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Review Article

Hypoxia-inducible factor-1: A possible link between inhalational anesthetics and tumor progression?

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ABSTRACT

Cancer remains one of the major causes of death worldwide, and the global burden of the disease is rising continuously. Clinical retrospective data suggested that inhalational anesthetics might affect the prognosis of cancer patients, but the underlying molecular mechanism remained unknown. Hypoxia-inducible factor-1 (HIF-1) is a dimeric transcription factor and mediates various cellular responses to hypoxia, including metabolism, cell death and survival, angiogenesis, oxygen delivery, immune evasion, and genomic adaptation. HIF-1 system has been shown to be the driving force of solid tumor progression and substantially contributes to the malignancy of cancer. Inhalational anesthetics such as isoflurane have been demonstrated to confer cytoprotection in a HIF-1-dependent manner in various vital organs. In addition, a recent study has demonstrated the pivotal involvement of HIF-1 in the impact of inhalational anesthetics on cancer cells. This review provides critical insights into the new understanding of cancer sensing of inhalational anesthetics and examines the recent understanding of the underlying molecular mechanisms. However, this area of research is just beginning and warrants further studies preclinically and clinically prior to making any conclusions that inhalational anesthetics may affect cancer outcomes. In addition, it is important to note that there is not enough evidence to support any change in the current clinical practice.

1. Introduction

Cancer is the third leading cause of death worldwide, and the global burden of the disease continues to increase due to population aging and growth in economically developed countries, as well as adoption of cancer-associated lifestyles in economically developing countries.[1] According to GLOBOCAN 2008, approximately 12.7 million cancer cases 7.6 million cancer deaths occurred globally. Solid tumors account for most of the cancer cases and cancer mortality.[2] Cancer morbidity and mortality trends are predicted to keep rising in the next few decades, and it is predicted that by 2030 there will be about 26.4 million incidences and 17 million deaths per year.[3] Surgery and/or chemo/radiotherapy are the main treatment options for cancer patients; however, complete cure of cancer is difficult to achieve and cancer recurs frequently. Inhalational anesthetics have been indicated or demonstrated to play a critical role in cancer malignancy and its progression. However, the detailed mechanisms of how anesthetics affect tumor progression are not fully understood. Here, we will present and review recent evidence from experimental and clinical studies pointing to a fundamental role of the effects of anesthetics on cancer.

Accumulating clinical evidence strongly supports the assumption that the choice of anesthesia and application technique can influence the long-term prognosis of cancer patients. Exadaktylos et al[4] observed a substantial reduction in tumor recurrence and metastases when breast cancer surgery was performed with paravertebral anesthesia and analgesia. Christopherson et al[5] investigated long-term survival after resection of colon cancer with different anesthetic techniques. They found that epidural anesthesia was associated with improved survival among patients initially, but with poorer survival in the later stage. The study by Schlagenhauff et al[6] demonstrated an increased risk of mortality for

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patients with melanoma anesthetized with general anesthesia for the primary excision of the tumor.

There have been limited studies to explain the molecular basis of how cancer cells sense inhalational anesthetic gas. However, an understanding of how cancer cells sense the oxygen level during hypoxia and the underlying molecular mechanisms can provide clues to the action of inhalational anesthetics on cancer cells. This review provides a perspective of the biology of the hypoxia-inducible factor (HIF) system and its activation by anesthetics, which may serve a vital link to cancer malignancy during the perioperative period.

2. Sensing of cancer cells to hypoxia

Approximately 90% of solid tumor cells live in a microenvironment with relatively low oxygen supply.[7] Recent findings have shown that tumor cells overcome hypoxia by triggering a series of cellular events in response to this hypoxic stress. Hypoxia is defined as an oxygen tension (pO_2) below the normal range of cellular oxygen demand.[8] There is no universal level of pO_2 that is considered as hypoxia, as pO_2 varies across different organs in the body. For example, the normal pO_2 level in the lung is around 150 mmHg, whereas in the retina, a pO_2 around 5 mmHg could still be considered normal.[9] However, hypoxic response would be triggered in most cancer tissues when venous pO_2 drops below 40 mmHg and the hypoxic stress increases gradually as oxygen tension goes down to about 1.6–0.8 mmHg, close to anoxia.[10,11] The major cellular response to hypoxia is the expression of a transcription factor–protein complex, known as HIF-1. HIF-1 transcriptionally activates a range of genes involved in processes such as angiogenesis, erythropoiesis, energy metabolism, cell proliferation, apoptosis, survival, cell migration, and tissue remodeling.[12]

3. HIF system

Currently, three HIF-α isoforms have been discovered: HIF-1α, HIF-2α, and HIF-3α. HIF-1α and HIF-2α share greater than 70% homology in their DNA sequences. Both HIF-1α and HIF-2α function similarly through dimerization with HIF-1β, although studies have shown that each has its own transcriptional targets to regulate; by contrast, HIF-3α produces multiple splice variants that lack domains such as the transactivation domain.[13–15]

HIF-1 stabilization is the primary response in hypoxia, and it has profound effects on tumor progression. HIF-1 is a heterodimeric protein composed of a constitutional HIF-1β subunit and an oxygen-sensitive HIF-1α subunit. HIF-1 is a basic helix–loop–helix protein, part of the PER-ARNT-SIM (PAS) DNA-binding protein family.[16] It orchestrates a series of downstream effects such as promoting angiogenesis.[17] Abundant and intact intracellular HIF-1α can translocate into the nucleus and dimerize with HIF-1β. The oxygen-insensitive subunit HIF-1β is an aryl hydrocarbon receptor nuclear translocator (ARNT) and is essential for the dimerization and subsequent binding of HIF-1 to DNAs, leading to transcription of downstream genes as a consequence.[18]

HIF-1α is regulated at both transcriptional and translational levels. Two major factors involved in this regulation are factor inhibiting HIF and prolyl hydroxylase domain proteins (PHDs).[19] Both proteins can function properly only in the presence of oxygen. Factor inhibiting HIF is a 2-oxoglutarate-dependent dioxygenase that catalyzes hydroxylation of asparagine 803 in the C-terminal transactivation domain of HIF-1α. The HIF complex, therefore, fails to assemble due to the loss of interaction between HIF-1α and the transcriptional coactivators CREB-binding protein.[20] PHD-2 is the key enzyme regulating HIF-1α degradation in normoxia.[21] PHDs require oxygen and 2-oxoglutarate as cosubstrates, as well as iron and ascorbic acid as cofactors to catalyze hydroxylation of the oxygen-dependent degradation domain of HIF-1α.[22] HIF-1α hydroxylation and/or HIF-1α acetylation by arrest defective-1 protein has been shown to increase the binding affinity of HIF-1α for the von Hippel–Lindau protein. Von Hippel–Lindau protein is a component of the E3 ubiquitin ligase complex that induces ubiquitin-mediated proteosomal degradation of HIF-1α.[23,24]

Because oxygen is critical for the function of both factor inhibiting HIF and PHD, HIF-1α is not hydroxylated or degraded in hypoxia. Studies have shown that other processes such as phosphorylation and nitrosylation can affect the stability and transcriptional activity of HIF-1α, which indicates other undiscovered regulatory pathways.[13,25,26] In addition, the mitochondrial electron transport chain has been shown to regulate HIF-1 stabilization.[27]

4. Downstream effects of HIF-1 in tumor progression

Many of the hundreds of genes that are regulated by HIF code for proteins are crucial for tumor progression. They influence tumor progression under hypoxic conditions via promoting or modifying several cellular processes, including metabolism, cell death and survival, angiogenesis, immune evasion, and genetic instability.[28]

4.1. Metabolism

Depletion of oxygen causes cancer cells to switch to anaerobic metabolism, which greatly increases their genetic instability.[29] HIF-1 regulates expression of a series of metabolic proteins, including glycolytic enzymes, glucose transporters (GLUT1 and GLUT3), hexokinase 1 and 2, phosphoglycerate kinase 1, and lactic dehydrogenase A.[30] The function of most of them is to overcome hypoxic stress by improving glucose uptake. The exception is phosphoinositide-dependent kinase-1. phosphoinositide-dependent kinase-1 inhibits the conversion of pyruvate to acetyl coenzyme A, so that lactate is produced by lactic dehydrogenases.[31] It also blocks excessive production of mitochondrial reactive oxygen species and promotes regeneration of NAD^+ for anaerobic glycolysis.[14,26]

Furthermore, hypoxia also attenuates biosynthesis of amino acids, proteins, lipids, and nucleotides by inhibiting mammalian target of rapamycin (mTOR).[32] The conserved serine/threonine protein kinase mTOR phosphorylates a number of substrates related to protein translation, including eukaryotic initiation factor 4E-binding protein-1 and ribosomal p70 S6 kinase.[33,34] The mTOR pathway has been shown to be suppressed by hypoxia. Hypoxia increases the level of AMP and induces AMP-activated protein kinases. AMP-activated protein kinases phosphorylate several downstream substrates including tuberous sclerosis complex 2 (TSC2) and subsequently activates the TSC2–TSC1 complex, a negative regulator of mTOR.[35] HIF-1 directly induces gene expression of REDD1/RTP801, which also activates the formation of the TSC complex.[36,37] HIF-1 has been shown to optimize the efficiency of respiration through cytochrome oxidase in mitochondria.[38] However, hypoxia-mediated metabolic adaptations remain partially understood and need further investigation.

4.2. Cell death and survival

Depletion of oxygen can enhance the production of the proapoptotic protein Bcl-2/adenovirus E1B 19 kDa interacting protein 3 (BNip3) more than 100-fold via action of HIF-1.[39] BNip3 accumulation is shown to be enhanced by acidosis caused by opening of the mitochondrial permeability transition pore during hypoxia.[18,19,40]

Paradoxically, hypoxia also contributes to tumor immortalization through HIF-1-induced mitogen-activated protein kinase