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EDITORIAL

Tumor microenvironment

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The tumor microenvironment (TME) has been a concept for many years, since 1889 with the presentation of Paget's "seed and soil" theory. Today, TME is now widely recognized as a hallmark of cancer, playing a critical role in cancer development. Traditionally, TME has been defined as the location where tumor cells survive within the organismal ecosystem. The classical theory indicates that oncogenes drive tumorigenesis, subsequently recruit and adapt surrounding non-malignant cells via diverse communicators like chemokines, cytokines, and vesicles [1]. However, the modern view of TME encompasses not only tumorous and nonmalignant cells but also intercellular components, intratumor microbiota, nerves, and metabolites surrounding the tumor lesion [2]. The updated TME landscape consists of six layers: tumor cell to tumor-cell environment, niche, confined tumor environment (TE), proximal TE, peripheral TE, and distal TE.

Within the TME, stromal cells such as fibroblasts, endothelial cells, and pericytes are the most abundant nonmalignant cells. Cancer-associated fibroblasts (CAFs) are the major nonmalignant stromal cells in the TME and exert diverse and prominent tumor-supporting effects. Physically, CAFs promote matrix adhesion and mesenchymal morphology that result in increased stiffness and collagen fiber alignment. This leads to increased secretion of type I collagen by CAFs, supporting tumor invasion and migration. Subsequently, CAFs release diverse matrix metalloproteinases (MMPs) to degrade and remodel the extracellular matrix (ECM), which contributes to the stimulation of stemness and epithelial-mesenchymal transition. CAFs secrete the primary chemokine, C-X-C motif ligand 12 (CXCL12), which promotes T cell retention by binding to its receptor atypical chemokine receptor 3 (ACKR3) on the surface of T cells [3]. However, CXCL12 also recruits C-X-C motif chemokine receptor 4 $(CXCR4)^+$ myeloid cells to form an immunosuppressive microenvironment [4]. Metabolically, CAFs exhibit a phenomenon called "metabolic symbiosis" where they consume glucose and produce lactate, which cancer cells prefer utilizing via monocarboxylate transporter 1 (MCT1) transporters [5]. Immunologically, CAFs orchestrate a particular structural tissue organization through dense and aligned fiber deposition to exclude T cells from tumor nests [6]. Additionally, leucine-rich-repeat-containing protein 15 $(LRRC15)^+$ CAFs directly suppress the effector function of tumour-infiltrating cluster of differentiation 8 $(CD8)^+$ T cells and restrict the efficacy of checkpoint blockade [7]. Further studies are necessary to better understand the complicated roles of endothelial cells and pericytes in cancer progression [8, 9].

The TME comprises a diverse population of immune cells, including myeloid-derived suppressor cells (MDSC), neutrophils, dendritic cells (DC), innate lymphoid cells (ILC), natural killer cells (NK), lymphocytes, and macrophages [10, 11]. Within the TME, cytokines manipulate immune function, leading to weakened immune responses that promote tumor progression [12]. $CD8^+$ T cells represent the primary adaptive immune cells in cancer and selectively recognize and eradicate tumor cells expressing tumor-specific antigens, including tumor-specific neoantigens and self-antigens [13]. However, over the course of tumorigenesis, tumor-reactive $CD8^+$ T cells become dysfunctional. Various immunosuppressive elements within the TME, such as forkhead box protein P3 $(FOXP3)^+$ and cluster of differentiation 4 $(CD4)^+$ regulatory T cells, MDSCs, tumor-associated macrophages (TAMs), interleukin-10 (IL-10), inhibitory checkpoints, and metabolic changes such as hypoxia or indoleamine

2,3-dioxygenase, contribute to this dysfunction [14, 15]. Overcoming the immunosuppressive TME and improving the functionality of $CD8^+$ T cells can enhance responses to therapeutic reprogramming.

Recent advancements in cancer biology have identified microbiota as an important component of the tumor microenvironment, specifically categorized as 'intratumor microbiota' [16]. Numerous studies have extensively supported the presence of intratumor microbiota, and their abundance is found to be tumor-specific. The enrichment of microbiota has been discovered in breast, bone, and pancreatic cancers, but not in cancer tissues exposed to external environment [17]. As few studies have specifically interrogated its original source, its origin remains a mystery. Intratumor bacteria have several similar characteristics, including lower diversity and abundance of the microbial community in cancer tissues [18]. Commensal organisms tend to survive in the intracellular space. Functionally, intratumor microbiota can modulate cancer cell-intrinsic and cell-extrinsic properties. Intratumor microbiota can induce a migratory and invasive phenotype, initiate stemness, and resist lethal stimuli [19]. Intratumor bacteria are also important regulators that can create a tumor-supporting microenvironment through the production of specific metabolites and immune modulation [20, 21]. This discovery provides a unique perspective to understand networks of the cancer ecosystem and reshapes the current conceptual framework of the TME.

The innervated microenvironment (IME) is a specialized micro-ecosystem that forms through communication between nerves and cancer cells via nerve-derived neurotransmitters or neuropeptides [22]. IMEs are categorized as intracranial or extracranial innervated niches. In the intracranial IME, active neurons promote the gliomas growth through the neuroligin-3 (NLGN3)-activated PI3K/mTOR pathway [23]. Perineural invasion (PNI) refers to cancer invasion in or around nerves, which is associated with poor cancer prognosis. Peripheral nerves, including sympathetic, parasympathetic, and sensory nerves, are present in the IME and make physical contact with cancer parenchyma or nearby nerves. The secretion of neuropeptides or neurotransmitters like catecholamine, acetylcholine and dopamine plays a crucial role in neuromodulation within the IME [24]. Additionally, Schwann cells from nerves facilitate cancer invasion. When activated by cancer cells, Schwann cells collectively function as tumor-activated Schwann cell tracks (TAST), promoting cancer cell migration and invasion [25]. TAST exhibit elevated HIPPO-transcriptional co-activator with PDZ-binding motif (TAZ)/yes-associated protein (YAP) expression, and hyperactivity of TAZ/YAP in Schwann cells activates oncogenic programs, including platelet-derived growth factor receptor (PDGFR) signaling, leading to high-grade nerve-associated tumors [26]. Recent studies have demonstrated a tumor-nerve-immunity cycle in TME that mediates communication among cancer cells, immune microenvironment, and innervation. The Hypothalamic-pituitary (HP) unit is able to expedite myelopoiesis and immunosuppression to promote tumor growth through the production of α-melanocyte-stimulating hormone (α-MSH). α-MSH combines to melanocortin receptor melanocortin 5 receptor (MC5R) to promote myeloid cell recruiting, immunosuppression, and tumor growth [27].

Various innovative approaches are available to gain detailed insights into the immunological features of tumors. For instance, single-cell and spatial multi-omics techniques provide a comprehensive understanding of TME [28]. Additionally, immunomics, based on next-generation sequencing (NGS) technologies and mass-spectrometric techniques, offers novel insights into tumor immunology. In recent years, strategies targeting the TME have gained significant attention due to its critical role in tumor progression and cancer treatment efficacy. These approaches primarily focus on cancer immunotherapy, such as vaccines, immune checkpoint blockade (ICB), adoptive immune cell therapy, as well as targeting tumor angiogenesis, ECM, and CAFs [29]. Despite inducing durable remissions in some patients and cancer types, these strategies fail to achieve long-term responses for most patients. However, continued advances in technology and therapy have the potential to integrate basic microenvironmental insights with clinical observations to benefit all cancer patients through TME-targeting therapies.

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