Abstract

Malignant gliomas have retained their dismal prognosis despite an aggressive, multimodal therapeutic approach, warranting the need for novel therapeutic modalities. Highly proliferating tumors frequently outstrip their vascular supply, leading to a tumor microenvironment characterized by low PO$_2$, low glucose levels, and an acidic pH. Regions of low PO$_2$ are indeed common findings in malignant tumors, being associated with increased frequency of tumor invasion and metastasis. The ability to initiate homeostatic responses and adapt to hypoxia is a crucial aspect of solid tumor growth. The hypoxia-inducible transcription factors HIF-1α and HIF-2α act as main regulators of hypoxia-induced gene expression, determining key parameters of the tumor phenotype such as angiogenesis, energy metabolism, pH regulation, and genetic instability, as well as tumor invasion/metastasis. These adaptive responses confer an increased resistance to the hostile tumor microenvironment. Recent insights into cellular and molecular crosstalk in this microenvironment suggest a model in which hypoxia, HIF, and several HIF target genes participate in the coordinated collaboration between tumor, endothelial, inflammatory/hematopoietic, and circulating endothelial precursor cells to enhance and promote tumor growth. Interestingly, however, the HIF pathway is known to encompass tumor growth-promoting as well as inhibiting effects, some of which may be offset by genetic alterations, suggesting a far more complex agrowth. Thus, despite its promise as a novel and potentially selective cancer treatment, therapeutic modulation of the HIF pathway may require an integrated and detailed understanding of the multifaceted nature of HIF action in tumor physiology.
11.1 Introduction

Each year 20,000 new primary central nervous system (CNS) neoplasms are diagnosed in the United States. Importantly, CNS tumors affect the organ that defines the “self,” they are among the most debilitating of human malignancies, often severely compromising quality of life. A multitude of different neoplastic CNS entities are recognized by the CNS tumor classification of the World Health Organization (WHO). Among them, malignant gliomas are the most common and most studied primary malignancies. Malignant gliomas have retained their dismal prognosis despite an aggressive, multimodal therapeutic approach, warranting the need for novel therapeutic modalities.

Tumor growth and progression occurs as a result of cumulative acquisition of genetic alterations affecting oncogenes or tumor suppressor genes selecting for tumor cell clones with enhanced proliferation and survival potential. Tumor growth depends on vascular supply to sustain the metabolic needs of the tumor tissue. Indeed, the acquisition of a functional blood supply seems to be rate-limiting for the tumor’s ability to grow beyond a certain size and metastasize to other sites. However, highly proliferative tumors frequently outstrip their vascular supply, leading to a tumor microenvironment characterized by low oxygen tension, low glucose levels and an acidic pH. Glioblastomas are characterized by a prominent, proliferative vascular component and necrotic areas, making them prototype tumors in the understanding of the role of hypoxia-induced mechanisms in tumor growth and progression. A series of recent cell and molecular biology studies have significantly extended our knowledge on how tumor cells exploit key regulatory mechanisms of oxygen homeostasis to adapt to changes in ambient oxygen concentrations. These studies have identified putative oxygen-sensing mechanisms, showing that reduced oxygen levels and tumor-specific genetic alterations synergistically control important physiological pathways by activating a key transcriptional system, the HIF (hypoxia-inducible factor) system, a potent inducer of gene expression in tumor cells. A mounting body of evidence suggests that hypoxia and HIF play a decisive role in tumor physiology and progression by setting and controlling a tumor-specific microenvironment essential for tumor growth. HIF and hypoxia are the major triggers for new blood vessel growth in malignant tumors, and, as recent evidence suggests, regulate a pro-invasive and -metastatic machinery crucially determining tumor aggressiveness. They induce a shift in energy metabolism from oxidative to glycolytic pathways, thus contributing to the acidic tumor microenvironment. Moreover, hypoxia induces genetic instability in tumor cells and, possibly involving HIF function, selects for apoptosis-resistant and thus malignant cell clones. Given the significance of HIF and hypoxia in tumor physiology, recent insight into the precise mechanisms of oxygen sensing and signaling may offer new promising and potentially selective targets for tumor therapy.

11.2 The Transcription Factor System HIF

Cells respond to changes in the microenvironment such as acidosis, hypoglycemia or changes in oxygen...