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Mini-review

Tumor microenvironment and cancer therapy resistance

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ABSTRACT

Innate resistance to various therapeutic interventions is a hallmark of cancer. In recent years, however, acquired resistance has emerged as a daunting challenge to anticancer treatments including chemotherapy, radiation and targeted therapy, which abolishes the efficacy of otherwise successful regimens. Cancer cells gain resistance through a variety of mechanisms in both primary and metastatic sites, involving cell intrinsic and extrinsic factors, but the latter often remains overlooked. Mounting evidence suggests critical roles played by the tumor microenvironment (TME) in multiple aspects of cancer progression particularly therapeutic resistance. The TME decreases drug penetration, confers proliferative and antiapoptotic advantages to surviving cells, facilitates resistance without causing genetic mutations and epigenetic changes, collectively modifying disease modality and distorting clinical indices. Recent studies have set the baseline for future investigation on the intricate relationship between cancer resistance and the TME in pathological backgrounds. This review provides an updated outline of research advances in TME biology and highlights the prospect of targeting the TME as an essential strategy to overcome cancer resistance and improve therapeutic outcomes through precise intervention. In the long run, continued inputs into translational medicine remain highly desired to achieve durable responses in the current era of personalized clinical oncology.

Introduction

The steps of tumor development implicate co-evolution of malignant cells and benign constituents of the surrounding stroma, while dynamic interactions between pathologically altered parenchyma and stroma within the TME represents a critical paradigm now considered among the typical hallmarks of cancer [1]. Histologically the association of infiltrating leukocytes and tumorigenesis was first described by Rudolf Virchow in 1863 to propose the potential relevance of chronic inflammation to neoplastic events [2]. Subsequently in 1889, Stephen Paget contributed a "seed and soil" concept to delineate the distinct patterns of recurrent metastatic sites in human breast cancer, and to plausibly interpret the tropism of tumor metastases to specific organs [3]. To date, a plethora of studies have disclosed the unique aspects of the TME, with its mystical veil removed and diverse characteristics ascertained. It is increasingly evident that individual compartments of the TME do not stay as quiet bystanders, but significantly regulate tumor initiation, disease progression, metastatic development, and more importantly, therapeutic response. Among multiple TME-implicated activities, clinical response to therapies is the major factor that directly determines the long term fate of patients who undergo anticancer interventions. In this review, an updated picture of tumor–stroma interaction is depicted, with a particular emphasis on the capacity of the TME in modifying cancer sensitivity to therapeutic agents. An appropriate, thorough and in-depth understanding of the functional roles of TME in disease evolution is essential for rational design, reasonable innovation and successful translation of novel anticancer approaches to precise medicine with substantially improved clinical outcomes.

The TME orchestrates disease progression and dominates therapeutic responses

As a most lethal age-related pathology that imperils human health, cancer progresses with the surrounding TME to achieve continuous outgrowth and ensuing metastasis that correlates with the majority of cancer-related death [4]. Despite considerable advancements in therapeutic concepts and techniques, disease relapse with limited response remains a major challenge and confers poor prognosis in clinical oncology. Cancer resistance involves intrinsic mechanisms that are determined by pre-existing genetic and/or epigenetic properties of malignant cells including enhanced drug efflux,

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blunted apoptotic signaling, increased metabolic activities, loss of specific oncogenes, gain of stem cell plasticity and strengthened DNA damage repair machinery, all fueled by mutation-selective pressure that engenders clonal expansion and creates tumor heterogeneity [5,6]. In contrast, extrinsic resistance of cancer cells driven by the TME represents a seemingly minor but essentially pivotal modality that substantially influences therapeutic efficacy.

First, the TME mediates innate resistance prior to cytotoxic treatment events, which is through regular mutual interactions between cancer cells and neighboring TME components. This force differs from inherent resistance which is based on original alterations at the genomic and/or epigenomic levels of cancer cells. Second, acquired resistance conferred by the TME usually emerges as a host adaptive response to pharmacological insults. Specifically, the TME-provoked resistance generates profound impacts to local disease foci and shapes cancer evolution path under varying treatment pressures in clinical settings.

Cancer-associated fibroblasts

In solid tissues, fibroblasts constitute the structural framework and maintain the physiological homeostasis as a predominant mesenchymal lineage. However, cancer-associated fibroblast (CAFs) are functionally distinct from their normal counterparts and frequently demonstrate pathological relevance. In the microenvironment milieu, normal fibroblasts can be transformed into CAFs once stimulated by local tissue-derived proteins such as fibroblast growth factor (FGF), monocyte chemotactic protein 1 (MCP-1), platelet-derived growth factor (PDGF), tissue inhibitor of metalloproteinase 1 (TIMP-1) and tumor transforming growth factor β (TGF-β) [7,8]. Besides, miR-27a/b-transfected normal fibroblasts show increased expression of TGF-β and α-smooth muscle actin (α-SMA, a marker of CAF), changes that correlate with reduced chemosensitivity of esophageal cancer cells to cisplatin [9]. Despite the tumor-suppressive capacity in certain malignancies including pancreatic ductal adenocarcinoma (PDA) [10,11], CAFs exhibit aggressive proliferation, augmented extracellular matrix (ECM) deposition, enhanced cytokine synthesis/secretion (for instance, FGF7; hepatocyte growth factor (HGF); interleukin 6 (IL-6); PDGF; stromal cell-derived factor 1 (SDF-1); vascular endothelial growth factor (VEGF)) [5], a unique stromal phenotype characterized with a chemoresistance-triggering secretome that can be abolished upon mTOR/4E-BP1 translation pathway blockade [12].

Following activation in the TME, CAFs generate proinflammatory factors that promote tumor progression in an NF-κB-dependent manner, drive leukocyte infiltration, stimulating angiogenesis and vascular permeability [13–15]. Primary tumors select for bone metastatic seeds in the TME based on the interaction between Src pathway-activated cancer cells and chemokine C-X-C motif ligand 12 (CXCL12)/insulin-like growth factor 1 (IGF1)-secreting CAFs, indicating the evolution of metastatic traits in a primary foci and the distant metastases [16].

In tamoxifen-resistant breast tumors, G protein-coupled estrogen receptor (GPER)/epidermal growth factor receptor (EGFR)/extracellular regulated protein kinase (ERK) signaling enhances β1-integrin expression and activates downstream kinases, contributing to CAF-induced cell migration [17]. Moreover, downstream kinases of β1-integrin including focal adhesion kinase, Src and AKT are activated in resistant cells, potentially involved in the interaction between cancer cells and CAFs [17], highlighting the persistent tumor–stroma communication in a biologically dynamic TME. More importantly, CAFs establish a synergistic relationship with cancer cells, contributing to their malignancy and therapeutic resistance. In clinics, standard chemotherapy can phenotypically and metabolically change stromal fibroblasts into CAFs, leading to the emergence of a highly glycolytic, autophagic and pro-inflammatory microenvironment, which subsequently activates stemness (Sonic hedgehog/GLI signaling), antioxidant response and interferon-engaged signaling in nearby cancer cells [18].

Vasculature system

The tumor vascular network is derived from new vessels, through co-option and modification of mature vessels, or via differentiation of endothelial precursors from bone marrow, each contributing to vascular development and heterogeneity [5]. Vessel formation involves remodeling of pre-existing vascular basement membranes, and the pattern varies depending on the tissue type. Although a functional vasculature is vital for both tumor survival and metastatic progression by supplying oxygen and nutrients, poorly organized tumor vasculatures cause emergence of hypoxia and limited growth factor feeding. Co-operation of several cell types in the TME, including endothelial cells, pericytes and bone marrow-derived precursor cells, is fundamental for tumor vascularization, although such synergism is often modulated by hypoxia [19,20].

Spatial distance from vasculatures to tumor foci generates an infiltration gradient associated with drug distribution to cancer cells within the tissue, while microvessel density (MVD) is a significant prognostic factor for clinical outcome in malignancies including breast, liver, lung and lower lip squamous cell carcinoma (LLSCC) [21–24]. Mesenchymal stem cells (MSCs), tumor-associated macrophages (TAMs) and CAFs, all contribute to tumor vascularization by secreting a variety of angiogenesis-related ligands into the TME. Particularly, increased expression of the pro-angiogenic factor VEGFA is correlated with worse prognosis in metastatic colorectal, lung and renal cell cancers [25].

Tumor associated endothelial cells (TECs) differ from normal endothelial cells (NECs) in multiple aspects and exhibit distinct gene expression signatures. Particularly, chemokine CXC motif ligand receptor (CXCR)7 is upregulated in TECs and promotes angiogenesis in the TME via ERK1/2 phosphorylation [26]. Interestingly, CXCL12, a ligand of CXCR7, is present in conditioned medium from TECs, but not NECs. The CXCL12–CXCR7 autocrine loop influences TEC-associated proangiogenesis, tumor growth, lung metastasis and resistance, thus is considered for antiangiogenesis-purposed therapies that specifically target tumor blood vessels [26].

Recently, increasing evidence indicates that resistance to VEGF receptor inhibition arises from hypoxia-driven residual VEGF and other proangiogenic factors, thus combinations of agents targeting these factors are hypothesized to improve treatment outcomes relative to single VEGF pathway blockade alone. However, sorafenib, temsirolimus, and bevacizumab administered in synergistic manners did not significantly improve median progression-free survival when compared with bevacizumab monotherapy, although further investigation is being performed to determine the resistance mechanisms [27].

Extracellular matrix

The ECM is produced by multiple TME cell types and weaves an intricate fiber network not only providing structural support but also regulating cellular activities [28]. In early life stages the ECM prevents cancer initiation as a safeguard, while at a later stage it actively increases pathological incidence particularly tumorigenesis [29]. TME-associated ECM essentially differs from that of the normal tissue, serving as a basic scaffold for cancer cell invasion driven by chemotaxis [30]. Interplay between cancer cells and ECM elements is dynamic and goes far beyond spatial contact. In breast cancer, malignant cell attachment to ECM alters their polarization and causes resistance to etoposide-induced apoptosis [31]. Specifically, cell adhesion-mediated drug resistance (CAM-DR) depends on association of integrin to ECM components including fibronectin,

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