programs at the genome scale allows more precisely the deciphering of heterogeneous cellular subsets in the TME and uncovers previously unappreciated functions. As an example, scRNA-seq identified a subset of CAFs characterized by LRRC15 expression ($LRRC15^+$) and TGF-β signaling activation as a determinant of resistance to immunotherapy[152]. Similarly, antigen-presenting CAFs (apCAF), which express MHC II and are capable of activating $CD4^+$ T cells in an antigen-specific fashion, were found in both a mouse PADC model and human PDACs for the first time[22]. These findings highlight the need to revise the cell subset structures based on unbiased analyses of scRNA-seq data instead of limited protein marker expression defined by previous studies.

Single-cell sequencing allows profiling of small quantities of tumor cells and TME cellular constituents simultaneously, which makes it valuable to study co-evolution of tumor cells and the TME during tumor development. Analysis of pancreatic cancer precursors at single-cell resolution revealed increased proinflammatory immune components in the TME at an early stage, which was progressively depleted and taken over by stromal myofibroblast populations during neoplastic progression[153]. Profiling of patients' melanoma at single-cell resolution uncovered two distinct tumor cell states, Melanocyte inducing transcription factor (MITF) dominant and AXL dominant, which corresponded to distinct tumor microenvironmental patterns[154], including specific interactions between cancer cells and their TME. Single-cell sequencing can also be applied to track the dynamic changes of the TME during therapeutic treatment. Using paired scRNA-seq and T-cell receptor sequencing of cells from patients with basal or squamous cell carcinoma before and after anti-PD-1 therapy, T-cells responding to checkpoint blockade were found to mainly derived from a distinct repertoire of T-cell clones that had not been observed before treatment, instead of pre-existing tumor-infiltrating T lymphocytes[155]. Taken together, single-cell sequencing of tumor cells and the TME cells will provide immense insights on tumor evolution, patients' tumor classification, and guidance for cancer therapies.

The phenotype and function of cells in the TME may be highly dependent on a cell's exact spatial location and interaction with adjacent cells. Coupling scRNA-seq with spatial information offers in-depth mechanistic insights into cell-cell interactions and relationships among different cellular components. Direct quantification of individual RNA in cells can be achieved in intact tissue by fluorescence *in situ* hybridization (FISH)[156,157]. Advances in spatially resolved technologies for tumor profiling, including multiplex tissue imagine[158], as well as the integration of data from disparate technologies, will significantly improve our understanding of cell-cell interactions and spatial effects in the TME[159,160].

Along with scRNA-seq, new methods and technologies to profile genetic, epigenetic, proteomic, spatial, and lineage information in individual cells have been invented and are

advancing rapidly[148,161]. These single-cell multiomics technologies can reveal cellular heterogeneity at multiple molecular layers. Integrative analysis of multiomics data will provide profound novel insights into the fundamental mechanisms driving cellular heterogeneity and help to identify targetable cellular subsets/signaling essential for cancer cell adaptation to the TME[162].

4.2 Organ chips for dissection of local TME

Animal models are precious for elucidating functions and mechanisms of the TME, but they do not always faithfully recapitulate human-relevant tissue and organ microenvironment. As a result, preclinical animal models generally perform poorly in predicting therapeutic responses in human clinical trials[163]. Even when orthotopic models effectively display some human cancer behaviors, it is difficult to decipher cellular interactions and physiological processes due to the lack of temporal resolution and sensitivity of human tissues in most animal models. To overcome these challenges, human organs-on-chips (also known as organ chips) based on microfluidic cell culture technology provide opportunities to model cancer cell behaviour within the human-relevant TME *in vitro*. Organ chips are microfluidic cell culture devices containing perfused hollow microchannels made from optically clear plastic, glass, or flexible polymers[164]. The microchannels are inhabited by tumor cells, normal epithelial cells, stromal cells, endothelial cells, and immune cells under conditions mimicking *in vivo* organ-level physiology and pathophysiology by recreating tissue-level and organ-level structures and functions *in vitro*[165]. Organ chips enable dissection of the local TME and study of the effects of a single microenvironmental component on cancer cells, cultured either alone or in various combinations with different cell types, numerous mechanical cues, and even microbiota, while visualizing key steps of the human cancer cascade, such as angiogenesis and invasion/metastasis, and responses to therapy in real time and a controlled manner at high resolution. As an example, a study using a lung cancer chip found that healthy alveolar epithelium promoted human non-small-cell lung cancer cell proliferation, while secreted factors from endothelial cells partially suppressed tumor growth[166]. In a breast cancer chip, a complex HER2+ breast cancer ecosystem, composed of cancer cells, endothelial cells, CAFs, and immune cells, was reconstituted and the therapeutic response to trastuzumab was visualized *ex vivo* in real time[167]. Along with more and more scRNA-seq data generated from human tissues/organs and patients' cancer samples, the emerging single cell expression atlas of human organs/tissues will guide the research and development of more human-relevant next-generation organ chips. The incorporation of human organ chips into drug development pipelines will significantly accelerate discovery of new drugs targeting the human TME, which could not have been realized using traditional *in vitro* systems and available preclinical animal models.

4.3 Artificial intelligence (AI) empowerment of TME research

Artificial intelligence (AI) has shown immense potential for recognizing patterns in large amounts of high dimensional data, deciphering relationships among complex features in big data (including images), and identifying characteristics in big data, all of which are critical for understanding the complex TME. It is conceivable that AI technology will become a key component of TME research to manage and analyze big data describing the highly heterogeneous and convoluted TME. AI-based analysis will be especially useful for

extracting quantitative information about the TME from using whole-slide histopathologic images[168,169], flow and mass cytometry, and bulk and single-cell transcriptomic approaches. Integration of AI technology and multiplex biomarker analysis will enable analysts to gain deep insights into the TME[170]. Using deep learning (DL), a subset of machine learning (ML) in AI technology that applies artificial neural networks to learn from data without supervision, Joel et al. analyzed tumor-infiltrating lymphocytes (TILs) based on H&E images from 13 TCGA tumor types[171]. DL helped to uncover relationships between TIL patterns and tumor genetic features, immune landscape, cancer type, and patient outcome. Another study applied an ML approach to analyze immune-related gene expression in patients with non-small cell lung cancer and identified an immune-related gene signature that successfully predicted patients' responses to immune checkpoint blockade therapies[172]. New paradigms arising from the incorporation of ML, organ chip technology, time-lapse microscopy analysis, and single-cell transcriptomic approaches may achieve reconstitution of human TME *ex vivo* and potentially diminish the gaps between *in vivo* and similar *ex vivo* scenarios. Furthermore, DL may even help to recapitulate and predict patients' therapeutic responses via *in silico* experiments.

5. Strategies to target the pro-tumor microenvironment

5.1 Elimination

Elimination of pro-tumor elements in the TME has been considered an effective way to target the TME and has been widely investigated in preclinical and clinical studies. For example, treatment with anti-CCL2 antibody or anti-CSF1R antibody can significantly reduce the amount of TAMs in the TME, whereas anti-FAP antibody is able to specifically deplete FAP^+ CAFs. However, some concerns have been raised recently in regards to its potential toxicity, off-target effects, and long term effects. Anti-FAP antibody targeted not only CAFs but potentially also muscle cells and bone marrow cells[37]. Similarly, anti-CSF1R antibody treatment depleted tissue resident macrophages, such as microglia in brain and Kupffer cells in liver[173], in addition to TAMs in the tumor. Elimination of these normal cells may induce toxicity during treatment. Moreover, depletion of an entire population of cells in the TME may eliminate potential subsets that have anti-tumor activities or are critical for therapeutic response. One example is eradication of SMA^+ CAFs in pancreatic cancer, which led to more aggressive cancer[139], suggesting that some subsets of SMA^+ CAFs might suppress PDAC cells[174]. Depletion of TAMs in the TME may also remove some macrophages with tumoricidal activities. Furthermore, emerging evidence indicates that macrophages in the TME play critical roles for anti-tumor immunity and immunotherapy response, suggesting that depletion of all the macrophages in the TME may not be totally beneficial[55]. Lastly, the long-term effects of the elimination procedure, including the compensatory response, may lead to the failure of the treatment. To achieve long-term therapeutic efficacy, cellular homeostasis will be a great challenge for monotherapies using elimination procedure (Fig 1, right).

5.2 Normalization

Other than direct elimination of pro-tumor elements, it is appealing to target the TME by blocking the pro-tumor activities of the TME or even reprogram the pro-tumor phenotype/

function of the TME to an anti-tumor phenotype/function. The idea of “normalization” is to revert the overall tumor-favoring TME to a normal tissue environment, which generally restrains early tumor development and improves the delivery and efficacy of anticancer therapeutics[175]. To reach this goal requires mechanistic insights into the pro-tumor phenotype/function in the TME. Some molecules/pathways contributing to the pro-tumor phenotypes/functions of TME have been identified and targeted to “normalize” TME. Blockade of GPR77-mediated signaling abolished pro-tumor activities of CAFs and made cancer cells vulnerable to chemotherapy[39]. Another example is PI3Kγ, which is highly expressed in myeloid cells in the TME, and inhibition of PI3Kγ signaling switched the immunosuppressive phenotype of TAMs to an immunostimulatory transcriptional program that restored CD8+ T cell anti-tumor immunity[89]. PD1 is also considered a target to achieve “immune normalization” for negating tumor-induced immune deficiency selectively in the tumor microenvironment[176]. Compared with elimination, normalization strategy intervenes to tip the balance toward anti-tumor activities by selective targeting of pro-tumor signaling in the TME, which reduces overall potential toxicity and off-target effects. However, whether “normalization” of one pro-tumor signaling pathway will be sufficient to convert the TME and achieve therapeutic efficacy is not clear. Meanwhile, given the high complexity and heterogeneity of the TME, different normalization approaches may be needed to target various subtypes of the TME. The recent discovery of six different immune subtypes of cancer across multiple cancer types has shed some light on the inter-tumor heterogeneity of the tumor immune microenvironment[177]. Biomarker-guided normalization approaches may be necessary to achieve precise targeting of the TME and improve therapeutic efficacy.

5.3 Targeting tumor cells to intervene in the pro-tumor microenvironment

Despite the advantages of targeting the TME directly, such an approach might achieve only transient and limited efficacy as monotherapy due to cellular homeostasis of the TME (Fig. 1, right). In the presence of cancer cells, which can recruit and manipulate non-cancerous cells, the TME will be replenished after withdrawal of the treatment. Without targeting cancer cells, it is difficult to achieve broad and sustainable effects on TME.

Cancer cells are the major driving force behind co-evolution of cancer cells and the TME. Many studies have indicated that cancer cells facilitate cancer progression by manipulating a cancer-favoring microenvironment. Compared with targeting TME directly, targeting cancer cells may treat the root cause of the pro-tumor TME instead of the symptoms[178]. Some oncogenic/suppressive signaling may modulate the pro-tumor TME, in addition to their well-known cell autonomous functions. For example, KRAS mutation in pancreatic cancer cells activates the Sonic Hedgehog (SHh) signaling, which drives CAF activation and promotes the synthesis of ECM components and MMPs[179]. Tp53 loss or mutation in cancer cells is associated with reduced CTLs and NK cells in TME[180], which can accelerate cancer cell immune evasion. Recent study indicated that loss of Tp53 in head and neck cancer also drives adrenergic transdifferentiation of tumor-associated sensory nerves, which in turn stimulate tumor progression[181]. NF1 loss in glioblastoma cells correlates with increased TAMs and altered immune landscape in glioma[182]. Despite these emerging findings, intrinsic drivers dictating stromal and immune contexture of the tumors are largely unknown.

The latest advances in technology offer unparalleled opportunities to investigate the biomarkers and intrinsic determinants of the TME by delineating the multi-omics profiles of tumor cells and the TME. Analysis of genetic alterations in cancer cells with matched tumor stromal/immune landscape may yield in-depth mechanistic insights and enable rational decision-making in the clinical use of personalized intervention strategies for cancer patients. Instead of normalizing one signaling pathway in the TME, targeting the intrinsic determinants of tumor stromal and immune landscape in cancer cells may rewire the over-all entire communication networks between cancer cells and the TME, which may switch TME from pro-tumor to antitumor activities.

6. Summary and perspectives

As the key element of the evolutionary and ecological process in cancer development and cancer therapy, the TME has been attracting more and more attention in research and drug development. Recent advances in cutting-edge technologies, such as single-cell multi-omics and AI, enable deciphering the TME via multi-omics profiling and will significantly reduce our current knowledge gaps. Emerging evidence suggests that in many cases, targeting elements of the TME alone may be inadequate for executing broad and sustainable therapeutic efficacy in cancer patients.

Despite important progress made in the past decade, many clinical trials targeting the TME have failed to show promising efficacy in cancer patients. The only exception is immunotherapy, including immune checkpoint blockade therapies. The success of developing immunotherapies from bench to clinic highlights several key points. Perhaps the first is the importance of basic research. The breakthrough of immunotherapies emerged from a careful deciphering of basic biology that spanned many years, including fundamental mechanisms of T-cell activation and inhibition. Our current understanding of fibroblasts, macrophages, and other TME elements has not reached a level similar to that for T-cells. Lack of an in-depth understanding of the fundamental mechanisms of these TME elements impedes the discovery and development of novel drugs targeting TME. The second point concerns biomarker-guided therapy. Immunotherapies, such as anti-PD1/PDL1 treatment, show significantly more efficacy in the treatment of tumors with pre-existing anti-tumor immunity, such as more T-cell infiltration and higher levels of IFNγ and PDL1 expression in tumors. Similarly, given the high heterogeneity of the TME, development of reliable biomarkers to guide TME-targeted therapies will be essential to achieve clinical efficacy. The third clue is the value of the combinatory approach. Despite remarkable and durable efficacy in some cancer patients who received immunotherapies, currently a majority of cancer patients do not benefit from immunotherapies. It has been recognized that combinatory therapy is promising for improving response to immunotherapy. TME-targeted therapies may have to be combined with other therapies to maximize efficacy and benefit more patients. With all these insights from success in immunotherapies, we expect that TME-targeted therapy will not take long to achieve a breakthrough and reach its first milestone.

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Abbreviations

α-SMA	alpha smooth muscle actin
AI	artificial intelligence
CAF	cancer-associated fibroblast
CAR	chimeric antigen receptor
CSC	cancer stem cell
CTC	circulating tumor cell
CTL	cytotoxic T lymphocytes
CXCL12	CXC-chemokine ligand 12
CXCR4	CXC-chemokine receptor 4
DL	deep learning
ECM	extracellular matrix
EMT	epithelia-mesenchymal transition
FAP	fibroblast activation protein
FISH	fluorescence in situ hybridization
HGF	hepatocyte growth factor
ICB	immune checkpoint blockade
LIF	leukemia inhibitory factor
mAb	monoclonal antibody
MDSC	myeloid-derived suppressor cell
MITF	melanocyte inducing transcription factor
ML	machine learning
MMP	matrix metalloproteinase
NLR	neutrophil-to-lymphocyte ratio
PDAC	pancreatic ductal adenocarcinoma

PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PSC	pancreatic stellate cell
scRNA-seq	single-cell RNA sequencing
SHh	Sonic Hedgehog
SIRP	signal regulatory protein
TAM	tumor associated macrophage
TAN	Tumor-associated neutrophil
TIL	tumor-infiltrating lymphocytes
TME	tumor microenvironment
VDR	vitamin D receptor
VEGF	vascular endothelial growth factor

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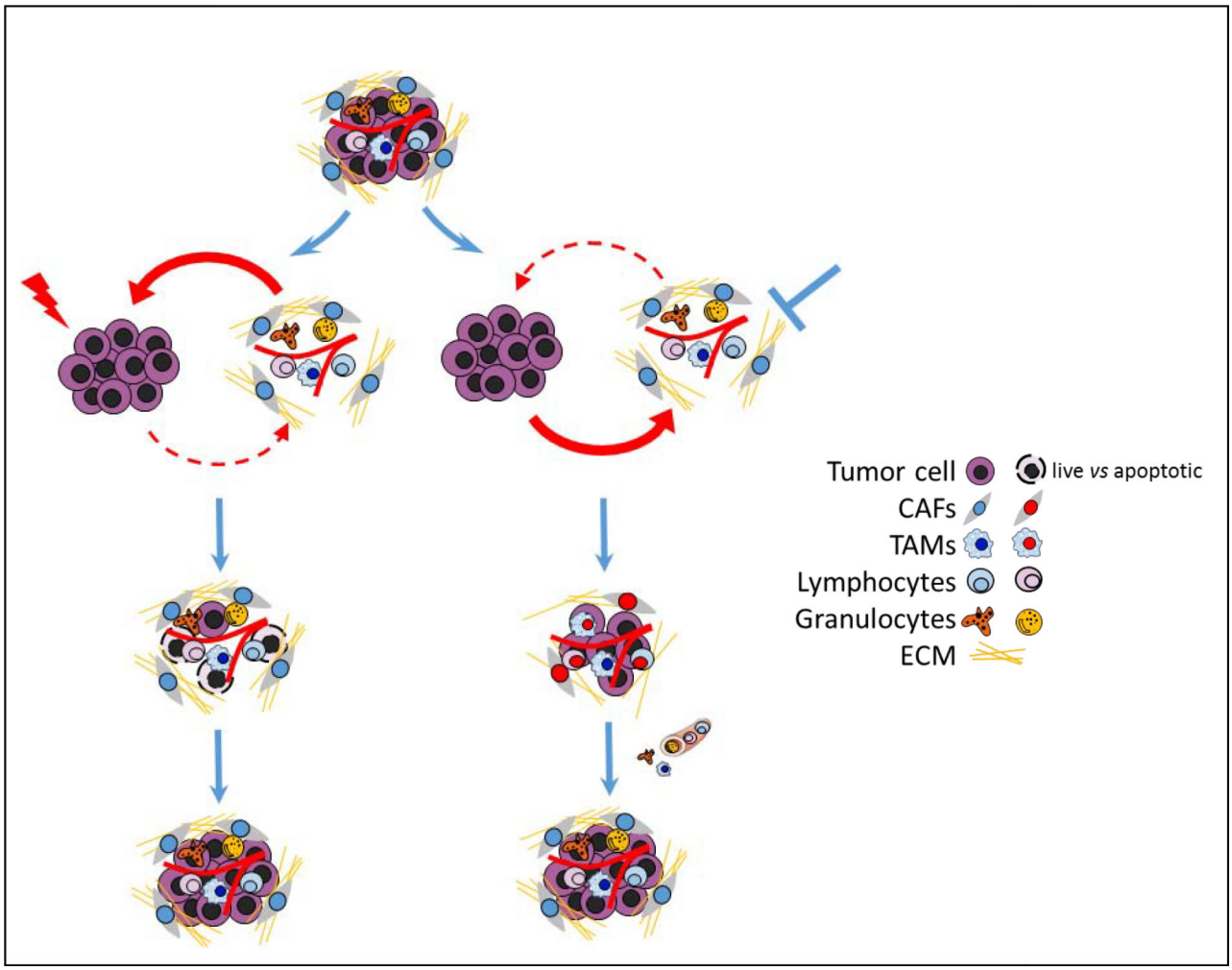

Fig.1.

Schematic diagram of targeting tumor cell or TME only and their potential resistant mechanisms. Left: Targeting tumor cell only (such as chemotherapies) kills majority tumor cells. However, the residue tumor cells may survive with the help from TME, leading to tumor relapse. Right: Targeting TME can inhibit recruitment and activation of pro-tumor cells (stromal cells and immune cells) and enhance anti-tumor responses. However, the TME will be reconstituted by tumor cells via active recruitment and programming of bone marrow derived cells or local resident stromal/immune cells.

Table 1.

Selected drugs potentially targeting cancer-associated fibroblasts (CAFs) or the extracellular matrix (ECM) in preclinical and clinical studies

Drugs	Target and mechanism	Cancer types	National Clinical Trial number	Status	Ref.
Sibrotuzumab	^{131}I-labeled anti-FAP mAb	Colorectal, non-small cell lung, breast, or head and neck cancers	NCT02198274 NCT02209727	Phase I	183
Calcipotriol Paricalcitol	Vitamin D analogue	Early-stage skin cancer, breast cancer, pancreatic cancer	NCT03596073 NCT04617067 NCT02030860 NCT03138720 NCT04054362	Phase I/II	40
Pamrevlumab (FG-3019)	Anti-CTGF mAb	Pancreatic cancer	NCT03941093	Phase III	184
Plerixafor (AMD3100) BL-8040 (motixafortide)	CXCR4 receptor antagonist	Pancreatic cancer	NCT04177810 NCT02179970 NCT02826486 NCT03193190	Phase I/II	30,45
IPI-926	Smoothened inhibitor	Pancreatic cancer	NCT01130142	Phase I	185
S-3304	MMP inhibitor	Advanced solid tumors	NCT00078390 NCT00033215	Phase I	48
^{131}I-m81C6	^{131}I-labeled anti-tenascin mAb	Brain tumors	NCT00002752 NCT00003461	Phase II	186
Imatinib	PDGFR inhibitor	Advanced solid tumors	NCT00161213 NCT00281996 NCT01048320 NCT00485485	Phase I/II	187
GS-6624 (simtuzumab)	LOXL2 mAb	Pancreatic cancer	NCT01472198 NCT01479465	Phase II	52
Tetrathiomolybdate	Copper chelator, target LOX	Breast cancer, prostate cancer	NCT00195091 NCT00150995 NCT00405574	Phase II	188
pegvorhyaluronidase alfa (PEGPH20; PVHA)	Recombinant Human Hyaluronidase	Lung cancer, Pancreatic cancer,	NCT01453153 NCT02563548 NCT01839487 NCT02715804	Phase I/II/III	

Table 2.

Drugs targeting monocyte/macrophage populations in preclinical and clinical studies

Drugs	Target and mechanism	Cancer types	National Clinical Trial number	Status	Ref.
FPA008, PLX3397, IMC-CS4, AMG 820, PLX7486,	CSF1R blocking antibodies or inhibitors	Advanced tumors, pancreatic cancer	NCT01346358 NCT02452424 NCT03336216 NCT01349036	Phase I/II	83,173
MLN1202, PF-04136309	CCR2 blocking antibodies or antagonists	Bone metastasis, pancreatic cancer	NCT01015560 NCT01413022 NCT02732938	Phase II	83,189
CP-870,893, APX005M	CD40 agonist antibodies	Melanoma, breast cancer, non-small cell lung cancer, renal cell cancer, esophageal cancer, brain tumor	NCT02157831 NCT01456585 NCT03165994 NCT03123783 NCT03719430 NCT04130854 NCT02482168	Phase I/II	90,190
IPI-549	PI3Kγ inhibitor	Advanced solid tumors	NCT02637531 NCT03961698	Phase I/II	91
Hu5F9-G4, CC-95251, SRF231	SIRPα or CD47 blocking antibodies, target CD47/SIRPα axis	Lymphoma, leukemia, colorectal cancer	NCT03783403 NCT02953782 NCT03558139 NCT02216409	Phase I/II	191
AZD9150	Stat3 inhibitors	Advanced pancreatic, non-small cell lung cancer, colorectal cancer	NCT03421353 NCT03394144 NCT01839604 NCT03334617 NCT02499328	Phase II	192
Reparixin, AZD5069, SX-682	CXCR1/2 antagonist	Metastatic breast cancer, Colon cancer, Prostate cancer	NCT02001974 NCT02370238 NCT02499328 NCT04599140	Phase I/II	193