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Guest editorial: hypoxia biology in health and disease

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Abbreviations

FIH	Factor-inhibiting HIF1α
HIF	Hypoxia inducible factor
PHD	Prolyl hydroxylase domain-containing protein
VHL	von Hipple-Lindau

In adult tissues, normal partial oxygen pressure is around 2–9 % (14–65 mmHg) [1], substantially lower than inhaled ambient oxygen tensions of 21 % (160 mmHg). Such low oxygen conditions do not compromise the activity of the mitochondrial respiratory chain, which retains its great potential to produce cellular energy ATP, and are, therefore, considered physiologically normoxic in this context. However, certain types of cells, such as kidney medulla, bone marrow, and pericentral hepatocytes, are exposed to even lower oxygen tensions (10–25 mmHg, physiological hypoxia) in physiological conditions, suggesting that appropriate oxygen concentrations varies by cell and tissue type and environment. Disease conditions such as cancer, ischemic heart disease, and obstructive pulmonary disease may, in contrast, impair the balance between oxygen supply and demand, exposing the affected cells and tissues to severely low oxygen conditions (pathological hypoxia) [2]. As such, cells in the body experience a wide range of oxygen tensions in physiological and pathological conditions and are, therefore, equipped to sense and respond to changes in oxygen concentration.

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Hypoxia-inducible factor (HIF) is a key transcription factor responsible for hypoxic responses, and consists of two distinct subunits: an oxygen-sensitive α subunit, and a constitutively expressed β subunit. HIF-1 is first described by Semenza and colleagues [3] as an inducer of erythropoietin gene expression in response to hypoxia; this discovery accelerated and expanded research into hypoxia biology dramatically. It has been reported that there are three HIFα isoforms in mammalian cells; of these, HIF-1α and HIF-2α have been extensively studied [4]. HIFs have been reported to play central roles in the adaptive response to hypoxic stress through the activation of genes involved in angiogenesis, erythropoiesis, energy metabolism, cell proliferation, and differentiation [5]. Much insight into the roles of HIFs have been gained from cancer research, and these have recently led to a better understanding of unexpected HIF functions in other pathological (e.g., ischemia heart disease, inflammation, diabetes, fatty liver) and physiological conditions, revealing a greater complexity of HIF-mediated regulations in isoform-, cell type- and context-specific manner than had previously been thought. In addition, central molecular mechanisms underlying the oxygen-mediated instability of HIFα have revealed a novel class of 2-oxoglutarate-dependent iron (II)-dioxygenases (e.g., PHD and FIH) as critical regulators of HIFα in the oxygen-sensing system [6]. In conjunction with the discovery of the molecular basis for VHL-dependent HIFα degradation [7], HIF transcriptional activity has been shown to be regulated largely at its protein levels by cellular oxygen concentrations. However, the biochemical properties of these enzyme reactions also suggest that the oxygen-dependent hydroxylation modification transmits clues not only of environmental oxygen concentrations, but also cellular metabolic and redox status of the nucleus, suggesting an intimate crosstalk between oxygen, cellular

metabolism, and oxidative stress [8]. Furthermore, HIF transcriptional activity also has been found to be regulated at the transcriptional level and by microRNAs [9], irrespective of oxygen availability, in certain disease conditions, such as inflammation and cancer, attracting many researchers to the growing world of hypoxia biology. Although key players have appeared on the center of stage in hypoxia biology, we still lack the information needed to understand the complete picture of the intimate and complex interactions among these factors in physiological and pathological conditions. Further investigations are needed to translate evidence from basic research to clinical medicine and public health.

In this PIH review series, four topics relating to HIF functions in physiological and pathological conditions are introduced. The first review gives an overview of the roles of HIFs in cellular energy metabolism that enable adaptation to hypoxia, and describes the complexities of in vivo roles on energy metabolism in normal and disease conditions. While it is widely accepted that HIF-1 activates a metabolic shift from mitochondrial oxidative phosphorylation to anaerobic glycolysis in hypoxic cells, the in vivo roles of HIF-1 and HIF-2 also show great effects on gluconeogenesis and lipid metabolism, respectively, both of which are barely detectable in cell culture systems. Simon and colleagues discuss the importance of hypoxia and HIF activation on cancer progression from the perspective of metabolism and the great promise of cancer therapy, focusing on hypoxia-associated cancer metabolism. This review also sheds light on metabolic interactions between cancer and stromal cells in tumor progression. The third review, presented by Johnson et al., argues that tumor-associated endothelia responds to hypoxia, promoting inflammation, angiogenesis, coagulation, and vascular permeability in the tumor, thus serving as a critical cellular compartment responsible for tumor growth and metastasis. HIF activation plays critical roles in endothelial cell-mediated tumor progression and metastasis, making endothelial HIF an attractive target for novel adjunctive cancer therapies. The final review, from Takubo and Suda, describes the significance of the hypoxic niche for the maintenance of hematopoietic stem cells, where constitutive HIF activation regulates proliferation, differentiation, senescence, and energy metabolism of hematopoietic stem, but not progenitor, cells. Furthermore, the authors mention that the HIF signaling system is involved in the pathogenesis of leukemia/lymphoma stem cells, although HIF activation appears to show opposing influences on tumor progression.

In conclusion, hypoxia is a fundamental and critical component of multiple microenvironments that have great influences on cell and tissue functions in physiological and pathological conditions, and for this reason further investigations of hypoxia biology will be needed not only to achieve a better understanding of the evolution of aerobic organisms and the importance of oxygen homeostasis in the regulation of normal cellular functions, but also to enable new developments in diagnostics and therapy focusing on hypoxia in a range of diseases.

Conflict of interest None.

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