Chapter 4

Updated Landscape of the Tumor Microenvironment and Targeting Strategies in an Era of Precision Medicine

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Additional information is available at the end of the chapter

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Abstract

Despite successive advances in clinical diagnosis and therapeutic intervention, cancer-associated morbidity and mortality keeps up with escalating cost to human society. Clinicians are confronted with an unprecedented challenge in curing cancers with *de novo* or acquired resistance. Failure to achieve effective and long-lasting treatment effects arises from the complexity of malignancies, particularly when plasticity of cancer cells is coupled with survival adaptability conferred by the pathologically co-opted stroma in the tumor microenvironment (TME). Targeting immune checkpoints, such as programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte antigen 4 (CTLA4), provide significant benefit in multiple tumor types and produce substantial anticancer responses. Tissue resident stromal cells, although damaged together with cancer cells upon cytotoxic treatments, represent an ever-replenishing source that contributes to tumor restoration from residual cancer cells in the post-therapy stage. The TME displays a continually changing landscape, generating significant impacts on treatment outcome in clinics. Moving forward, implementing patient-specific analysis in clinical oncology with TME-oriented agents will significantly improve the specificity and efficacy of targeted therapies, thereby accelerating the translation of novel conceptions and groundbreaking discoveries in the TME biology through multiple bench-to-bed pipelines in current settings of precision cancer medicine.

Keywords: tumor microenvironment, cancer treatment, secretory phenotype, acquired resistance, precision medicine

1. Introduction

Tumor development implicates the coevolution of transformed cells and the surrounding TME. In solid organs, the TME comprises extracellular matrix, neovasculature and multiple stromal cell types, conferring neoplastic cells multiple capabilities including sustained growth, elevated migration, accelerated invasion, promoted drug resistance and more importantly, enhanced metastasis [1]. In contrast to cancer cells, stromal components in the TME are generally stable in genetics and represent a potentially ideal target for therapeutic intervention.

There is accelerated progress in both the design and application of anticancer therapies. However, to date, most clinical regimens including chemotherapy, radiation and targeted therapy fail to cure patients, even with the integration of cutting-edge techniques and facilities. The case is, cancers that show overt initial responses to treatments frequently relapse as resistant malignancies, and pathological relapse remains as a major challenge in clinical oncology. Tumor outgrowth and disease exacerbation relies on not only genetic modifications in somatic cells but also fitness advantages of such mutations provide within the TME. It is increasingly evident that heterologous cell lineages within the TME actively alter therapeutic response and shape cancer resistance [2]. The distinct TME attributes within a given tumor select for mutations that allow survival, expansion and repopulation of cancer cells, while significantly creating tumor heterogeneity. Such a plasticity promotes the development of drug resistance through several mechanisms, including mutations of the target genes, reactivation of the targeted pathways, and cancer cross talk with the surrounding TME, with the latter largely overlooked in the past decades [3]. Besides, mounting data support that stromal cells, either naïve or therapeutically damaged, can produce and secrete a large group of soluble factors into the TME milieu, which act as critical signals delivered in a paracrine fashion and dramatically confer therapeutic resistance on cancer cells. Therefore, the TME is biologically active in the course of disease progression and exerts pathological impacts in a spatiotemporally volatile manner, underscoring the necessity of considering the TME as a dynamic entity in designing novel agents and developing therapeutic strategies. In this chapter, we propose to offer a body of essential information that delivers an updated account of the newly emerging TME biology, provide a significant guide to the most recent literature, and envision prospects for future research in basic, translational and clinical medicine.

2. Main body

2.1. Pathological characteristics of the TME

In the microenvironment of healthy tissues, the stroma functions as a physical barrier against tumorigenesis. Nevertheless, cells transformed by intrinsic or extrinsic events can make major changes that stimulate the adjacent microenvironment to support disease progression. Such changes include remodeling of extracellular matrix (ECM), recruitment of fibroblasts, chemoattraction of immune cells, migration of neuroendocrine cells and networking of endothelial cells (vascularization). How do the genetic and/or epigenetic variations present

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within cancer cells generate a phenotypically complicated TME, which further exert profound influences on tumor development? The differences in selective pressures of *in vivo* conditions, such as local acidity, intermittent hypoxia and growth factor production within a tumor can actively shape the pathway of disease progression. Besides all the autonomous factors generated by the tumor itself, distinct environmental landscapes within the tumor foci select for mutations that engender increased malignancy, foster tumor heterogeneity and enhance therapeutic resistance, all factors closely correlated with decreased treatment efficacy and increased clinical failure.

As cancer cells expand at a given site and generate early insults that form the initial tumor niches, host-resident benign cell types coevolve with the neoplastic cells in the same tissue, both populations are continuously engaged in aging-related pathologies (**Figure 1**).

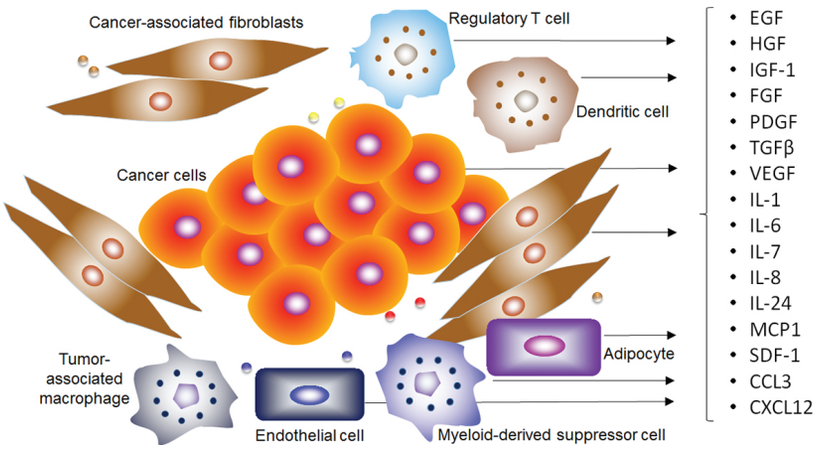

Figure 1. Schematic outline of cell type components within a typical TME. Although intercellular interactions confer various malignant potentials on cancer cells in the tumor foci, soluble factors released from cell subpopulations can actively suppress the local immune/inflammatory activities, thereby creating an inhibitory and hostile environmental niche for infiltrating cells recruited into the tumor from other sites. EGF, epidermal growth factor; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; TGF-β, tumor growth factor-β; VEGF, vascular endothelial growth factor; IL, interleukin; MCP-1, monocytic chemotactic protein 1; SDF-1, stroma-derived factor 1; CCL3, chemokine C-C motif ligand 1; CXCL12, chemokine C-X-C motif 12.

2.1.1. Cancer-associated fibroblasts

Fibroblasts represent an abundant and predominant cell type that maintains the structural framework in the connective tissue of solid organs. Normal fibroblasts typically suppress tumor formation; however, cancer-associated fibroblasts (CAFs), to the contrary, mainly promote tumorigenesis and facilitate metastasis. Compared with their normal counterparts, CAFs exhibit increased proliferation, enhanced ECM production, accumulated basement membrane deposition, strengthened cytokine synthesis and secretion including hepatocyte growth factor (HGF), multiple interleukins (ILs), platelet-derived growth factor (PDGF), stromal cell-derived factor 1 (SDF1), tumor growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) [4]. Alternatively, other mesenchyme-derived cell types, such as

adipocytes, can also contribute to tumor growth and disease progression. For instance, adiponectin from the differentiated adipocytes increases VEGF-A expression in human chondrosarcoma cells through adiponectin receptor (AdipoR), hypoxia-inducible factor-1α (HIF)-1α, phosphoinositide 3 kinase (PI3K), Akt and mammalian target of rapamycin (mTOR) signaling cascades [5].

There are debates on the origin of CAFs during cancer progression. Some data suggest that CAFs are derived from the endothelial-to-mesenchymal transition, whereas other studies support that epithelial-to-mesenchymal transition (EMT) is responsible for CAF production [6, 7].

CAFs accumulated in the TME are subject to activation by cytokines and growth factors present in the nearby niches, such as fibroblast growth factor (FGF), monocyte chemotactic protein 1 (MCP1), PDGF, TGF-β and secreted proteases [8, 9]. Once activated, CAFs release pro-inflammatory factors to activate the nuclear factor (NF)-KB signaling in transformed cells, a typical cell-cell cross talk that significantly promotes tumorigenesis [10]. In addition, CAFs in the mammary TME select for bone-specific metastatic traits in primary tumor cells, partially based on the mutual interaction between Src^+ breast cancer cells and CAFs that produce chemokine C-X-C motif ligand 12 (CXCL12) and insulin-like growth factor 1 (IGF1) [11]. A recent study suggested that circulating CAFs (cCAFs) with co-expressed fibroblast-associated protein (FAP) and α-smooth muscle actin (α-SMA) are distinguishable in the peripheral blood of patients with metastatic breast cancer. Furthermore, both cCAFs and circulating tumor cells (CTCs) are of significantly higher number in the metastatic group than in the localized breast cancer group, implying that cCAFs may complement CTCs as a clinically specific biomarker in metastatic breast cancer [12]. This also consolidates that functional roles of CAFs in tumor progression involve malignant activities not only in the primary foci but also in the systemic delivery of cancer cells of high metastatic potential to colonize in a foreign microenvironments, further supporting the interactions between cancer and TME in both the local and distant niches.

2.1.2. Neovasculature

Development of the tumor-associated vascular network is dynamic and dramatically influences tumor behaviors. Starting from regional angiogenesis, vascular networks are strengthened by co-opting mature vessels within the tissue, recruiting endothelial precursors from bone marrow. Specifically, neovascularization involves degradation and reconstruction of existing vascular basement membranes in a tissue-specific manner, as it evidenced by the fact that concurrent targeting of VEGF and Angiopoietin-2 (Ang2) potentiates the effectiveness of VEGF inhibition and prevents basement membrane destruction [13]. It is likely that newly co-opted vessels sustain certain properties of the original tissue, which exerts critical influences on the resulting vascular network.

However, deficient tumor vasculature such as unbalanced vessel development results in formation of hypoxic microenvironments with limited nutrient supplementation. Spatial interval from vascular beds to tumor foci creates a local gradient, a crucial factor for the distribution of anticancer agents within a given tumor tissue. In clinics, angiogenesis is

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assessed by microvessel density (MVD), an important prognostic factor for clinical outcomes of multiple tumor types. In prostate cancer, CD105-MVD reflects the angiogenic conditions in patients treated with neoadjuvant hormonal therapy (NHT) and acts as an emerging independent predictor of biochemical recurrence in prostate cancer patients after radical prostatectomy with NHT [14]. In addition, upregulation of pro-angiogenic ligand VEGFA is associated with a worse prognosis in metastatic colorectal, lung and renal cell cancers. For example, high VEGF expression was subsequently correlated with a short overall survival rate for colorectal cancer patients exhibiting lymph node metastasis [15].

2.1.3. Immune system

Upon disease progression, both the innate and adaptive immune systems are implicated in tumor-associated activities. Despite the ability of the immune system to mount antitumor responses, immune suppression mechanisms, however, often prevent such a process. Particularly, T-cell activation engages both positive and negative checkpoint signals to finely tune responses to avoid overt damage and autoimmunity. Particularly, cancer immunoediting is a process by which the immune system can paradoxically restrain or facilitate cancer progression [16]. The interaction between tumor and immune system is now regarded as a crucial factor relevant for the clinical management of cancer patients [17].

2.1.3.1. Checkpoint-associated immunosuppression

Blockade of immune checkpoints including cytotoxic T lymphocyte antigen 4 (CTLA4), programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) has achieved significant benefits in multiple cancer types by minimizing inhibitory signals while amplifying effective antitumor responses. Anti-CTLA4, PD-1 or PD-L1 administration as mono-immunotherapy have demonstrated clinical activity in more than 15 cancer types, including bladder carcinoma, Hodgkin lymphoma, melanoma, non-small cell lung carcinoma (NSCLC) and renal cell carcinoma (RCC) [18]. Although immune-based regimens for cancer treatment are expected to increase substantially within the next years, combinatorial inhibition of PD-1 and CTLA4 holds the potential to further enhance antitumor efficacy. Clinical efficacy of the combination of ipilimumab and nivolumab in the setting of malignant melanoma at advanced stage is recently witnessed, and successfully passed approval by the FDA for the treatment of patients with unresectable or metastatic melanoma harboring wild-type $BRAF^{V600}$ [19].

Thus, clinical data support that antitumor immunity is operative even in the most advanced cancer stages, and multiple immunosuppressive pathways are active in the TME which need to be co-targeted to release the full effector function of tumor-associated immune cells [20]. In fact, diverse additional immunomodulatory pathways and suppressive factors produced or secreted by stromal cells in the TME can be exploited as useful targets for immune checkpoint targeting [21]. However, some critical questions still remain open. For example, which combinations should move toward practical development? What type of patients will benefit most from such therapies? Systematic consideration of these issues by determining the leading drug targets expressed by cancer cells will allow substantial enhancement of the immune responses to eradicate the disease.

Immunological pathway	Examples in clinical trials	Most advanced stage of clinical development
CTLA4	Ipilimumab	FDA approved
	Tremelimumab	Phase III
PD1-PDL1	Pembrolizumab (PD1)	FDA approved
	Nivolumab (PD1)	FDA approved
	Atezolizumab (formerly MPDL3280A) (PDL1)	Phase III
	MEDI4736 (PDL1)	Phase III
	Avelumab (PDL1)	Phase I
	PDR001 (PD1)	Phase I
TNF and TNFR superfamilies		
4-1BB–4-1BB ligand	Urelumab, PF-05082566	Phase II
OX40–OX40 ligand	MEDI6469	Phase II
GITR	TRX518	Phase I
CD27	Varlilumab	Phase II
TNFRSF25–TL1A	–	Preclinical
CD40–CD40 ligand	CP-870893	Phase I
HVEM–LIGHT–LTA	–	Preclinical
HVEM–BTLA–CD160	–	Preclinical
IGSF		
LAG3	BMS-986016	Phase I
TIM3		Preclinical
Siglecs		Preclinical
B7 and CD28-related proteins		
ICOS–ICOS ligand	–	Preclinical
B7-H3	MGA271	Phase I
B7-H4	–	Preclinical
VISTA	–	Preclinical
HHLA2–TMIGD2	–	Preclinical
Butyrophilins, including BTNL2	–	Preclinical
CD244–CD48	–	Preclinical
TIGIT and PVR family members	–	Preclinical
Natural killer cell targets		
KIRs	Lirilumab	Phase II
ILTs and LIRs	–	Preclinical

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NKG2D and NKG2A	IPH2201	Phase I
MICA and MICB	–	Preclinical
CD244	–	Preclinical
Suppressive myeloid cells		
CSF1R	Emactuzumab	Phase I
Soluble mediators		
IDO	INCB024360	Phase II
TGF-β	Galunisertib	Phase I
Adenosine–CD39–CD73	–	Preclinical
CXCR4–CXCL12	Ulocuplumab (BMS-936564), BKT140 (BL-8040), Plerixafor	Phase I/II*
Other		
Phosphatidylserine	Bavituximab	Phase II/III
SIRPA–CD47	CC-90002	Phase I
VEGF	Bevacizumab	FDA approved
Neuropilin	MNRP1685A	Phase I

BTLA, B and T lymphocyte attenuator; BTNL2, butyrophilin-like protein 2; CSF1R, macrophage colony-stimulating factor receptor 1; CTLA4, cytotoxic T lymphocyte antigen 4; CXCL12, chemokine (C-X-C motif) ligand 12; CXCR4, C-X-C chemokine receptor type 4; GITR, glucocorticoid-induced tumor necrosis factor receptor (TNFR)-related protein; HHLA2, HERV-H LTR-associating protein 2; HVEM, herpes virus entry mediator; ICOS, inducible T cell co-stimulator; IDO, indoleamine 2,3-dioxygenase; IGSF, immunoglobulin superfamily; ILT, immunoglobulin-like transcript; KIR, killer inhibitory immunoglobulin-like receptor; LAG3, lymphocyte activation gene 3 protein; LIR, leukocyte immunoglobulin-like; LTA, lymphotoxin-α; MIC, MHC class I polypeptide-related sequence; PD1, programmed cell death protein 1; PDL1, programmed cell death 1 ligand 1; PVR, poliovirus receptor; SIRPA, signal-regulatory protein-alpha; TGF-β, transforming growth factor-β; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domains; TIM3, T cell immunoglobulin mucin 3; TL1A, TNF-like ligand 1A; TMIGD2, transmembrane and immunoglobulin domain-containing protein 2; TNFRSF25, TNFR superfamily member 25; TNFR, TNF receptor; VEGF, vascular endothelial growth factor; VISTA, V-domain immunoglobulin suppressor of T cell activation.
*Plerixafor (Mozobil; Genzyme/Sanofi) is approved by the US Food and Drug Administration not as an antitumor therapy but as a bone marrow mobilizing agent for bone marrow transplantation including autologous cases. However, it is currently in clinical trials of chronic lymphocytic leukemia, multiple myeloma and non-Hodgkin''s lymphoma patients.
Contents of Table 1 adapted from Mahoney et al. [25] with permission from Nature Reviews Drug Discovery, copyright 2015.

Table 1. Representative immunotherapeutic targets currently in clinical or preclinical pipelines.

Concurrent inhibition of PD-1 and CTLA4 significantly increases response rate in melanoma patients and is now in Phase III trials in multiple cancer types [19, 22]. Since immunosuppression is dominant, it makes sense that a standard immunotherapy begins with immune checkpoint blockade instead of a direct immune stimulation. Release from immunosuppression will allow for combination with multiple immunotherapies that eventually activate the immune response. Results from the Phase I trial of synergistic CTLA4 and PD-1 blockade suggest that such a combination is clinically effective, but highly toxic to patients [19]. In this

case, alternative combinations with the anti–PD-1 pathway backbone will likely produce better response in cancer clinics with fewer side effects. A group of immunological pathway candidates for combinatorial inhibition of the immune checkpoint is in various stages of clinical trials (**Table 1**). The corresponding agents are designed to directly stimulate cytotoxic T cells, block immunosuppressive factors, inhibit regulatory T cells (Treg) functions, interfere with the natural killer cell inhibitory activities or abolish the effects of soluble factors produced by stromal cells.

2.1.3.1.1. Tumor-associated macrophages (TAMs)

In solid tumors, TAMs compose 5–40% of the tumor mass and are usually correlated with poor prognosis. Distinct from M1-macrophages, the immune cell subpopulation of pro-inflammatory and anti-cancer properties, M2-macrophages are immunosuppressive, contributing to the matrix-remodeling and favor tumor progression [23]. TAMs are either tissue-resident or derived from peripheral sites including the bone marrow (BM) and spleen. Increasing lines of evidence suggest an active role for TAMs in supporting multiple malignant behaviors such as invasiveness at the leading edge of tumors. Particularly, studies have demonstrated that TAMs promote cancer cell invasion through a paracrine signaling loop involving tumor-associated granulocyte macrophage colony stimulating factor (GM-CSF) and macrophage-derived epidermal growth factor (EGF) in breast cancer and glioma [24, 25]. Additionally, the close vicinity of cancer cells in epithelial-mesenchymal transition (EMT) and TAMs at the invasive tumor front implies that these two cell type may mutually interact with each other. Beyond the leading edge, TAMs represent a major source of proteases including cysteine cathepsins, which promote tumor progression and therapeutic resistance in multiple cancer types [26].

However, it remains so far unclear how macrophages switch from tumor suppressing to tumor promoting upon disease progression. It is likely that environmental factors such as tumor hypoxia are involved in such a transition. Specifically, TAMs accumulate at sites of hypoxia in growing tumors, and their recruitment is mediated by macrophage chemoattractants such as endothelin-2 and VEGF [27]. Recent data further suggest that coexistence of hypoxia and free fatty acids (FFAs) exacerbates macrophage-mediated inflammation [28]. As noteworthy, TAM accumulation in these regions enhances angiogenesis and subsequent acquisition of invasive phenotype, supporting that the initial hypoxic response in growing tumors may induce a phenotypic switch of macrophages, which is correlated with their changed polarization [29].

2.1.3.1.2. Myeloid-derived suppressor cells (MDSCs) and Treg cells

In a typical TME, immunosuppressive effects may also be exerted by myeloid-derived suppressor cells (MDSCs), which result from aberrant myelopoiesis that occurs in developing tumors [30]. Functionally identified as an immunosuppressive subpopulation, MDSCs are immature myeloid cells that sustain normal tissue homeostasis upon stimulation of the host by various systemic insults such as viral infection and traumatic stress [31]. However, MDSCs dramatically promote tumor growth by supporting angiogenesis, cancer cell survival, tumor metastases and pre-metastatic niche formation [32]. In particular, the process of tumorigenesis

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can mobilize MDSCs which subsequently infiltrate developing tumors and promote local vascularization and disrupt routine immunosurveillance, including dendritic cell (DC) antigen presentation, M1 macrophage polarization, T cell activation and natural killer (NK) cell cytotoxicity blockade [33]. Depletion of MDSCs in animal models with neutralizing antibodies markedly reduced metastasis, further consolidating that MDSCs promote tumor progression [31]. Furthermore, cancer patients display elevated numbers of peripheral MDSCs, which is positively associated with the disease aggravation extent and therapeutic failure rate [34]. Interestingly, monocytic MDSCs can be reprogrammed to exhibit an antitumorigenic phenotype upon bacteria-elicited activation of the immune system in animal models [35]. In such a case, increased T helper type 1 (T_H1) cytokines, decreased T cell-inhibitory factors and differentiation of MDSCs toward M1-like macrophages were observed, suggesting that immunotherapies are able to subvert autonomous responses of MDSCs to extrinsic stimuli to maintain homeostasis, an exploitable aspect of such an immune cell subgroup in cancer treatment.

Phenotypically, Treg cells represent another TME cell type with multiple immune modulatory functions in human cancer patients. As an essential part of the normal tissue under physiological conditions, Treg cells control the proliferation and activation of adaptive immune system including T and B cells, thus having a critical role in homeostasis maintenance. However, Treg cells can generate diverse effects on tumorigenesis. For example, increased numbers of Treg cells are correlated with poor survival of several pathologies including lung, colorectal and estrogen receptor (ER)-negative breast cancer; however, their role on prostate and ER-positive breast tumor development remains uncertain [36]. Similar to MDSCs, Treg cells prevent tumor-associated antigen presentation and suppress cytotoxic T cell function by blocking the release of cytolytic granules [37].

In nature, tumor-associated Treg cells have heterogeneous phenotypes, and they may accumulate through various mechanisms including peripheral recruitment, TME-based proliferation or progenitor-initiated differentiation upon stimulation by tumor-secreted factors [38]. Thus, CD25 antibody-involved Treg-targeting or other treatment regimens may promote immunotherapy responses, like agents designed for MDSCs [39].

2.1.3.1.3. Other stromal cell types implicated in tumor progression

Several stromal cell types recently emerged with the potential to generate remarkable influences on human cancer. Particularly, adipocytes and their progenitors in obese populations promote tumorigenesis across a handful of obesity-related cancer types [40, 41]. Adipocytes cause the enrichment of prostate cancer stem cells (CSCs) through a distinct cycle of autocrine amplification, suggesting a novel mechanism underlying the mutual interaction between adipocytes and prostate CSCs [42]. Moreover, adipose cells can be recruited to growing tumor foci, differentiating into pericytes and incorporating into vessel walls [43]. In both the basement membrane (BM) and local environment of solid tumors, atypical stem-promoting functions of nerves can enhance the aggressiveness of cancer cells, including those in gastrointestinal, pancreatic and prostate tumors [44–46]. Furthermore, inflammation associated with the gut microbiome is considered as one of the major contributing factor of

colorectal cancer outcomes. The US National Institutes of Health has recently launched an initiation to thorough study the human microbiome in various anatomical sites including the gut [47]. Targeting agents with anti-inflammatory (such as aspirin) or antimicrobial efficacy can prevent colorectal cancer tumorigenesis, thereby elongating patient survival [48]. Given the emergence of non-classical stromal cell types in solid tumors, creative combination anticancer therapies are being continually developed in the industrial pipelines and will show promising benefits in mitigating disease progression.

2.1.4. Tumor-associated exosomes

Diverse signaling activities within the TME involve autocrine and/or paracrine signaling loops of cytokines, chemokines and growth factors. Besides such a typical aspect, exosome-based shedding has recently emerged as an alternative modality of cell-cell communication. In particular, tumor-derived exosomes from the primary site reprogram the surrounding TME to form a pro-tumorigenic niche, orchestrating BM-derived progenitors to facilitate metastatic dissemination [49]. A recent study demonstrated that tumor-associated exosomes express unique integrins and determine organotropic metastasis through creating pre-metastatic niches via integrin-mediated fusion with organ-specific resident cells [50]. Aggressive melanoma-derived exosomes increase tumor metastasis rates and programs BMDCs at the pre-metastatic sites to form a proangiogenic phenotype [51]. More importantly, multiple stromal cell types can release exosomes, as exemplified by fibroblast-secreted exosomes which promote cell migration through WNT-PCP signaling in breast cancer [52]. In such a case, NK cell-derived exosomes from human blood harbor proteins to induce the tumor cytotoxicity and activate immune cells *ex vivo*. Conversely, new data demonstrated that endometrial cancer cells transmit small regulatory RNAs to endometrial fibroblasts through exosomes, suggesting a reciprocal mode of intercellular communication between cancer cells and related fibroblasts in human tumors [53]. Distinct prostate cancer (PCa) cell populations release exosomes that contain miRNAs to modify the local or pre-metastatic niche, and such miRNAs have different patterns between PCa bulk and CSCs exosomes that function collaboratively in tumor progression and metastasis [54]. The most abundant exosomes-related miRNAs thus can be regarded as potentially significant biomarkers and therapeutic targets in clinical oncology.

2.2. The therapeutically remodeled TME alters clinical outcome

Recent studies have recognized benign or noncancerous cells of the TME are major determinants of treatment efficacy in a large number of preclinical and clinical cases, an important mechanism of acquired resistance that is beyond the intrinsic characteristics of cancer cells but use to be masked by the *de novo* resistance of malignancies. Insightful appreciation of mechanisms involved in regulation of drug tolerance is crucial for improved cancer treatment. Specifically, host resident cells of the TME actively modulate tumor responses to chemotherapy and targeted therapies through production of secreted factors [55].

Neoadjuvant or conventional chemotherapy-induced DNA damage can cause WNT16B overexpression, a phenomenon found in the TME of prostate, breast and ovarian cancer

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patients. Upon genotoxic insults, NF-κB acts as a key signaling node that actively mediates WNT16B production. Cell-based experiments and tumor transplant models demonstrated the protective effect of fibroblast-derived WNT16B, indicating that WNT16B secreted by stroma attenuates cancer cell apoptosis induced by genotoxicity, and counteracts drug response through activation of a DNA damage secretory program (DDSP) [56–59] (**Figure 2**). The study presents new opportunities for future advanced treatments that rationally integrate agents to confine the TME activities. For instance, depleting stroma-derived WNT16B, which would specifically overcome such a "new" but not "minor" TME-associated resistance mechanism [57, 60]. As supporting evidence, CAFs are similarly enriched in colorectal cancer (CRC) during the post-therapy stage and display enhanced cytokine IL-17A, which helps maintain the tumor infiltrating cells (TICs) through activation of NF-κB signaling [61].

Besides overturning traditional law of nature that anticancer treatments mainly restrain cancer cells, the discovery raises the novel appreciation that genotoxic regimens including chemotherapy and radiation indeed activate the stroma to promote disease resistance, an important advancement corroborated by several other concurrent but mutually independent reports of breast cancer models that strongly imply DNA damage-elicited alterations of the TME as an pathological entity that eventually minimizes the overall therapeutic response [62, 63]. The BM is enriched with cells of varying progeny beyond myeloid cell populations that are mobilized and recruited to the TME in response to treatments. Importantly, BM-derived mesenchymal stem cells (BMMSCs) can secrete polyunsaturated fatty acids, chemoprotective factors that favor cancer cell survival [64]. Although the data showed that only the cisplatin-involving therapy can induce such a change, the TME-derived fatty acids eventually conferred resistance to multiple agents even at a systemic level. Alternatively, therapeutic evasion by cancer propagating cells (CPC) represents a major obstacle in leukemia clinics. Recent data showed that the BM niche is created by acute lymphoblastic leukemia (ALL) cells following cytarabine and daunorubicin treatment [65]. Mesenchymal cells recruited by leukemia cell-derived CCL3 can build a therapy-induced shelter and evolve from Nestin+ cells to a smooth muscle actin (a-SMA)+ cells under TGF-β influence, ultimately developing into fiber residues. Formation of such an early protective niche significantly contributes to the failure of therapeutic intervention by preventing complete remission.

Cocultured fibroblasts regulate the *in vitro* sensitivity of head and neck squamous cell carcinoma (HNSCC) to epithelial growth factor receptor (EGFR) antibodies or matrix metalloproteinase (MMP) inhibitors [66]. Furthermore, tumor-stroma cross talk plays a crucial role in the acquisition of lung cancer resistance to EGFR-tyrosine kinase inhibitors (TKIs) through activating the c-Met/PI3K/Akt pathway *in vitro* and *in vivo*, implying such an interaction may be therapeutically targeted for lung cancer patients with EGFR-activating mutations [67]. HGF represents one of the major stroma-released soluble regulators of lung cancer sensitivity, whereas gefitinib in synergy with anti-HGF antibody or the HGF antagonist NK4 showed decent efficacy in abolishing fibroblast-induced EGFR-TKI resistance. Similarly, co-inhibition of EGFR and c-Met signaling with a novel bi-specific EGFR/c-Met antibody effectively blocked malignant development including resistance additively compared with the single-agent treatments [68].

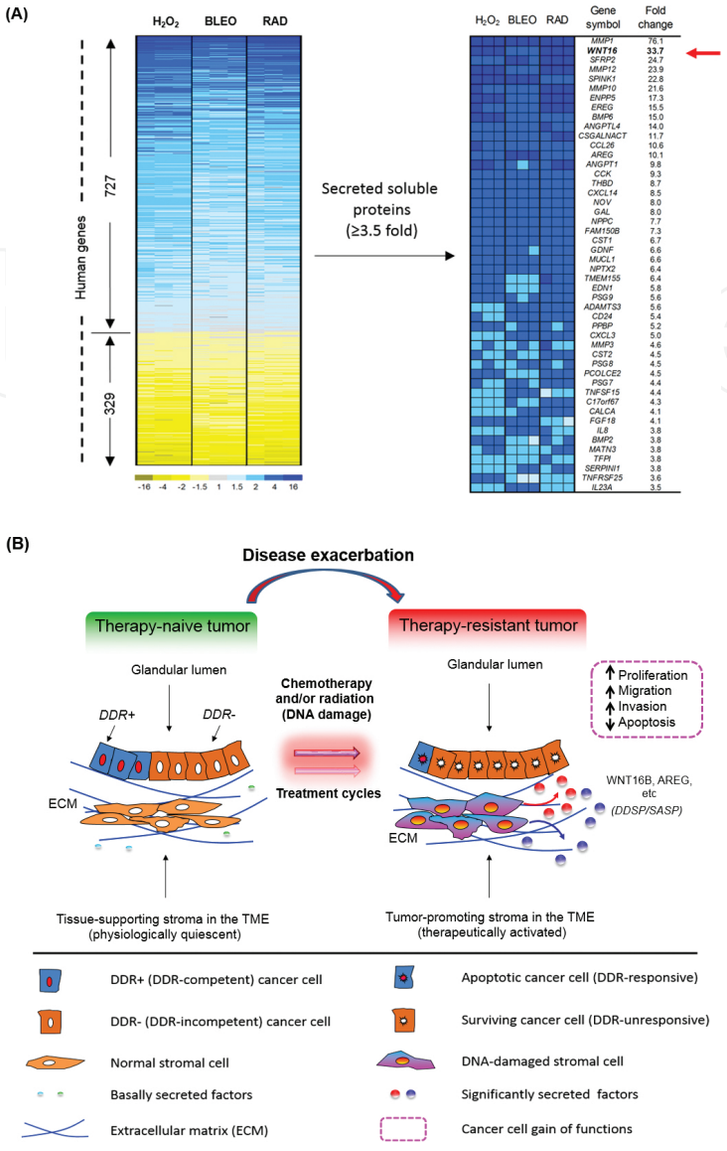

Figure 2. WNT16B is significantly produced upon genotoxic damage to human stromal cells and promotes therapeutic resistance to surviving cancer cells. (**A**) Genome-wide expression pattern of normal human primary prostate stromal cells. Heatmap depicts the relative mRNA abundance after exposure of cells to typical DNA damaging agents (H_2O_2, hydrogen peroxide; Bleo, bleomycin; Rad, ionizing radiation). (**B**) Top list of upregulated human genes annotated as extracellular or secreted factors, with average expression fold change ≥3.5 by comparison of post-treatment vs. pre-treatment samples. Note, WNT16B shows up among the overexpressed genes, with outstanding expression fold change. (**C**) Working model for cancer cell non-autonomous therapeutic resistance acquired from the TME upon genotoxic treatments including chemotherapy and radiation. Therapeutic agents cause apoptosis in subsets of cancer cells by eliciting a DNA damage response (DDR), while cancer cells with DDR deficiency (DDR-insensitive, or DDR-) may escape from such insults. Simultaneously, senescence is induced in stromal cells adjacent to epithelial cells surrounding the gland, with a secretory phenotype DDSP developed after DDR events. A persistently activated signaling network is triggered by the DNA strand breaks. The DDSP is usually characterized by a spectrum of autocrine- and paracrine-acting proteins. The soluble factors reinforce the senescent phenotype in damaged cells, enhance cancer cell repopulation, with increased occurrence of tumor relapse and distant metastasis. A handful of co-synthesized factors including WNT16B and SPINK1 holds the potential to serve as both a serum biomarker to determine treatment index and a therapeutic target to minimize the TME-conferred therapeutic resistance. DDR, DNA damage response; ECM, extracellular matrix; TME, tumor microenvironment. Color images of (**A**) adapted from Xu et al. with permission from Trends in Cancer, copyright 2016.

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The development and maintenance of vasculature is regulated by diverse pathways, including those engaging proangiogenic factors produced by both the tumor and stroma [69]. Upon genotoxic treatments, stromal expression of VEGF and other angiogenic factors including angiopoietin 1 (ANGPT1) and angiopoietin-like 4 (ANGPTL4) is enhanced, potentially contributing to vasculature development within the therapeutically damaged TME [56, 70]. Expression of the secreted frizzled-related protein 2 (SFRP2), a typical modulator of Wnt signaling, is increased in the stroma damaged by the chemotherapeutic cycles [56]. Beyond holding the potential to promote angiogenesis via the calcineurin/NFAT signaling in a non-canonical Wnt pathway [71, 72], SFRP2 can interact directly with WNT16B to enhance its canonical activities, eventually generating a substantially strengthened malignant phenotype including remarkable drug resistance in prostate cancer [73]. Data from targeting angiopoietins (Ang1, Ang2, Ang4) which cause CAF accumulation and neoangiogenesis in the TME, and TEK (referring to Tie1/Tie2) receptors responsible for the maturation and plasticity of blood vessels, are recently reported [74, 75]. Inhibiting angiogenesis in patients to overcome one of the side effects caused by cytotoxic agents is thus a novel strategy to block neoplastic growth and deprive cancer of acquired resistance.

Increasing lines of evidence support that the TME is critical for the development of chemoresistance through multiple mechanisms including drug distribution regulation and inflammatory response control. Particularly, the infiltration of myeloid-derived cells is increased in human breast cancer post-chemotherapy, with the cellular composition as a strong clinical predictor of overall survival [63]. Furthermore, myeloid cell-derived MMP9 influences both vascular leakage and response to chemotherapeutic drugs including doxorubicin. Therefore, tumor response to classical chemotherapeutic agents can be improved by targeting the TME with chemicals or antibodies that modify MMP activity and/or chemokine signaling. In another perspective, cancer treatments currently applied as the mainstay of clinical oncology indeed represent a double-edged sword, which is frequently compromised in reality by a therapeutically remodeled TME. The structural change, and more importantly, the functional modification of such a TME, casts a critical step toward development of more advanced malignancies including but not limited to the phenotypic switch via EMT, generation of circulating tumor cells (CTCs), local invasion in primary foci and metastasis to distant organs [76].

2.3. Development of targeting strategies in precision medicine

While the functional constituents of the TME generate profound impacts on disease progression and minimize the efficacy of anticancer therapies, experimental data indicate that such alterations are indeed exploitable and can open new avenues to develop advanced strategies and design innovative cancer regimens.

To date, there are a few leading research groups that have made progress in the TME biology by generating relevant databases and presenting therapeutic opportunities to prevent TME-induced cancer resistance. First of all, cytokines, growth factors and survival-associated proteins released by the TME are straightforward and valid therapeutic targets. As an efficient growth stimulator, IL-6 enhances resistance by counteracting chemotherapy and hormone therapy of multiple myeloma; it is also a therapeutic target in Castleman's disease and several

epithelial malignancies including mammary, breast ovarian, prostate cancers [77]. Recent data demonstrated that HGF is a critical TME determinant of resistance to BRAF inhibitors, setting the baseline for combinations of HGF-targeting monoclonal antibodies and RTK inhibitors that dampen the receptor c-Met activation [78, 79]. Identification of the distinct role of stroma-derived WNT16B in prostate cancer strongly supports translational studies in cancer therapy, as evidenced by the pilot preclinical trial integrating a monoclonal WNT16B antibody and routine chemotherapy to treat prostate tumors [73]. It is tempting to compare the efficacy of WNT16B-implicated pathway blockade and a wider suppression of the TME response to genotoxicity by inactivating the NF-κB complex. As the NF-κB activity differs between various stromal cell lineages upon therapeutic insults, it would be necessary to compare the effects of NF-κB suppression in individual TME-derived cell types. Nevertheless, there are caveats when selecting NF-κB as a general therapeutic target, although accumulating experimental data have established the NF-κB complex as a key regulator of inflammation and a driver of cancer progression. However, reverse but convincing data proved that activated NF-κB components enhance the sensitivity of cancer cells to chemicals that induce apoptosis and senescence, a special mechanism that controls tumorigenesis [80, 81]. As a supporting point, canonical NF-κB is found to be a Fas transcription activator, though the alternative NF-κB acts as a Fas transcription repressor [82]. In such a case, NF-κB promotes Fas-mediated cancer cell apoptosis, while suppression of NF-κB may abolish the Fas-initiated cell death and interfere with tumor regression achieved by the host immune system.

Strategies to inhibit the cancer resistance acquired from the TME in the course of either chemotherapy or targeted therapy have the value to improve overall therapeutic outcome. Generally, the TME exerts pathological influence on cancer cell survival as an early stage, while subsequent repopulation frequently occurs via the activation of signaling networks that elicit a typical secretory phenotype and/or tumor-stroma cross talk. To date, an array of agents are developed to minimize these activities, particularly small molecule inhibitors against key signal pathway nodes including the ATM/ATR-associated DDR repair machinery, p38MAPK cascade, mTOR subunits, JAK/STAT axis, NF-κB complex and CCAAT/enhancer binding protein (C/EBP) components. Alternatively, cytostatic antibodies with the ability to neutralize major soluble factors of significant roles in shaping advanced cancer phenotypes, such as those targeting MMPs, IL-6, IL-8, WNT16B, SFRP2, SPINK1 and AREG are also strong candidates that can be exploited to target the TME [57]. Fortunately, a handful of agents successfully acquired FDA approval for the systemic intervention of cancer patients while many others are in the industrial pipelines or clinical trials. As scientific acumen, an optimal therapeutic strategy is to consider the cancer a systemic disease at diagnosis and to pursue combinational therapy that incorporate cytotoxic agents and feasible cytostatic drugs either concurrently or sequentially, the latter actually more preferred [83]. Continued efforts in future will consolidate preclinical studies with novel therapeutics that deprive cancer of TME-conferred resistance, which is administered synergistically with cancer-targeting agents in pathological conditions that implicate a stress-responsive and functionally active TME.

Recently achieved in-depth profiling of cancer mutations by deep sequencing has enabled appreciation of the importance of tumor neoantigens in the immune surveillance of cancer,

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with the dream of "personalized immunotherapy" now realized. In particular, conceptual developments in cancer biology have caused a paradigm shift in the perspective we look at the TME when taking account of the immune system and its interaction with cancer. A simple but useful pragmatic framework allowing to stratify the TME into four classes according to the presence or absence of tumor-infiltrating lymphocytes (TILs) and PD-L1 expression was raised [84]. The proportion of tumors categorized as type I (~38%) and type II (~41%) by this framework is high in melanoma, and type I TME-harboring patients have the best prognosis and highest likelihood to respond to anti–PD-1/PD-L1 agents [85, 86]. Some malignancies such as prostate and pancreatic cancers, however, may not contain a high proportion of type I TME; in such a case, anti–PD-1/PD-L1 monotherapies are not expected to be highly effective [87]. Therefore, it is important to clarify which aspects of cancer immunity need to be targeted by novel immunotherapies, with the aim to provide benefit for patients with non-type I TME tumors. Different types of therapeutic interventions may need to be combined to generate a strong antitumor response, by effectively engaging immunity to suppress specific types of TME [17].

To treat various types of cancer-immune microenvironments, anti–PD-1 and anti–PD-L1 drugs will probably set the baseline of many future treatments for cancer, whereas the opportunities to combine these agents with surgery, radiation, immunogenic chemotherapy and targeted therapy and in class I tumors can be easily foreseen. The alternative strategy of chimeric antigen receptor T (CAR-T)-cell immunotherapy is essentially a combination treatment in nature. Providing earlier combination therapies to cancer patients, it is likely that approximately 50% or more of cancer types particularly some solid tumors such as melanoma and renal cell carcinoma are effectively prevented or controlled

3. Concluding remarks and future directions

Traditional anticancer treatments with cytotoxic drugs have generated limited promotion in the cure rates of various malignancies. Chemotherapy, radiation and targeted therapy, however, still have a large place in cancer clinics. Using novel approaches derived from the development of systems medicine, we will have a more thorough and accurate understanding of human cancer complexity and will be able to stratify patients appropriately. Personalized medicine has the potential to bring the best outcome for cancer patients, while healthcare costs should be made affordable and, most importantly, the combination therapies must be designed in a safe, rational, and effective way.

The fast moving research areas have undoubtedly set the stage for future investigation on interactions between cancer cells and the surrounding shelter, the TME. Development of methods for high content profiling of this complex biological landscape, and the other side, advancement of therapeutic strategies to overcome the pathological problem at a systemic level, thus turns out to be a very important task for prospective research and clinical practice.

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Abbreviations

ADCC	Antibody-dependent cellular cytotoxicity
AdipoR	Adiponectin receptor
ADP	Antibody-dependent phagocytosis
ALDH	Aldehyde dehydrogenase
ALL	Acute lymphoblastic leukemia
α-SMA	α-Smooth muscle actin
AML	Acute myeloid leukemia
ANGPTL4	Angiopoietin-like 4
ANGPT1	Angiopoietin 1
BM	Basement membrane or bone marrow
BMSC	Bone marrow stroma cell
CAF	Carcinoma-associated fibroblast
CAM-DR	Cell adhesion-mediated drug resistance
CAR-T	Chimeric antigen receptor T
cCAF	Circulating CAF
CCL2	Chemokine (C-C) ligand 2
CCL18	Chemokine (C–C) ligand 18
C/EBP	CCAAT/enhancer-binding protein
CLL	Chronic lymphocytic leukemia
CPC	Cancer-propagating cell
CSC	Cancer stem cell
CSF-1	Colony-stimulating factor 1
CTC	Circulating tumor cell
CTL	Cytotoxic T lymphocyte
CTLA4	Cytotoxic T lymphocyte antigen 4
CXCL12	Chemokine (C-X-C) ligand 12

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CXCR4	Chemokine (C-X-C) ligand receptor 4
DC	Dendritic cell
DDR	DNA damage response
DDSP	DNA damage secretory program
ECM	Extracellular matrix
EGF	Epidermal growth factor
EMT	Epithelial-mesenchymal transition
ER	Estrogen receptor
ErbB2 (or Her2)	Human epidermal growth factor receptor 2
FAP	Fibroblast-activating protein or fibroblast-associated protein
FGF	Fibroblast growth factor
FSP1	Fibroblast-specific protein 1
GM-CSF	Granulocyte macrophage colony-stimulating factor
HGF	Hepatocyte growth factor
HIF1α	Hypoxia-inducible factor 1α
HNSCC	Head and neck squamous cell carcinoma
hTERT	Human telomerase reverse transcriptase
IGF-1	Insulin growth factor 1
IL	Interleukin
MAPK	Mitogen-activated protein kinase
MCP1	Monocyte chemotactic protein 1
MDR	Multiple drug resistance
MDSC	Myeloid-derived suppressor cell
MMP	Matrix metalloproteinase
MRD	Minimal residue disease
mTOR	Mammalian target of rapamycin
MVD	Microvessel density
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NHT	Neoadjuvant hormonal therapy
NK	Natural killer
NSCLC	Non-small cell lung cancer
PCa	Prostate cancer
PDGF	Platelet-derived growth factor
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PI3K	Phosphoinositide 3 kinase

RCC	Renal cell carcinoma
RTK	Receptor tyrosine kinase
SCLC	Small-cell lung cancer
SDF-1	Stromal cell-derived growth factor 1
SFRP2	Secreted frizzled-related protein 2
TAM	Tumor-associated macrophage
TGF-β	Transforming growth factor-β
T_H1	T helper type 1
TIC	Tumor-infiltrating cell
TIL	Tumor-infiltrating lymphocyte
TKI	Tyrosine kinase inhibitor
TME	Tumor microenvironment
TNBC	Triple-negative breast cancer
TNF	Tumor necrosis factor
Treg	Regulatory T cell
uPAR	Urokinase plasminogen activator receptor
Vegf	Vascular endothelial growth factor

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