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REVIEW ARTICLE

The role of hypoxia-inducible factors in tumor angiogenesis and cell metabolism☆

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Abstract Hypoxia-inducible factor (HIF) is a main heterodimeric transcription factor that regulates the cellular adaptive response to hypoxia by stimulating the transcription of a series of hypoxia-inducible genes. HIF is frequently upregulated in solid tumors, and the overexpression of HIF can promote tumor progression or aggressiveness by blood vessel architecture and altering cellular metabolism. In this review, we focused on the pivotal role of HIF in tumor angiogenesis and energy metabolism. Furthermore, we also emphasized the possibility of HIF pathway as a potential therapeutic target in cancer.

Introduction

Solid tumors are known for a long time to contain poorly vascularized regions, including low pH, severe hypoxia and nutrient starvation.[1] The unlimited proliferation of tumor cell results in increased oxygen consumption, thus, most part of solid tumors develop hypoxia as compared to surrounding normal tissue.[2] Tumor hypoxia is typically correlated with poor prognosis, partly because of refractory to therapy, in particular to radiotherapy that kills tumor cells

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by generating reactive oxygen species (ROS). In laryngeal cancer, hypoxia has been shown to promote cell invasion and metastasis via epithelial—mesenchymal transition (EMT).[3] Hypoxia-inducible factor (HIF) plays an important role in the adaptive cellular response to hypoxia in tumor microenvironment.[4]

Hypoxia-inducible factors (HIFs) are a heterodimer consisting of an oxygen-dependent α-subunit (HIF-α) and an oxygen-independent β-subunit (HIF-β). The HIF-α has three isoforms, HIF-1α, HIF-2α, and HIF-3α.[5] There are two isoforms of HIF-β that also called as the aryl hydrocarbon receptor nuclear translocator (ARNT), namely, HIF-1β and HIF-2β.[6] Among those HIFs, the most important is HIF-1α, responsible for activating transcriptional responses under hypoxia. Similar to HIF-1α, HIF-2α is involved in the regulation of hypoxia. Nevertheless, their ability to transcriptionally regulate specific hypoxia-responsive genes, HIF-2α and HIF-1α have distinct functions and only partially overlap. For example, HIF-2 is the predominant regulator of fatty acid storage, whereas glycolytic genes appear to be primarily regulated by HIF-1.[5] HIF-3α acts as a down-regulator, reducing the anoxia response by a HIF-1α inhibitor mediator.[7] As a consequence of the hypoxia-inducible transcription factors stabilization, the cell constitutively upregulates the hypoxic response pathway resulting in gene expression programs, which are responsible for global shift in glucose uptake, cell proliferation, differentiation, apoptosis, energy metabolism, erythropoiesis, and angiogenesis.[8] These physiological adaptive responses are also commonly observed in human cancer. Thus, Warburg effect (altering glucose metabolism), resistance to apoptosis and angiogenic switch are all hallmarks of cancer. Recently, HIFs have been shown to control cancer stem cells (CSCs) proliferation, differentiation and pluripotency through activating specific signaling pathways such as Oct4, Wnt and Notch.[1,9,10] Furthermore, these features are important during tumor progression. Accordingly, hypoxia-inducible factor (HIF) contributes to tumor progression in a positive feedback loop.[11,12]

HIF expression in cancer

A recent survey found that HIF-1α and HIF-2α were commonly upregulated in a variety of human tumors, including breast, bladder, brain, glial, hepatocellular, colon, ovarian, pancreatic, prostate, and renal tumors.[13] Clinically, high levels of HIF-1α expression positively correlate with tumor progression and poor patient outcome in non-small cell lung cancer,[14] head and neck cancer,[15] colon cancer,[16] gastric cancer,[17] breast cancer,[18,19] prostate cancer,[20] pancreatic cancer,[21] esophageal cancer,[22] osteosarcoma,[23] endometrial carcinoma,[24] ovarian carcinoma,[25] bladder carcinoma,[26] and nasopharyngeal carcinoma,[27] while elevated HIF-2α expression correlate with tumor progression and poor patient outcome in non-small cell lung cancer,[14] bladder cancer,[28,29] breast cancer,[30] colorectal cancer,[31] clear cell renal cell carcinoma (ccRCC),[32] and hepatocellular carcinoma,[33] HIF-3α expression is commonly found in various human tissues and cancer cell lines, and while the dominant-negative HIF-3α inhibits the transcriptional activity of HIF-1α.[34,35] Moreover, HIF-3α was discovered to be down-regulated in renal cell carcinomas.[34] Generally, HIFs activation is a common incident in human cancer and the overexpression of HIFs may play a significant role in tumorigenesis. However, there are a couple of examples to the contrary. A study by Acker et al reported that overexpression of HIF-2α reduced the growth of rat glioma tumors, in part by increasing tumor cell apoptosis, and Knock-down of HIF-2α in human malignant glioblastoma reduce apoptosis.[36] Nevertheless, Raval et al showed that overexpression of HIF-2α promoted tumor growth, while overexpression of HIF-1α inhibited tumor progression.[37]

HIF activation in cancer

Hypoxia, is the most common mechanism of HIF activation in neoplasms. Vaupel, et al estimated that hypoxic and/or anoxic tissues, developing as a consequence of an imbalance between tumor cell oxygen consumption and supply, was present in 50—60% of solid tumors.[38] Hypoxia is defined as having an internal partial pressure of oxygen of less than 10—15 mm Hg in solid tumors.[39] Under hypoxic conditions or in VHL−/− cells, stabilized HIF-1α dimerizes with HIF-1β and interacts with the transcriptional coactivators p300/Creb-binding protein (p300/CBP) before binding to DNA on hypoxia-response elements (HREs), finally activating target gene transcription and mRNA, and protein synthesis.[40,41]

The activation of HIF also can be influenced in tumor with normoxia conditions by genetic alterations in its oxygen-signaling pathway. As mentioned before, VHL (von Hippel—Lindau) plays a central role in the oxygen-sensing pathway promoting HIFα proteosome-mediated degradation.[42] Therefore, inactivation or loss of VHL results in activation of the HIF pathway in normoxia,[43] which in turn results in transactivation of HIF target genes. Germline mutations in the VHL tumor-suppressor gene lead to VHL disease, a familial cancer syndrome that associates with the development of multiple vascular and benign tumors. The main tumor manifestations include central nervous system and retina haemangioblastomas, phaeochromocytomas, clear cell renal cell carcinoma (CCRCC), pancreatic islet tumors, endolymphatic sac tumors, epididymal cystadenomas and pancreatic and renal cystadenomas.[44]

There are also some evidence that HIF activity can be induced by oxygen-independent manner, such as the activation of the mitogen-activated protein kinase (MAPK) and phosphoinositol 3-kinase (PI3K) pathways. It was found that HIF activity was increased via the activation of PI3K/Akt pathway through enhancing positive regulators such as Ras and receptor tyrosine kinases or inactivation of negative regulators include tensin homolog (PTEN) and tuberous sclerosis (TSC) 1 or 2.[45] The PI3K signaling pathway can regulates HIF activity in mammalian target of rapamycin (mTOR)-independent or mTOR-dependent mechanisms. All together, the activation of HIF is a complex process and may involve different tumor-suppressor genes and relevant oncogenes during tumor progression.

HIF and angiogenesis

Angiogenesis is critical for the process of solid tumor formation and progression since the supply of oxygen and