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Review

# Cell physiology regulation by hypoxia inducible factor-1: Targeting oxygen-related nanomachineries of hypoxic cells

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ABSTRACT

Any dysfunctionality in maintaining the oxygen homeostasis by mammalian cells may elicit hypoxia/anoxia, which results in inescapable oxidative stress and possible subsequent detrimental impacts on certain cells/tissues with high demands to oxygen molecules. The ischemic damage in turn can trigger initiation of a number of diseases including organs ischemia, metabolic disorders, inflammatory diseases, different types of malignancies, and alteration in wound healing process. Thus, full comprehension of molecular mechanism(s) and cellular physiology of the oxygen homeostasis is the cornerstone of the mammalian cells metabolism, energetic pathways and health and disease conditions. An imbalance in oxygen content within the cellular microenvironment activates a cascade of molecular events that are often compensated, otherwise pathologic condition occurs through a complexed network of biomolecules. Hypoxia inducible factor-1 (HIF-1) plays a key transcriptional role in the adaptation of cell physiology in relation with the oxygen content within a cell. In this current study, we provide a comprehensive review on the molecular mechanisms of oxygen sensing and homeostasis and the impacts of HIF-1 in hypoxic/anoxic conditions. Moreover, different molecular and biochemical responses of the cells to the surrounding environment are discussed in details. Finally, modern technological approaches for targeting the hypoxia related proteins are articulated.



**Contents**



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## 1. Introduction

In human, the maintenance of oxygen homeostasis within the biological microenvironment is accomplished through several key molecular mechanisms that are necessary for the survival of living cells in the oxygen deficiency conditions (the so-called hypoxia/anoxia). In fact, hypoxia is deemed to play central roles in the pathobiology and induction of several deadly diseases such as ischemic stroke, cancer, and chronic lung disease [1,2]. Within the cells, the mitochondrial reduction of oxygen to water is an essential mechanism supplying the metabolic needs of the cell, while its incomplete reduction can give a rise to reactive oxygen species (ROS) that are oxygen ions or oxygen-containing radicals and can induce profound cytotoxic impacts [3]. Cells use sensitive cellular mechanisms to delicately maintain an equilibrium between the production of ROS and the antioxidant defences, which can be however compromised and disturbed resulting in marked ROS-induced cellular dysfunction and cell death.

To avoid the emerging detrimental impacts of hypoxia, the mammalian cells recruit arrays of specific molecular compensatory mechanisms to adapt to the low oxygen level and to restore the synthesis of ATP. In line with the adaptive mechanisms, the first holistic response is an increase in the red blood cells content–a phenomenon so-called erythropoiesis [1,4]. During the hypoxic condition, the enzymatic activity of the oxidative phosphorylation pathway is lower than the normal condition, while the enzymatic activity of the glycolytic pathway is augmented and the bio-energetic path is altered. As a result, some specific cellular molecular changes may affect the activities of a wide spectra of enzyme, the normal function of mitochondria, the architecture of cytoskeleton, the pattern and functional expression of membrane transport machineries, and responsiveness and defence mechanisms of cell [5]. These measures may be evolved in order to overcome the shortage of oxygen in the cells and adapt with the surrounding environment. Surprisingly, cancerous cells within solid tumours evolve and recruit complex adaptive mechanisms in response to the hypoxia, including: inadvertent alterations in molecular pathways, biological changes in cell functions within tumour microenvironment (TME) such as dysregulation of pH [6], irregular angiogenesis and tumour growth [7], and apoptosis inhibition, invasiveness and metastasis [8]. Further, depending on cells/tissue types, the molecular cellular setting during hypoxic situation may lead to different responses and physiologic behaviours. For instance, the bone marrow cells can well tolerate the hypoxic condition [9], and hence prevail the detrimental condition.

Different cells/tissues at different stages are able to sense even trivial changes of oxygen content within their surrounding microenvironment, at which point they may opt diverse responses depending on their physiological needs. Nevertheless, to settle a compensatory adaptation and maintain metabolic homeostasis, the hypoxic cells need to express certain molecular machineries (e.g., sensing receptors, enzymes and transporters) for fine detection of the intracellular and surroundings oxygen level in various chemoreceptive tissues. For example, during the embryo development, the reduced mitochondrial oxidative phosphorylation, due to low oxygen level, can give an exponential rise to the cellular AMP/ATP ratio that can in return activate some key enzymes involved in regulation of energetic path balancing the cellular ATP supply and demand. As a result, AMP is converted to adenosine by 5′-nucleotidase, which can activate the adenosine A2A receptors necessary for sensing of oxygen by both carotid bodies and the brain [10].

Cellular adaptation to the oxygen content occurs through marked activities of various proteins, whose functions during hypoxia/anoxia is related to the activity of one of the most important transcription factors, hypoxia inducible factor-1 (HIF-1). As a key regulator, it plays a vital role in the functional expression of a number of genes involved in adaptation and survival of cells, tissues and organs under the normoxic (~21% $O_2$) or hypoxic (~1% $O_2$) condition [11]. However, there is striking evidence that the HIF-1 play divers roles in different diseases. In the case of solid tumours, its functional expression is notably high and there exists an association between its increase and metastasis that is the major causes of cancer death worldwide [8,12]. Accordingly, most of malignant and aggressive solid tumours display some degrees of resistance to the conventional chemo/radiotherapy and form a permissive hypoxic TME even in the excess of oxygen [13,14]. Inhibition of HIF-1 can stop the growth and invasiveness of hypoxic solid tumours, and there is an increasing body of evidence demonstrating that specific inhibition of HIF-1 in hypoxia could provide a promising cancer treatment modality in combination with conventional chemo-/radio-therapies. Some studies have highlighted that a wide range of natural compound and synthetic/semi-synthetic chemotherapeutic agents can induce apoptosis through inhibition of HIF-1 [15,16]. In the current review, we will provide insights on the hypoxia and discuss remarkable roles of HIF-1 transcription factor in the hypoxia-related diseases such as solid tumours. We will also provide significant overviews on how to target the oxygen-related biomachineries of the hypoxic cells/tissue.