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PERSPECTIVE

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Molecular Regulation and Therapeutic Potential of Hypoxia-Inducible Factors in Ischemic Diseases

Eleanor Valdes*
Department of Molecular Biology, Bilkent University, Ankara, Turkey

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About the Study

Hypoxia-Inducible Factors (HIFs) play an important role in cellular adaptation to low oxygen availability, particularly in ischemic diseases where tissue perfusion and oxygen supply are weakened. Through controlling the activity of many genes involved in angiogenesis, erythropoiesis, metabolism, and cell survival, these transcription factors connect an extensive range of responses to hypoxia. HIFs are heterodimeric transcription factors composed of an oxygen-sensitive α-subunit (HIF-α) and a constitutively expressed β-subunit (HIF-β, also known as ARNT). The α-subunits include HIF-1α, HIF-2α, and HIF-3α, each of which displays distinct but overlapping functions. Under normoxic conditions, HIF-α proteins are rapidly degraded through the ubiquitin-proteasome system. This process is mediated by the activity of Prolyl Hydroxylase Domain (PHD) enzymes, which hydroxylate specific proline residues on the HIF-α subunit. The hydroxylation enables recognition by the Von Hippel-Lindau tumor suppressor protein (pVHL), an E3 ubiquitin ligase, which targets HIF-α for proteasomal degradation. The activity of PHD enzymes is oxygen-dependent, as molecular oxygen acts as a substrate for hydroxylation. In hypoxic conditions, PHD activity is inhibited due to the lack of available oxygen, leading to the stabilization and accumulation of HIF-α subunits.

Once stabilized, HIF-α translocates to the nucleus, where it combines with HIF-β. This HIF complex binds to Hypoxia Response Elements (HREs) within the promoter regions of target genes, initiating their transcription. The transcriptional activity of HIFs is further regulated through post-translational modifications, including acetylation, phosphorylation, and sumoylation. These modifications fine-tune HIF stability, nuclear localization, DNA binding, and interaction with co-activators or repressors. For example, phosphorylation by kinases such as Mitogen-Activated Protein Kinase (MAPK) and mammalian Target of Rapamycin (mTOR) can modulate HIF activity under specific cellular conditions. Additionally, the transcriptional co-activator p300/CBP plays an important role in enhancing HIF-mediated gene expression by facilitating the utilization of transcriptional machinery. HIF-1α is primarily involved in the acute response to hypoxia, promoting glycolytic metabolism, angiogenesis, and cell survival. It causes important glycolysis-related enzymes to be produced, such as Lactate De Hydrogenase A (LDHA) and phosphofructokinase, allowing cells to maintain ATP production under anaerobic conditions. HIF-1α also regulates the expression of Vascular Endothelial Growth Factor (VEGF), a potent angiogenic factor that stimulates new blood vessel formation, thereby improving oxygen delivery to ischemic tissues. HIF-2α is associated with chronic hypoxia and plays a role in erythropoiesis and metabolic adaptation. It activates the expression of Erythropoietin (EPO), which promotes red blood cell production to enhance oxygen transport capacity. The differential regulation of HIF-1α and HIF-2α enables cells to adapt dynamically to varying oxygen levels.

The regulation of HIF activity is influenced by factors beyond oxygen availability. Metabolic intermediates, Reactive Oxygen Species (ROS), and cellular signaling pathways modulate HIF stability and function.

The PI3K/Akt/mTOR and MAPK signaling pathways also regulate HIF activity through multiple mechanisms. Activation of the PI3K/Akt pathway enhances HIF-α protein synthesis by promoting the activity of mTOR, a key regulator of translation. mTOR stimulates the translation of HIF-α mRNA, ensuring sufficient protein levels for hypoxic

Contact: Eleanor Valdes, Email: valdes.ele99@gmail.com

adaptation. Additionally, MAPK signaling provides the post-translational modification of HIF-α, enhancing its transcriptional activity. These signaling pathways are activated in response to growth factors, cytokines, and other extracellular stimuli, highlighting the integration of hypoxic signaling with deep cellular responses. In ischemic diseases, dysregulation of HIF signaling can have major consequences. While HIF activation is need for tissue adaptation to hypoxia, excessive or prolonged HIF activity may exacerbate pathological processes. For example, sustained HIF-mediated VEGF expression can allow abnormal angiogenesis, leading to leaky and dysfunctional blood vessels. Similarly, prolonged HIF activation can drive metabolic reprogramming that supports cell survival under hypoxic conditions but may also provide pathological tissue remodeling. The balance between adaptive and maladaptive HIF responses is finely regulated and context-dependent.