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Review

The biological kinship of hypoxia with CSC and EMT and their relationship with deregulated expression of miRNAs and tumor aggressiveness

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ABSTRACT

Hypoxia is one of the fundamental biological phenomena that are intricately associated with the development and aggressiveness of a variety of solid tumors. Hypoxia-inducible factors (HIF) function as a master transcription factor, which regulates hypoxia responsive genes and has been recognized to play critical roles in tumor invasion, metastasis, and chemo-radiation resistance, and contributes to increased cell proliferation, survival, angiogenesis and metastasis. Therefore, tumor hypoxia with deregulated expression of HIF and its biological consequence lead to poor prognosis of patients diagnosed with solid tumors, resulting in higher mortality, suggesting that understanding of the molecular relationship of hypoxia with other cellular features of tumor aggressiveness would be invaluable for developing newer targeted therapy for solid tumors. It has been well recognized that cancer stem cells (CSCs) and epithelial-to-mesenchymal transition (EMT) phenotypic cells are associated with therapeutic resistance and contribute to aggressive tumor growth, invasion, metastasis and believed to be the cause of tumor recurrence. Interestingly, hypoxia and HIF signaling pathway are known to play an important role in the regulation and sustenance of CSCs and EMT phenotype. However, the molecular relationship between HIF signaling pathway with the biology of CSCs and EMT remains unclear although NF-κB, PI3K/Akt/mTOR, Notch, Wnt/β-catenin, and Hedgehog signaling pathways have been recognized as important regulators of CSCs and EMT. In this article, we will discuss the state of our knowledge on the role of HIF-hypoxia signaling pathway and its kinship with CSCs and EMT within the tumor microenvironment. We will also discuss the potential role of hypoxia-induced microRNAs (miRNAs) in tumor development and aggressiveness, and finally discuss the potential effects of nutraceuticals on the biology of CSCs and EMT in the context of tumor hypoxia.

Contents

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1. Introduction

Low concentrations of oxygen in cells or tissues, referred to as hypoxia, are one of the most pervasive microenvironmental stresses and are recognized as the most common features of solid tumors. Hypoxia has been known to be associated with many aspects of biological processes during tumor development and progression such as cell survival, invasion, angiogenesis, and cellular metabolic alterations. Clinically, hypoxia and its signaling pathway have been shown to be associated with resistance to radiotherapy and chemotherapy, contributing to increased risk of tumor recurrence and metastasis, leading to reduced overall survival rate and increased mortality [1–5]. It is estimated that up to 60% of locally advanced solid tumors exhibit hypoxic (1% O_2 or less, compared to 2–9% O_2 in the adjacent tissues) and/or anoxic (<0.01% O_2, or no detectable oxygen) conditions throughout the whole tumor tissues [6]. Transient hypoxia is related to inadequate blood supply while chronic or prolonged hypoxia is related to increased oxygen diffusion distance due to tumor expansion. Both types of hypoxic conditions are associated with poor outcome of patients diagnosed with solid tumors.

Tumor hypoxia is usually induced by several microenvironmental factors such as inadequate vascularization due to tumor angiogenesis leading to aberrant vessels with altered perfusion; an increase in oxygen diffusion distances due to rapid expansion of tumor cells; and tumor- or therapy-associated anemia leading to the reduced capacity of oxygen transportation [6,7]. Tumor cells usually have a greater capacity to adapt to a hostile, hypoxic environment for survival, compared to normal cells, which contributes to their malignant and aggressive behavior. This adaptation is controlled by many factors, including transcriptional and post-transcriptional changes in gene expression. It has been estimated that up to 1.5% of the human genome are responsive to hypoxia at transcriptional levels [6,7]. Hypoxia inducible factors (HIF) are one of the most critical transcriptional regulators that mediate the adaptation of tumor cells to a hypoxic tumor microenvironment.

In this review, we will discuss the role of HIF signaling pathways in the maintenance of hypoxic cellular response within the tumor microenvironment, and will discuss the role of hypoxia and its signaling pathway in the regulation and sustenance of the phenotypes of cancer stem cells (CSCs) and epithelial-to-mesenchymal transition (EMT). Moreover, we will summarize the molecular interrelation between HIF signaling pathway and other known cellular signaling pathways such as nuclear factor of κB (NF-κB), phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B)/mammalian target of rapamycin (mTOR), Notch, Wnt/β-catenin, and Hedgehog in defining tumor aggressiveness. We will also discuss the state of our knowledge on the potential role of hypoxia-mediated microRNAs (miRNAs) in tumor development and aggressiveness. Finally, we will discuss the state of our knowledge on the role of natural product-derived agents (nutraceuticals) as potential molecular regulators of hypoxia-associated biology of tumor aggressiveness as a potential therapeutics.

2. Hypoxia, HIF, and clinical prognosis in tumor

HIF proteins are the master transcriptional regulators of the cellular response to hypoxic tumor microenvironment [8,9], which are involved in the regulation of many key aspects of tumor development and progression. For example, cell proliferation and survival are mediated through the regulation of the gene expression of HIF downstream targets, cyclin-dependent kinase inhibitor 1A (CDKN1A) and B-cell lymphoma 2 (Bcl2)/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), a cell death inducer during hypoxia; adaptive cellular metabolism mediated through the regulation of glucose transporter 1 (GLUT1), GLUT3, lactate dehydrogenase A (LDHA) and pyruvate dehydrogenase kinase 1 (PDK1); microenvironmental acidity mediated through the regulation of carbonic anhydrase 9 (CAIX); invasion and metastasis through the regulation of C–X–C chemokine receptor type 4 (CXCR4), mesenchymal–epithelial transition factor (c-MET), matrix metalloproteinases (MMP), and lysyl oxidase (LOX); angiogenesis through vascular endothelial growth factor (VEGF), VEGFR1, and angiopoietin-2 (Ang-2); and stem cell maintenance *via* the regulation of octamer-binding transcription factor 4 (Oct4) [6,10–13]. The function of these HIF downstream target genes are reviewed elsewhere [14,15], and thus these are not the focus of this article.

A large number of clinical evidence suggest that HIF and its downstream targets are considered as key markers of clinical prognosis of