Feature Review

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Microenvironmental regulation of therapeutic response in cancer

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The tumor microenvironment (TME) not only plays a pivotal role during cancer progression and metastasis but also has profound effects on therapeutic efficacy. In the case of microenvironment-mediated resistance this can involve an intrinsic response, including the co-option of pre-existing structural elements and signaling networks, or an acquired response of the tumor stroma following the therapeutic insult. Alternatively, in other contexts, the TME has a multifaceted ability to enhance therapeutic efficacy. This review examines recent advances in our understanding of the contribution of the TME during cancer therapy and discusses key concepts that may be amenable to therapeutic intervention.

The TME orchestrates tumorigenesis and malignant progression

While cancer was long considered a disease defined and driven by genomic instability, chromosomal alterations, and genetic mutations [1], the influence of nonmalignant, stromal cells of the TME is now widely appreciated [2,3]. Tumors are complex tissues comprising not only malignant cells but also genetically stable stromal cells [4], including endothelial cells, fibroblasts, and immune cells among many others (Figure 1), in addition to the extracellular matrix (ECM) they produce. As in healthy organs, the various cellular compartments of the microenvironment are not mere bystanders, but instead critically regulate tumorigenesis [5]. This extends not only to tumor initiation, malignant progression, and metastasis but importantly also to response to therapy. Moreover, the realization that distinct stromal cell types in different contexts can exhibit tumor-promoting or opposing tumoricidal capacities has further complicated our understanding of cancer biology. While the role of the TME during tumorigenesis has recently been reviewed in detail elsewhere [2,3], this review focuses on how the TME regulates therapeutic response, a field that has been rapidly expanding in recent years. As in the context of malignant progression, the TME exhibits a multifaceted ability to influence therapeutic outcome in either a positive or a negative manner. Harnessing this expanding knowledge to improve therapeutic response or even to develop new treatment options through normalization and re-education of the TME is increasingly within reach. The recent clinical success of immune checkpoint inhibitors serves as an illustrative example of this goal. A brief overview of the major components of the TME highlighted in Box 1 provides the necessary background to introduce the reader to the different concepts contributing to both TME-intrinsic and -acquired/-adaptive resistance with regard to traditional anticancer therapies, molecularly targeted therapies, and agents targeted against the TME itself, which are summarized in Box 2.

Therapeutic response is significantly influenced by the TME

Although an increasing number of cancers can be treated successfully if detected at an early stage, the presence of disseminated disease or recurrence of the primary tumor still confer a poor patient prognosis [6,7]. This is due in part to the current paucity of effective therapeutic options in this setting [8]. An initial response to treatment is often followed by disease progression, which, accompanied by a diminution of therapeutic options, ultimately leads to treatment failure and death from recurrent or metastatic disease [9]. Intriguingly, at least some of the traits that promote metastasis appear to be intertwined with resistance to chemotherapy [10–12]. In line with a tumor cell-centric view, this lack of a sustained treatment response has been largely attributed to either intrinsic or acquired therapeutic resistance of the malignant cells via a plethora of mechanisms including increased drug efflux, drug inactivation, altered DNA repair machinery, dysregulation or alteration of the drug targets, upregulation of growth factor and survival signaling, and evasion of apoptosis [8,13]. These mechanisms appear to be partially fueled by a pre-existing intratumoral heterogeneity that supports the outgrowth of resistant clones [14].

In addition to tumor cell-intrinsic mechanisms, an increasing number of examples of TME-mediated resistance have been reported, representing an alternative means to interfere with therapeutic efficacy. Early seminal work by Teicher *et al.* elegantly linked the development of resistance to chemotherapy *in vivo* to interactions with the host's normal tissues [15]. The discrepancy they observed between the *in vitro* efficacy of, and *in vivo* resistance to, a panel of various chemotherapies has subsequently been confirmed and extended by numerous studies [16,17], providing many examples of where TME-mediated resistance may be at play. However, there are also instances where

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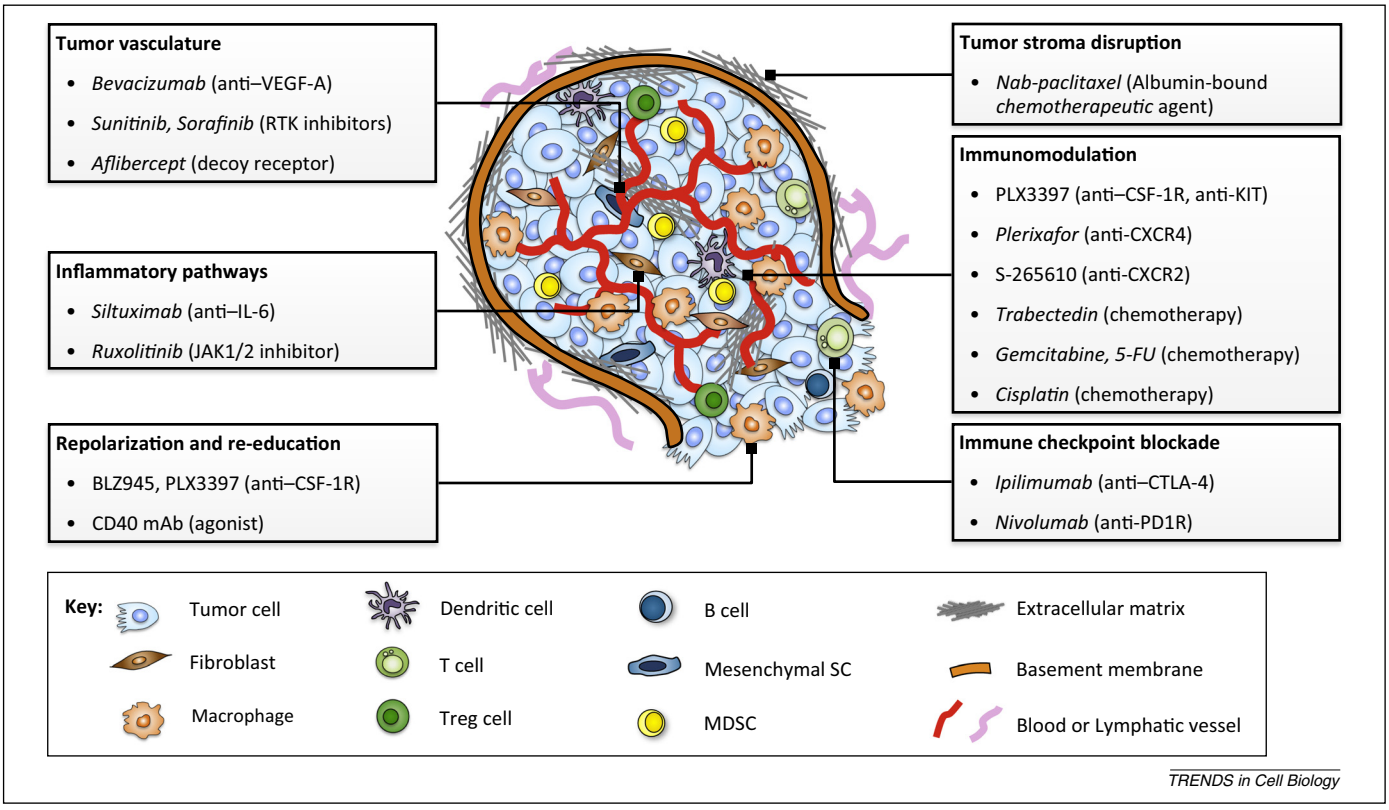

Figure 1. Major constituents of the tumor microenvironment (TME) and TME-targeted therapies. The TME comprises various cell types that modulate treatment response and are putative candidates for therapeutic intervention. The tumor vasculature can be targeted with various drugs, such as the vascular endothelial growth factor (VEGF)-A antibody bevacizumab, the multitarget receptor tyrosine kinase (RTK) inhibitors sunitinib and sorafenib, and the decoy VEGF receptor aflibercept [260]. Inflammatory pathway activation can be inhibited by the interleukin-6 (IL-6) antibody siltuximab [79] or the pan-JAK inhibitor ruxolitinib [166]. Cancer-associated fibroblasts are activated by multiple growth factors and cytokines within the TME and in turn acquire a proinflammatory phenotype and become a major source of soluble mediators that drive angiogenesis and enhance tumor cell survival. The immune cell compartment within the TME exhibits extraordinary plasticity: tumor-associated macrophages (TAMs) and myeloid derived suppressor cells (MDSCs) orchestrate an immunosuppressive and protective phenotype that extends to T cells, T regulatory (T_{reg}) cells and B cells. Repolarization or re-education of macrophages or other myeloid cells can be achieved by colony-stimulating factor 1 receptor (CSF-1R) inhibition (for example, BLZ945) [162] or agonistic CD40 antibodies that activate antigen-presenting cells (e.g., dendritic cells) to process and present tumor-associated antigens to local cytotoxic T lymphocytes [158,167]. This immune landscape within the tumor can be sculpted by inhibition of critical cytokine axes such as CSF-1R and/or KIT (PLX3397) [168], chemokine (C-X-C motif) receptor (CXCR) 4 (plerixafor), and CXCR2 (S-265610) [169]. The chemotherapeutic agent trabectedin has been proposed to selectively deplete monocytes and/or macrophages [170]. Both gemcitabine and 5-fluorourocil (5-FU) have been shown to deplete MDSCs [171,172]. Platinum-based cytostatic drugs can not only alter macrophage polarization but also induce increased antigen-presenting ability of dendritic cells. The blockade of immune checkpoints is another promising avenue of therapeutic intervention. This can be achieved through blockade of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) (ipilimumab) or the programmed death 1 (PD1) receptor (nivolumab). Finally, several extracellular properties also shape the therapeutic response, such as high interstitial fluid pressure and changes in the composition of the extracellular matrix (ECM). Albumin-bound nab-paclitaxel has been postulated to disrupt the stromal composition [173]. FDA-approved drugs are indicated in italics while agents in preclinical or clinical trials are non-italicized.

radiotherapy (RT) and certain chemotherapies require an active immune cell response for optimal efficacy, as in the case of immunogenic cell death [18]. Interestingly, a simple quantification of the tumor-to-stroma ratio in breast and colon cancers predicts worse clinical outcome in patients undergoing adjuvant chemotherapy as an independent variable [19,20]. Furthermore, analysis of stromal gene expression in various cancers not only yielded tumor type-specific prognostic benefit [21,22] but also exhibited predictive value regarding response to neoadjuvant chemotherapy [23]. Thus, analysis of the TME could convey significant clinical information to aid in the evaluation of treatment options.

TME-mediated therapeutic resistance can be broadly separated into two types. Inherent or intrinsic resistance is present before drug or RT exposure and is therefore evident without any selective pressure. This type of resistance is based on the multitude of pre-existing reciprocal interactions between tumor cells and the surrounding TME. This is in contrast to tumor cell-intrinsic resistance, which is due to existing genetic alterations within the biochemical or molecular target [8]. Acquired TME resistance, by contrast, evolves in response to the effects of therapy and is defined by an adaptive host response to therapeutic perturbation. This can result in pronounced changes in the microenvironment and the emergence of new tumor–TME dialogs operating at the local and/or systemic level.

Ultimately, the protective effect of the TME on tumor cells can lead to persistent residual disease that further increases the risk of recurrence [17]. Therefore, deciphering this complex network and introducing targeted perturbations will be critical for improving therapeutic efficacy and ultimately patient survival. However, it is essential to emphasize that these effects are organ, context, and stage dependent, as the TME can also confer a beneficial effect on treatment response. This concept has been demonstrated both in drug screens that incorporate the tumor stroma [16] and in many studies revealing the importance of various immune cell types in modulating therapeutic efficacy (reviewed in [18]).

In the following sections we discuss intrinsic and acquired responses of the TME to traditional, cancer cell-targeted, and microenvironment-targeted therapies.