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Mini-review

Tumor microenvironment: Sanctuary of the devil

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ABSTRACT

Tumor cells constantly interact with the surrounding microenvironment. Increasing evidence indicates that targeting the tumor microenvironment could complement traditional treatment and improve therapeutic outcomes for these malignancies. In this paper, we review new insights into the tumor microenvironment, and summarize selected examples of the cross-talk between tumor cells and their microenvironment, which have enhanced our understanding of pathophysiology of the microenvironment. We believe that this rapidly moving field promises many more to come, and they will guide the rational design of combinational therapies for success in cancer eradication.

Introduction

In the past two decades, many oncogenes and tumor suppressor genes have been identified. Subsequently, these genes were mapped to the signaling pathways that regulate cell growth or apoptosis, and various anti-tumor agent and therapeutic methods were developed. The survival of cancer patients has been significantly extended; however, the tumor relapse or recurrence is almost always developed eventually with resistance to the initially effective drugs. The cancer therapy has encountered a bottleneck. An emerging concept is that the maintenance and expansion of tumors also strongly depend on external signals from their microenvironment [1–3].

To fully understand tumor development and progression, a deeper knowledge of the interactions between cancer cells and their microenvironment is needed [3,4]. Important open questions have been announced:

- What are the specific components of a Tumor Microenvironment (TME)?
- Which signals do cancer cells transmit to and receive from the TME?
- What is the role of infiltrated immune cells to tumor progression?
- How do cancer cells develop chemoresistance in the TME?

Indeed, a series of studies work on the tumor microenvironment were published throughout the past few years. Here we put a brief overview of the TME and highlight a few major recent studies focusing on the cross-talk between tumor cells and their microenvironment. We hope that this mini-review can offer a taste of this rapidly moving field, as well as suggestions regarding further advances.

Unique tumor microenvironment at a glance

The TME is the cellular environment in which the tumor exists. Apart from the tumor cells, the TME includes surrounding blood vessels, the extracellular matrix (ECM), other non-malignant cells, and also signaling molecules [4,5]. By using cell-type-specific markers, researchers have identified different types of normal cells in the TME, including stromal cells, fibroblasts, immune cells (such as T lymphocytes, B lymphocytes, natural killer cells and natural killer T cells, Tumor-associated macrophages, etc.), as well as pericytes and sometimes adipocytes (Fig. 1). The stromal cells and fibroblasts in TME can secrete growth factors, such as hepatocyte growth factor (HGF), fibroblast growth factor (FGFs) and CXCL12 chemokine, which can not only promote growth and survival of malignant cells but also function as a chemoattractant that stimulates the migration of other cells into the TME [6]. Different T cell populations and B cells can be found at the invasive margin of tumors; however, it is still controversial whether the presence of these cells in TME reflects a good or bad prognosis [7]. For many solid tumors, the appearance of natural killer cells and natural killer T cells in TME predicts a good prognosis [8]. Tumor-associated macrophages are abundant in most human and experimental murine cancers, and their activities are usually pro-tumorigenic [9]. Beyond the contributions of specific cell types to TME, the extracellular matrix (ECM) is another major component. ECM is composed of a large collection of biochemically distinct components including proteins, glycoproteins, proteoglycans, and polysaccharides with different physical and biochemical properties [10]. ECM can not only provide a physical scaffold for all cells in the TME but also is abundance of

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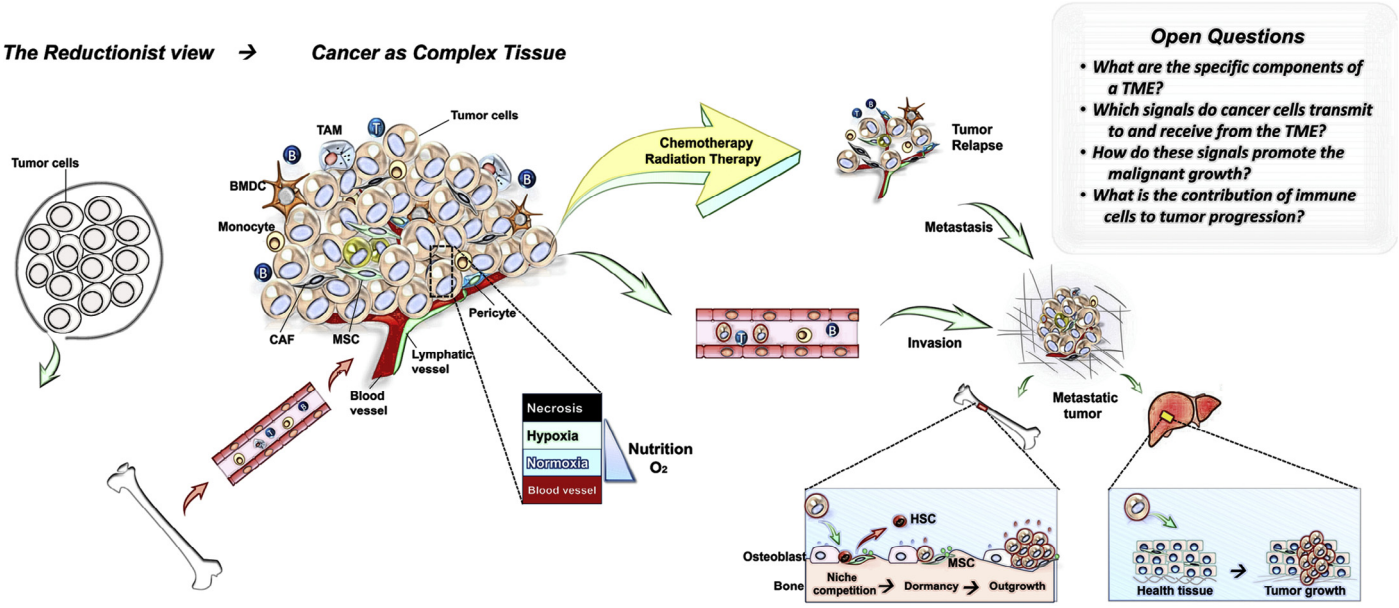

Fig. 1. A schematic depiction of evolution of cancer view. The tumor was seen as a "foreign" component that grew as a homogeneous mass. In parallel with the exploits of new biotechnologies, basic researchers and clinicians have recognized the complexity of cancer and of its interaction with the microenvironment. Unique characteristics of the tumor microenvironment, such as hypoxia and high interstitial fluid pressure, distinguished it from the corresponding normal tissues. In addition, tumor cells can foster their own expansion and aggressiveness by transforming normal adult stem cell niches. CAF, cancer-associated fibroblast; TAM, tumor associated macrophage; BMDC, bone marrow-derived dendritic cell; MSC, mesenchymal stem/stromal cells; ECM, extracellular matrix.

key growth factors. Different cell types in the TME supply distinct ECM proteins. ECM plays a critical role in the development of tumor, which is commonly deregulated and becomes disorganized in later stage of tumor progression. Abnormal ECM can also dysregulate the behavior of stromal cells in the TME and facilitate angiogenesis and inflammation [11]. Interestingly, primary tumors of diverse metastatic potential differ in their composition of ECM components. Indeed, the composition of the extracellular TME has been used a predictor of clinical prognosis [2,11]. The tumor vasculature is abnormal in almost every aspect of its structure and function [12]. The vasculature of the tumor is always inadequate to meet the demands of the growing mass, leading to hypoxic and acidotic regions of the tumor. When a quiescent blood vessel senses an angiogenic signal from the hypoxic conditions in the TME, angiogenesis is stimulated and heterogeneous new vessels with chaotic branching structures sprout from the existing vasculature [13]. In addition, the tumor blood vessels exhibit an uneven vessel lumen and are usually leaky, which raises interstitial fluid pressure leading to unevenness of blood flow and nutrient, as well as drug distribution, in the TME. This, in turn, increases hypoxia and facilitates tumor development. These unique characteristics of the TME distinguished it from the corresponding normal tissues, and there is emerging evidence that extrinsic stimulations mediated by the microenvironment play a pivotal role in survival and drug resistance of the tumor cells [14].

Deregulated communication between cancer cells and the organism

Cancer cells foster their own expansion and aggressiveness by transforming normal adult stem cell niches

Hematopoietic stem cells (HSCs), which were localized in bone marrow (BM), are one of the best characterized adult stem cell types. The relevance of the BM microenvironment in regulating HSC behavior has only recently been established [15–17]. Complex bidirectional interactions between the BM niche and HSCs were essential for the maintenance of HSC quiescence and normal hematopoiesis. Moreover, there are growing evidence supporting the idea that the BM microenvironment also plays a pivotal role in the initiation and propagation of leukemia [1,18].

Recent data indicated that leukemic cells hijack the homeostatic mechanisms of normal HSCs and take refuge in the BM niche [19,20] (Fig. 1). By using dynamic *in vivo* imaging system in a mouse model, Colmone et al. showed that leukemic cell growth disrupts normal HSC BM niches, and the niches were converted into an environment that favors cell proliferation and growth in parallel with the leukemogenic events [20]. The normal oxygen saturation is relatively low in BM compared to other organs. It is advantageous for stem cells to localize at the sporadic hypoxic niches, since the exposure to high levels of ROS induces senescence and dysfunction in stem cells. It has been proved in both animal models and clinical samples that the BM is highly hypoxic in the context of hematologic malignancies [21]. Researchers believe that the progression of leukemia is associated with expansion of hypoxic niches and stabilization of the oncogenic hypoxia inducible factor-1α (HIF-1α). In a very recent study, Duan et al. recorded that normal BM niche of immune-deficient mice was damaged by the dissemination of human acute lymphoblastic leukemia (ALL) [22]. The authors characterized the initial HSC niche in a mouse model, which was primarily composed of nestin-expressing mesenchymal stem or stromal cells (MSCs). With the progression of leukemia, these nestin positive cells in the niche were mostly lost and replaced by α-smooth muscle actin (αSMA) expressing stromal cells. Furthermore, similar results were observed in mice bearing xenografts from primary human ALL samples. Moreover, Alexandre et al. also confirmed that B-CLL clone has markedly impact on MSCs and disrupts BM niches *in vivo* by quantifying the colony forming unit-fibroblasts (CFU-Fs) [23].

Abnormal microenvironment function as a determinant of tumorigenesis

Osteoblasts are first defined as specialized, terminally differentiated products of MSCs. Subsequently, osteoblasts have been implicated in normal hematopoietic processes, as they can synthesize dense, cross-linked collagen, and several additional specialized