Trends in Pharmacological Sciences

CellPress

Feature Review

Reprogramming of the Tumor in the Hypoxic Niche: The Emerging Concept and Associated Therapeutic Strategies

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Hypoxia exerts a profound impact on diverse aspects of cancer biology. Increasing evidence has revealed novel functions of hypoxia in cancer cell epigenomics, epitranscriptomics, metabolism, and intercellular communication, all hotspots of cancer research. Several drugs have been developed to target intratumoral hypoxia and have entered clinical trials to treat refractory tumors. However, direct targeting of hypoxia signaling still has limitations in the clinic with regard to cancer progression and resistance to therapy. Comprehensive understanding of the molecular mechanisms by which hypoxia reshapes tumors and their microenvironment, as well as how tumor cells adapt to and thrive in hypoxic conditions, will therefore continue to be a focus of cancer research and will provide new directions for hypoxic tumor treatment.

Hypoxia: Master Regulator of Cancer Biology

The importance of the tumor microenvironment is increasingly recognized, and recent years have witnessed an explosion of studies on intratumoral hypoxia. In a broad range of solid tumors, hypoxia is a common and persistent feature arising from an imbalance between increased oxygen consumption driven by cancer cell expansion combined with inadequate oxygen supply owing to defective tumor vascularization [1]. In response to hypoxia, complex mechanisms are triggered to allow cell adaptation to low-oxygen conditions, and these are largely mediated by hypoxia-inducible factors (HIFs) and their downstream gene expression networks [2,3]. Hypoxia-induced signaling has been regarded as a master regulator of cancer hallmarks such as stemness, dormancy, invasion, metastasis, angiogenesis, immunity, and metabolic reprogramming, as well as resistance to anticancer therapies [3–7] (Figure 1), and intratumoral hypoxia is highly correlated with tumor aggressiveness and poor prognosis. Hypoxia and HIFs have long been considered as key targets for cancer therapeutics, and many studies have focused on detecting and eliminating intratumoral hypoxia as well as on inhibiting HIF signaling [1,8]. In this review we not only underscore the complex regulation of hypoxia signaling, the development of experimental models of hypoxia, and the multifunctionality of hypoxia in cancer biology, but also discuss advances in hypoxia detection and the development of targeted therapies to modulate hypoxia-induced signaling. We propose that, instead of focusing on individual tumor cells, a comprehensive understanding of hypoxia in the context of the tumor microenvironment is essential.

Trends

Hypoxic signaling induces profound adaptive changes in cancer cells as a consequence of defective vascularization in most solid tumors.

Tumors utilize the hypoxic response to rewire their metabolic program and transcriptional profile.

Hypoxia signaling can trigger resistance to conventional and immune therapies, mainly by inducing cancer cell stemness, dormancy, and enhanced tumor heterogeneity. Hypoxia can reprogram the metabolism, epigenetics, and epitranscriptome of tumors via HIF signaling.

The exosome emerges as a novel signal transmitter between different cellular components in the hypoxic microenvironment.

Recent advances in molecular probing of hypoxic signaling facilitate the detection of hypoxia within a tumor *in situ*.

Hypoxia-targeted therapeutics are being investigated in preclinical studies. Some compounds have entered clinical trials whereas others need further optimization.

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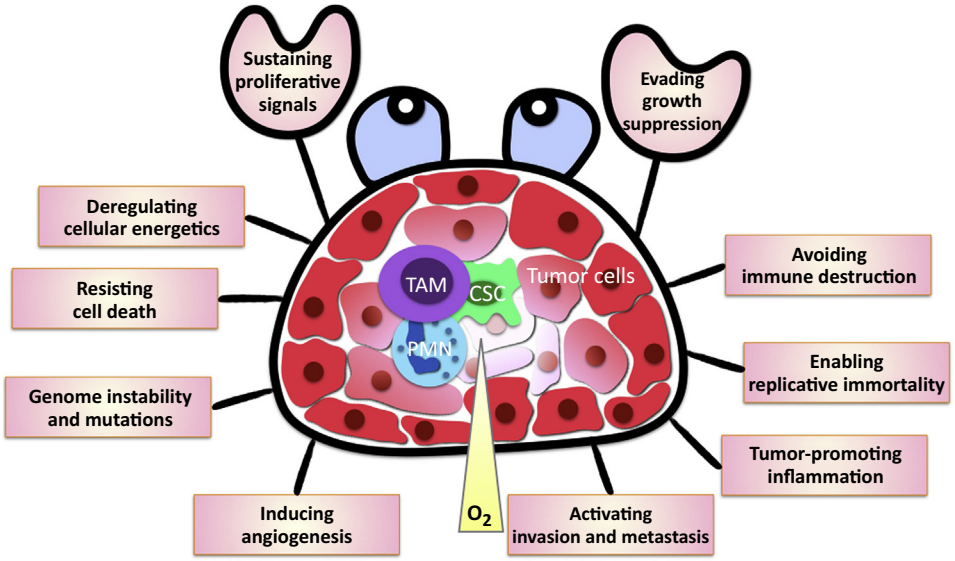

Figure 1. Hallmarks of Cancer Regulated by Hypoxia. Hypoxia can not only impact on cancer cells such as CSCs but also on other components in the tumor microenvironment such as PMNs and TAMs. These regulate of multiple aspects of cancer such as sustaining proliferative signals, deregulating cellular energetics, genome instability, and mutations, angiogenesis, activating invasion and metastasis, and immune suppression. Abbreviations: CSCs, cancer stem cells; PMNs, polymorphonuclear leucocytes; TAMs, tumor-associated macrophages.

Hypoxia, HIFs, and the Regulation of HIFs in Cancer

In solid tumors, the extent of hypoxia depends on tumor cellular heterogeneity and the distribution of the vasculature. Under hypoxic conditions, HIFs are stabilized and permit the activation of genes essential for cellular adaptation to low-oxygen conditions [2] (Figure 2). HIFs belong to the highly conserved PER/ARNT/SIM (PAS) subfamily of basic helix-loop-helix (bHLH) transcription factors. In response to hypoxic stress, HIFs form an active heterodimeric complex that consists of an oxygen-sensitive α subunit and a constitutively expressed oxygen-insensitive β subunit [9]. Three HIFα members have been identified so far. HIF1α and HIF2α play a vital role in positive hypoxic response while HIF3α is speculated to be a negative modulator [10].

Experimental Models of Hypoxia

In recent years, with the development of genomic editing, the transgenic mouse has been widely used as an *in vivo* model to explore the impact of hypoxia or HIFs on different cellular activities [11–13]. Beyond that, to model the *in vivo* condition of hypoxia, there are three primary models for *in vitro* study. The first is by physically creating a hypoxic environment within a multi-gas incubator. The second is by oxygen deprivation using chemicals in cell culture media, such as cobalt salts and deferoxamine mesylate [14,15]. Third, in recent years 3D organoid cultures have been used to mimic both hypoxic conditions and *in vivo* intratumoral heterogeneity. The organoid culture model has many advantages over the traditional 2D culture for modeling the complex hypoxic tumor microenvironment [16]. For example, both hypoxia heterogeneity and organoid growth patterns are more similar to those of *bona fide* tumors. Hence, organoid cultures have been developed models that can recapitulate many aspects of the *in vivo* tumor microenvironment, especially the hypoxic conditions [16].

HIFs and Their Regulation

The adaptive response to hypoxia centers on the transactivation of a series of target genes downstream of HIF signaling. This involves a multistep signaling cascade including HIFα

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