



Tipping Tumor Microenvironment against Drug Resistance

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Abstract

Tumor microenvironment (TME) represents a structural hallmark of solid neoplasms, and plays a critical role in multiple aspects of oncologic pathogenesis such as local invasion and immune escaping, thus substantially contributing to malignant metastasis and anti-cancer drug resistance. TME is composed of highly heterogeneous and dynamic components including vascular cells, immune network, adipocytes, fibroblasts, among others. Pathologically meaningful interactions occur between malignant cells and TME, also between the stromal cells within TME itself, consequently raising a challenging hurdle for a broad spectrum of anti-cancer agents to achieve the therapeutic efficacy. Herein, we sort out an updated understanding of TME biology with an emphasis on its roles in affecting clinical outcomes, and propose to better manage anti-cancer drug resistance through timely targeting the principal cellular components in TME by utilizing clinically available medicines.

Keywords: Tumor microenvironment; Drug resistance; Cancer cell

Introduction

It has been over four decades since the war on cancer was declared in order to inspire a cure for malignant disease [1,2]. During this period of time, dramatic breakthroughs in many aspects of cancer biology have shed light on the delineation of particular molecular/cellular alterations that control proliferation, cell death/differentiation, angiogenesis, and metabolism. In parallel, pharmaceutical innovation and therapeutic strategies in oncology have accordingly evolved through several milestones, including cytotoxic compounds, hormonal treatments, targeted therapies and combinational regimens [3]. Throughout a number of campaigns against neoplastic disorders, clinical outcomes to date, however, are still far from what we expected, because age-adjusted mortality rates of all cancers in general show only a modest overall 13% decline during the past 40 years [4,5]. Moreover, it is well known that drug-resistant metastasis represents a challenging issue for most therapeutic approaches in oncology, and significantly contribute to cancer mortality [2-4].

Drug-resistant modes of conventional cytotoxic medicines which inhibit DNA synthesis or cell mitosis are mainly attributed to dysregulated pharmacokinetic processes such as increased drug efflux out of responding cells mediated via multidrug resistance (MDR) gene-encoded protein transporters [3,6]. To circumvent this serious clinical problem, working protocols regarding maximum tolerated dose (MTD) and combining drugs with distinct mechanisms of action, including MDR inhibitors, have been in practice [4,7]. On the other hand, drug resistance to contemporary targeted therapy in oncology usually results from target gene mutation(s) and redundant activation of alternative growth-augmenting signaling cascades [3]. In regard of this notion, development of therapeutic strategies with forthcoming next-generation agents targeting resistance-associated mutations and complimentary pro-survival pathways appears to be a helpful means to

deal with the emerged challenge [3,8]. Nevertheless, it is worth noting that, to optimize clinical outcomes of anti-cancer medicines, more efforts still need to be made to prevent or diminish therapeutic resistance.

Upon analysis of the cancer mortality data into more details, a striking distinction is revealed between leukemia/lymphoma and a wide spectrum of solid tumors. While the mortality of hematological cancers has been reduced by 40 ~ 70% over past four decades with various chemo-therapies, it has basically no major improvements in most types of solid malignancies except colon and breast cancers [4]. Reduced mortality of the latter two types of tumors appears due, at least in part, to early detection/polypectomy and surgical operations [9,10]. Intriguingly, why has therapeutic sensitivity of solid malignancies been much lower than that of hematological cancers? Notably, there is a fundamental difference in tissue structures of solid tumor versus leukemia. Compared to leukemia, besides malignant cells, solid neoplastic tissues contain a highly complex stromal compartment known as tumor microenvironment (TME), which makes their biological behaviors significantly different from those of disseminated malignancies [4,11]. Consisting of vasculature, immune network, adipocytes, fibroblasts, among others, TME provides a pro-survival milieu for cancer cells, and in turn creates a formidable barrier for anti-cancer drug therapies to cross [11,12]. In this review, we outline a systematic paradigm to manage anti-cancer drug resistance through manipulating the major components in TME with approved medicines (Figure 1).

Vascular cells

Vascular endothelial cell growth factor (VEGF) to its cognate receptor (VEGFR) signaling plays a pivotal role in new vessel formation termed angiogenesis, and this activity is significantly up-regulated in solid tumor tissues upon growth beyond one millimeter in size [11,13]. While VEGFA-VEGFR2 axis signaling mainly induces

cancer blood vessel (BV) angiogenesis, VEGFC/D-VEGFR3 pathway activity usually promotes tumor lymphatic vessel (LV) angiogenesis (lymph-angiogenesis) [14]. In addition to providing blood supply for tumor growth and facilitating cancer spreading, local endothelial cells (EC) also directly function as a pro-survival player against apoptosis of cancer cells because VEGF and VEGFR are expressed by both EC and tumor cells [11,15].

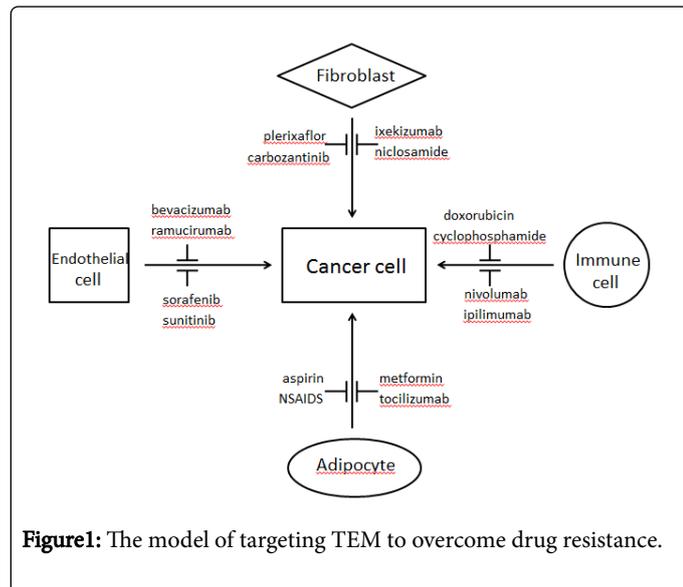


Figure1: The model of targeting TEM to overcome drug resistance.

On the other hand, lymphatic endothelium secretes CXCL12 and CCL21 chemokines which recruit the responding receptor CXCR4- or CCR7-expressing cancer cells through chemo-attraction, thereby promoting malignant cell migration and metastasis [14]. It is thus not surprising that VEGF-VEGFR-mediated cancer cell-EC interactions have been reported to contribute to chemo-therapy resistance in several tumor types including lungcolon cancer and soft tissue sarcoma [11,13].

In this light, approaches targeting tumor angiogenesis appear an exciting option in anti-cancer drug resistance through modulating vascular cell in the microenvironment. Bevacizumab (Avastin), a humanized VEGF-A neutralizing antibody, represents the first generation agent of anti-tumor angiogenesis drug, and has been approved to treat several types of malignancies in combination with cytotoxic chemotherapy, including colon, lung, and renal cancers [16]. Later on, inspired by this idea more VEGF/VEGFR antagonists, including ramucirumab, aflibercept, were developed and have also achieved clinical success [17,18]. Interestingly, several small molecular inhibitors of VEGFR, such as sorafenib and sunitinib, are capable of targeting multi-kinases and therefore exerting additive anti-tumor efficacy [18]. Meanwhile, plerixaflor came up as an efficacious CXCR4-blocking agent to suppress activity of the chemokine pathway induced via VEGFC/D-VEGFR3 axis [19].

Moreover, angiogenesis pathology can be orchestrated by a comprehensive array of signaling cascades. There are a variety of alternative signaling molecules, such as placental growth factor (PlGF), fibroblast growth factor (FGF) and angiopoietin, which potentially bypass VEGF/VEGFR inhibition and restore tumor angiogenesis. In this regard, adding inhibitors against these alternative angiogenesis targets to therapeutic programs has been proposed for overcoming anti-VEGF resistance [8,18,20]. Furthermore, continued inhibition of

angiogenesis creates a hypoxic environment and in turn induces secondary pathologic alterations in tumor tissues including increased hypoxia inducible factor 1 α (HIF1 α), and cancer stem cells (CSCs). As a transcription factor, HIF1 α up-regulates a wide array of genes associated with cell survival and anaerobic metabolism [21]. Recently, CSCs have been recognized as a particular subpopulation of cancer cells that are responsible for metastasis and therapeutic resistance [3,22]. In this sense, to optimize anti-angiogenesis therapy in the long-term, the hypoxia-induced secondary pathologic changes need to be reversed with certain therapeutic means accordingly.

Immune network

Physiologically immune network serves as body's defensive system to eliminate etiological identities including tumor cells, which is termed immune surveillance [11,12]. Under pathological circumstances, however, cancer cells can escape from immune network-mediated defensive responses against neoplastic development due to reduced immunogenicity, and then outgrow beyond the controlling capacity of host immune system. Moreover, malignant cells and the stromal components tend to manipulate the behaviors of many immune cells in TME which sabotage anti-tumor immunity and subsequently facilitate neoplastic progression, thereby profoundly impacting on therapeutic outcomes [4,11,12].

The myeloid-derived suppressor cell (MDSC) population down-regulates anti-cancer immune responses and promotes tumor angiogenesis through secreting transforming growth factor β (TGF- β) and VEGFA [12,23]. Depending on the biological contexts and pathological stages, macrophages in TME can be activated into two subgroups with opposite functions, of which M1 suppress tumor growth and conversely M2 enhance cancer development [11,24]. Likewise, there are two distinct phenotypes of T helper (Th) lymphocytes. Th1 cells secrete positive cytokines such as interferon γ (IFN- γ) up-regulates CD8+T cell-mediated anti-tumor immune responses, and is associated with longer disease-free survival of cancer patients. In contrast, Th2 cells produce negative cytokines such as interleukin4 (IL-4) to promote tumor progression, and is implicated in resistance to chemotherapy [11,25,26]. Recently, a Fox3p+ subset of CD4+T lymphocytes, known as regulatory T cells (Treg), has been recognized to play a role in suppression of anti-tumor immune activities. Impressively, a high Fox3p+/CD8+ ratio is linked to a poor response to platinum-based chemotherapy [27,28].

Emerging evidence suggests that certain chemotherapeutic drugs in oncology, including cyclophosphamide and doxorubicin, can up-regulate anti-cancer immune responses to eliminate malignant cells, namely immunogenic cell death (ICD), through enhancing immunogenicity or lowering Fox3p+/CD8+ ratio in tumor-infiltrating lymphocytes [29,30]. Interestingly, some targeted anti-cancer agents are also able to induce ICD. For example, while sunitinib blocks STAT3 to diminish MDSCs and Treg cells, bevacizumab promotes dendritic cell (DC) maturation and antigen-presentation to prime anti-cancer immune activities [31]. Recently, the blocking antibodies (ipilimumab and nivolumab) of co-suppressing molecules cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1)/ programmed death-ligand 1 (PD-L1) in immune cells have been approved to treat immunity-associated malignancies such as melanoma and lung cancer [3,12]. Excitingly, the therapeutic response duration with nivolumab has been extended beyond two years [32]. Besides, several cellular immunity-boosting strategies, including a DC-mediated anti-prostate cancer vaccine (sipuleucel-T) [12] and

expanded activated autologous lymphocytes (EAALs) [33], have delivered additional clinical benefits to patients beyond conventional treatments.

Adipocytes

It is well known that adipocytes exist abundantly in TME components of breast cancer, and that invasion of malignant cells into adipose tissues correlates with poor clinical outcomes in prostate, pancreas, kidney, colon and ovarian cancers [11,34]. The adipocytes around malignant cells *in vivo* are termed cancer-associated adipocytes (CAAs), which confer a variety of tumor-promoting effects through the paracrine activities [34]. CAAs secrete a broad spectrum of hormones and cytokines referred as adipokines, of which leptin and interleukine-6 can activate Janus kinase2-signal transducer and activator of transcription3 (JAK2-STAT3) signaling cascade in cancer cells upon binding to the surface receptors, stimulating proliferation, survival and subsequently inducing therapeutic resistance [35]. Meanwhile, the adipocyte-derived collagen VI mounts a potent growth-enhancing effect on malignant cells through up-regulating Akt, β -catenin and cyclin D1 [36]. Moreover, numerous stress factors such as hypoxia and tumor-growing pressure on adipose tissue trigger a vicious cycle of chronic inflammation, which in turn contributes to drug resistance [4,34]. In these pathological processes, CAAs produce additional inflammatory cytokines including tumor necrosis factor- α (TNF- α) and interleukine-1 β (IL-1 β), which have been linked to cancer progression and worse clinical outcomes [34,37,38].

Historically there has been a consensus to utilize inflammation-controlling agents, such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), to prevent inflammation-associated cancer [4,34]. Low-dose aspirin application for over 3 years was able to reduce colon cancer incidence by 25% in the clinic [4]. Moreover, it has also been noticed that dosing aspirin can diminish local spread and distant metastasis of cancer as well. In particular, long-term daily use of aspirin was observed to reduce the systemically spreading cancer by 48% [4,34,39]. In addition, some natural products, including curcumin and resveratrol, were demonstrated to exert anti-cancer activities through suppressing NF- κ B pathway-mediated inflammation [4]. Interestingly, metformin, a popularly used anti-diabetic drug based upon insulin sensitization of muscle and adipocytes, can delay tumor progression through inducing adenosine monophosphate-activated kinase (AMPK) and thereby inhibiting the mammalian target of rapamycin (mTOR) [34]. Recently, among the waves of targeted therapeutic innovation, IL-6 blocking antibody (tocilizumab) and JAK2 inhibitor (ruxolitinib) have been showed to be capable of improving clinical outcomes in cancer patients through suppressing adipokine (leptin)-mediated adipocyte- malignant cell interaction [40,41].

Fibroblasts

Representing another important cellular component in TME, the stromal fibroblasts are activated in response to nearby cancer cells, and known as cancer-associated fibroblasts (CAFs), which significantly contribute to anti-cancer drug resistance [11,12]. CAFs highly express the trans-membrane glycoprotein CD44 to maintain the stemness phenotypes of cancer stem cells via direct interactions. Functioning as the paracrine niche meanwhile, CAFs secrete an important array of growth factors, including hepatic growth factor (HGF) and PDGF which bind to their specific receptors (c-MET and PDGFR respectively) on cancer cells, to activate downstream signaling kinase

casades and to consequently augment proliferation and survival of malignant cells [42,43]. CAFs can also produce CXCL12 and activate CXCR4 pathway, thereby enhancing tumor cell migration and cancer metastasis [44]. Besides, it has been found that, upon anti-cancer chemical compound treatment, CAFs strikingly up-regulate interleukine-17A (IL-17A) secretion, which is associated with promoting CSC renewal. Interestingly, an IL-17A neutralizing antibody delivers anti-tumor efficacy in a synergy with chemotherapy, and thus is able to overcome anti-cancer drug resistance [45]. In addition, a peptide fragment derived from adipocyte-secreted collagen VI upon cleavage of matrix metalloproteinases11 (MMP11) produced by CAFs has recently been revealed to activate the stemness pathway wnt/ β -catenin, to augment CSC phenotypes and cancer progression [22,36].

Given that CAFs play an important role in many aspects of malignant pathogenesis including anti-cancer drug resistance, interfering CAFs has been proposed as an attractive idea to improve outcomes in cancer patients. Therapeutic compounds targeting CXCR4 (plerixafor) and PDGFR (sorafenib) have been in clinical practice, and delivered encouraging anti-tumor efficacy through inhibiting both cancer cells and the stromal components [18,19]. Recently, cabozantinib, an approved anti-cancer drug targeting c-Met, has been further observed to overcome the therapeutic resistance in certain small cell lung cancer patients [46]. In consistent, some chemotherapeutic regimens were noticed to increase CAFs in colorectal TEM with over-expressing IL-17A to promote drug resistance [45]. Fortunately, therapeutic IL-17A antibodies such as ixekizumab have been clinically available to treat autoimmunity-mediated disease [47], corroborating its human safety and pharmacological profiles. In this context, there is a good corollary to expand ixekizumab's clinical indications to circumvent the cancer drug resistant issue resulted from IL-17A-bearing stromal CAFs. Additionally, to suppress the stemness-signaling activation mediated by CAF-derived MMP11, niclosamide, a traditional anti-helminthic agent, has been repositioned to exert exciting anti-tumor efficacy through targeting multiple CSC-associated pathways including wnt/ β -catenin [48].

Conclusion and perspective

Culminating evidence demonstrates that TME plays a significant role in most phases of oncologic pathogenesis including neoplastic progression and anti-cancer drug resistance, which fundamentally contribute to high mortality rates of solid tumors [4]. It has been increasingly recognized that, within a neoplastic architecture, reciprocal interactions between cancer cells and components in TME occur frequently in a dynamic and universal manner. While cancer cells secrete a variety of active peptides to orchestrate pathological processing events in the stromal compartments, such as angiogenesis and immune tolerance, toward benefiting tumor growth/survival, in return non-malignant cells in the adjacent TME produce numerous signaling molecules to accelerate cancer progression by means of multiple mechanisms [11,12], including activating survival signaling pathways and up-regulating MDR gene expression [49]. Simultaneously, differential cell types in TME also elicit various effects on each other, generating vicious cycles to potentiate cancer progression. For example, upon tumor growth hypoxia in cancer-associated adipose tissues stimulates angiogenesis, and the adipocytes in TME to secrete adipokines, subsequently triggering immune cell

infiltration and fibroblast activation, all of which add to escalating therapeutic resistance [11,34].

Whereas target gene mutations in cancer cells represent one of the dominate mechanisms behind therapeutic resistance to contemporary medicines in oncology, non-malignant cellular members in the TME are in general stable genetically and/or epigenetically [11,43]. In this sense, the stromal cells within neoplastic tissues should thus be more susceptible to various therapeutic interventions, underscoring a rationale to target components in TME beyond cancer cells [12]. Impressively, a handful of anti-cancer compounds in the clinic suppress multiple kinase signaling pathways, being therefore capable of targeting both cancer cells and stromal cells [12]. For instance, sorafenib can simultaneously inhibit VEGFR, PDGFR and rearranged during transfection onco-gene (RET), implying to exert anti-tumor efficacy via suppressing angiogenesis, CAFs and cancer cells [3,43].

A rational forward-thinking is supposed to anticipate more comprehensive drug combinations with manageable adverse event profiles, to target multiple components in tumor tissues [4,12]. For example, while co-administering cytotoxic drugs with anti-angiogenic agents have been demonstrated to improve clinical outcomes, there is an emerging problem that chronic angiogenesis suppression results in reduced drug uptake by tumor cells [50]. To address this issue, intermittently therapeutic strategies are accordingly proposed to increase anti-cancer drug exposure [50]. Alternatively, a sequential treatment schedule was designed to optimize therapeutic benefits and to mitigate the overlapping side-effects of combining cytotoxic compounds with immune-modulating agents [51]. On the other hand, combined inhibition of immune checkpoints and VEGF has been shown to synergistically augment anti-cancer immune responses in several aspects and therefore potentiate therapeutic efficacy [52]. Meanwhile in this case, VEGF blockade may be concerned to complicate the vascular lesion triggered by ipilimumab [53,54]. Interestingly in parallel, certain traditional Chinese herb medicines, such as Qingyihuaji and Yanzheng Xiaoji, are recently emerging to show promising anti-tumor activities through inhibiting multi-therapeutic targets and harmonizing disease-associated biological networks [55,56]. Moreover, Chinese herb medicines have been utilized in the clinic as an adjuvant treatment to alleviate the side-effects resulted from anti-cancer chemo- and radio-therapies [57].

Serving as a pro-survival niche for the malignant residents, TME contains a wide variety of biological components and co-evolves with cancer cells during tumor progression [11,12]. To deal with therapeutic resistance timely and even to prevent it in better scenarios, precision medicine, an emerging concept that engages biomarkers detected in tumor tissues [43] and particularly circulating samples to predict therapeutic sensitivity [3,11,38], should thus go beyond the malignant compartment to cover the stromal cells as well. For example, elevated levels of PIGF in cancer patients indicate effluences of multiple pro-angiogenic factors, and therefore require medicines in addition to a VEGF inhibitor [20,58]. Meanwhile, over-expression of PD-L1 in cancer tissues has been linked to drug resistance and proposed to predict susceptibility to PD-1 antibodies [12,59]. On the other hand, increased IL-6 and HGF may be associated with activities of CAAs and CAFs [37,42], respectively, suggesting the clues for relevant therapeutic options. Of note, recently emerged studies increasingly implicate that multi-potent mesenchymal stromal cells (MSCs) behave as an intriguing player in TME, potentially contributing to cancer progression and drug resistance [60]. Deriving from the bone marrow, MSCs migrate towards neoplastic tissues and become an active

component of TME, which are capable of generating various types of stromal cells including CAAs and CAFs. Moreover, MSCs suppress anti-tumor immunity, and also augment resistance to a broad spectrum of medicines, through cell-cell contact and paracrine activities [12]. To date, the biomarkers and functional phenotypes of MSCs are yet to be well validated. Anyhow, there has been some evidence showing that blockade of CXCR4 or TGF- β can diminish the pathological effects of MSCs on cancer progression [11]. Hence, it is worthy of more efforts on manipulating MSCs to improve clinical outcomes such as managing the TME-mediated anti-cancer drug resistance.

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