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Review article

Exploiting the cancer niche: Tumor-associated macrophages and hypoxia as promising synergistic targets for nano-based therapy

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ABSTRACT

The tumor microenvironment has been widely exploited as an active participant in tumor progression. Extensive reports have defined the dual role of tumor-associated macrophages (TAMs) in tumor development. The protumoral effect exerted by the M2 phenotype has been correlated with a negative outcome in most solid tumors. The high infiltration of immune cells in the hypoxic cores of advanced solid tumors leads to a chain reaction of stimuli that enhances the expression of protumoral genes, thrives tumor malignancy, and leads to the emergence of drug resistance. Many studies have shown therapeutic targeting systems, solely to TAMs or tumor hypoxia, however, novel therapeutics that target both features are still warranted. In the present review, we discuss the role of hypoxia in tumor development and the clinical outcome of hypoxia-targeted therapeutics, such as hypoxia-inducible factor (HIF-1) inhibitors and hypoxia-activated prodrugs. Furthermore, we review the state-of-the-art of macrophage-based cancer therapy. We thoroughly discuss the development of novel therapeutics that simultaneously target TAMs and tumor hypoxia. Nano-based systems have been highlighted as interesting strategies for dual modality treatments, with somewhat improved tissue extravasation. Such approach could be seen as a promising strategy to overcome drug resistance and enhance the efficacy of chemotherapy in advanced solid and metastatic tumors, especially when exploiting cell-based nanotherapies. Finally, we provide an in-depth opinion on the importance of exploiting the tumor microenvironment in cancer therapy, and how this could be translated to clinical practice.

Contents

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1. Introduction

Cancer is amongst the leading causes of mortality and morbidity worldwide. The latest statistics point to an estimated 14.1 million new cases and 8.2 million cancer-related deaths [1]. It has been characterized by an uncontrolled cell proliferation, which is often associated with vascular abnormalities and cell invasiveness. In the past few years, the hallmarks of cancer have been revised and an active participation has been assigned to the tumor microenvironment (Fig. 1) [2]. Studies have shown that cancer cells evolved to promote angiogenesis, metastasis and survival in response to several factors within the tumor microenvironment, such as pH, growth factors, oxygen levels and the presence of immune cells [3–5]. Tumor cells adaptation to the environment is considered essential to maintain their survival and growth. For instance, tumor cells grow under low levels of oxygen and nutrients, develop new blood vessels, a process called '*de novo* angiogenesis' to compensate for the lack of oxygen and nutrients. These newly formed blood vessels contain discontinuous endothelium, which renders them leaky in nature. This vascular hyperpermeability, in combination with impaired lymphatic drainage, are known as enhanced permeation and retention effect (EPR) [6]. Surgery, radiotherapy, and classical chemotherapy are still the first options for many types of tumors [7]. However, the associated side effects and the emergence of multidrug resistance (MDR), have limited the clinical use of most common therapeutic compounds [8]. Therefore, there is an unmet need to develop novel approaches and therapeutics to target the tumor cell and its microenvironment. The heterogeneity and complexity of tumor microenvironment promote cancer survival and progression. Lately, research has focused on the involvement of tumor-associated macrophages (TAMs) in cancer progression. Studies have explored the link between the secretion of TAM chemoattractants by the tumor cells and the consequent upregulation of tumor-promoting genes by these immune cells, in response to the microenvironment stimuli [9,10]. Additionally, hypoxia has been found as a critical factor for the survival of large tumor masses and therefore a key target for the development of targeted therapies [11]. Furthermore, high infiltration of TAMs are found in hypoxic tumor cores, promoting resistance to classical chemotherapeutics. This microenvironment may be used to develop sophisticated fine-tuned nano-based systems, capable of enhancing therapeutic extravasation into tumor hypoxic cores. Great efforts should be made to promote the rational design of delivery systems that could achieve high therapeutic efficacy by simultaneously targeting TAMs and hypoxia.

2. Cancer hypoxia

Structural abnormalities in tumor vessels lead to reduced oxygen diffusion to tumor cells and eventually, necrotic cores. It has been fifty some years since Thomlinson and Gray first postulated the role of hypoxia in human tumors [12]. Hypoxia has an active role in oncogenesis and contributes to the overall survival of tumors. In normal tissues, oxygen levels are heterogeneous and physiological pO2 can range between 20 mmHg in the liver and brain to 70 mmHg in the kidney (3.1–8.7% O2). In contrast, a decrease to about 10–30 mmHg of pO2 is observed in tumors. Most importantly, 82% of all oxygen readings taken from solid tumors, present a 0.33% O2 reading (as low as 2.5 mmHg) [13,14]. The level of hypoxia within tumors increases during tumor progression. Chronic hypoxic cells have been described as prone to higher proliferation and survival. Aggressive phenotype with increased resistance to therapy has been associated with patients with highly hypoxic tumors, highlighting the clinical significance of hypoxia [15].

Hypoxia-inducible factors (HIFs), essentially HIF-1 have been linked to hypoxic tumor microenvironments. It is commonly overexpressed in solid and metastatic tumors including breast, prostate, colon, lung, pancreatic, head and neck cancer [16]. This molecule functions as a heterodimeric transcription factor composed of HIF-1α and HIF-1β, whose dimerization is regulated by an oxygen-dependent prolyl hydroxylase. When oxygen levels decrease, HIF-1α accumulates and translocates to the nucleus, where it forms the active transcription factor HIF-1 by binding to HIF-1β. This molecule regulates a plethora of genes in cancer biology and metabolism, controlling the proliferation rate, metastasis, and aggressiveness of cancer cells [17]. It also potentiates tumor cells

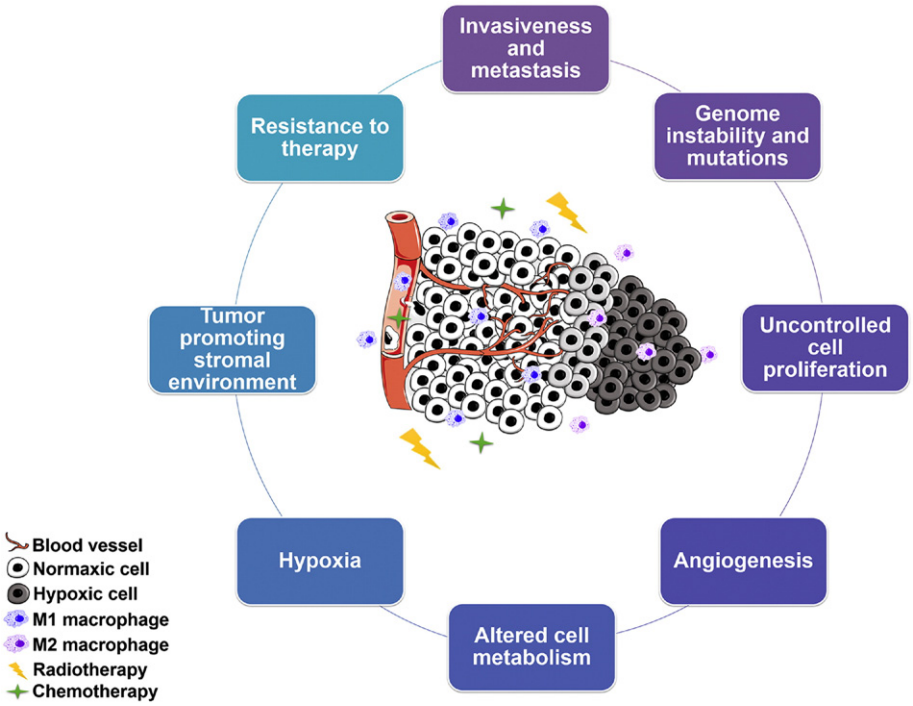

Fig. 1. Main hallmarks of cancer. The cancer niche is a complex network of endothelial, stromal and malignant cells, comprised of evolutionary genomic features that enhance survival and thrive tumor cells to uncontrolled proliferation and metastasis. This enriched tumor microenvironment supports a shifted metabolism in cells, which allows a quick preadaptation and survival under nutrient and oxygen deprivation (hypoxia) which lead to therapeutic resistance.