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Hydroxylation-independent HIF-1α stabilization through PKA: A new paradigm for hypoxia signaling

Eóin N. McNamee,1,2 Christine Vohwinkel,1,3 Holger K. Eltzschig1,2,*

In this issue of Science Signaling, Bullen et al. demonstrate that protein kinase A (PKA) phosphorylates and stimulates the transcriptional activity of hypoxia-inducible transcription factor–1α (HIF-1α). This finding may have implications in diseases processes that occur at the interface of hypoxia and inflammation, where HIF-1α stabilization can function to dampen hypoxia-driven inflammation.

Hypoxia-inducible transcription factors (HIFs) are an ancient family of transcription factors that are critical for cellular adaptation to different oxygen concentrations. Because metazoan diversification occurred during a time when atmospheric oxygen concentrations fluctuated between 15 and 30%, it is likely that atmospheric oxygen concentrations may have provided a selection force for the development of cellular oxygen-sensing pathways (1). The transcription factor HIF-1α is a central component of oxygen sensing, which was identified by Semenza and colleagues as a protein that binds to the EPO promoter and can increase the production of its gene product, erythropoietin during hypoxic conditions (2). Besides EPO, HIF-1α functions as the transcriptional regulator of numerous genes that are critically important in physiology and medicine (3). The mechanism by which HIF-1 is functionally inactive during normoxic conditions involves a set of oxygen-sensing prolyl hydroxylases (PHDs) that hydroxylate conserved prolyl residues within the α subunit of HIF-1, thereby targeting HIF-1α for proteasomal degradation. As such, the PHD-HIF pathway is responsible for the inactivation of HIF-1α in the presence of oxygen. However, because PHDs require oxygen as a cofactor for hydroxylation, the PHD-HIF pathway becomes inactivated during conditions of hypoxia or inflammation (4), leading to the stabilization of HIF-1α. HIF-1α subsequencestly forms a transcriptionally active heterodimer with the HIF-1β subunit, translocates to the nucleus, and binds to promoter regions of hypoxia-regulated genes, typically a “hypoxia response element” within these promoters (5). In this issue of Science Signaling, Bullen et al. now add an alternative pathway of HIF-1α activation that involves protein kinase A (PKA)-dependent phosphorylation as a means to stimulate the transcriptional activity of HIF-1α (6).

Both HIF-1 and PKA are implicated in the pathogenesis of cancer and heart disease, and the authors found that these proteins interacted in neonatal cardiomyocytes. Subsequently, the authors showed that activators of PKA (such as isoproterenol) increased HIF-1α protein abundance under normoxic conditions and that PKA directly stimulated HIF-1α transcriptional activity by inhibiting its proteasomal degradation independently of prolyl hydroxylation. To determine whether HIF-1α was a direct phosphorylation target of PKA, the team of Semenza performed additional in vitro kinase assays using glutathione S-transferase fusion proteins. These studies determined that PKA directly phosphorylated Thr53 and Ser582 within the HIF-1α subunit, and these phosphorylation events were required for PKA to increase HIF-1α transcriptional activity. In addition, the authors showed that PKA-elicited HIF-1α stabilization was involved in enhancing the expression of genes encoding components in purinergic signaling pathways (7), thereby providing evidence for a functional role for PKA in promoting the expression of endogenous HIF-1α target genes.

Besides regulating the hypoxic induction of EPO, HIF-1α also transcriptionally controls genes encoding glycolytic enzymes and vascular growth factors. Furthermore, many studies have implicated a direct link between hypoxia signaling and inflammatory diseases (4). On the one hand, inflammatory processes are frequently characterized by profound tissue hypoxia, referred to as “inflammatory hypoxia.” Inflammatory hypoxia is caused by multiple factors, including increased demand for oxygen and other metabolites by inflamed tissues, while simultaneously oxygen supply is frequently decreased because of vascular occlusion or other microcirculatory alterations. On the other hand, hypoxia can cause inflammatory changes in tissues. The inflammatory changes that accompany ischemic conditions during organ transplantation are dampened by HIF-1α—for example, through the stimulation of anti-inflammatory purinergic signaling events (7). As such, the finding that PKA is a critical regulator for HIF-1α may have implications for disease processes that involve hypoxia and inflammation (Fig. 1).

Several studies have identified a protective role of HIF-1α in acute lung injury (ALI), a leading cause of morbidity and mortality of critically ill patients in Western countries. Stabilization of HIF-1α during ALI provides lung protection through the stimulation of anti-inflammatory purinergic signaling pathways (8) or through the optimization of alveolar epithelial metabolism (9). These findings are somewhat surprising, because it is not entirely intuitive that HIF-1α is stabilized in a highly oxygenated environment such as the lungs. However, studies in HIF-reporter mice provided strong evidence that despite high oxygen availability, there are substantial increases in HIF reporter activity during inflammatory lung diseases (9). Several mechanisms have been suggested to promote HIF-1α stabilization during acute lung inflammation, including the inhibition of succinate dehydrogenase and the subsequent accumulation of succinate, a PHD inhibitor, thereby accounting for HIF-1α stabilization despite the abundance of oxygen. However, the present study provides an important alternative mechanism for HIF-1α stabilization during ALI.

Similarly to HIF activation, systemic or inhaled activators of PKA are protective in ALI (10). Activation of the adenosine A2B receptor (Adora2b) provides potent lung protection by increasing cyclic adenosine monophosphate (cAMP) concentrations, which stimulate PKA. Thus, the current study suggests that PKA activators and purinergic signaling events could function in a feed-forward signaling loop with HIF-1α at its center. Increased adenosine

*Corresponding author. Email: holger.eltzschig@ucdenver.edu

1Organ Protection Program, Department of Anesthesiology, University of Colorado School of Medicine, Aurora, CO, USA. 2Mucosal Inflammation Program, Department of Medicine, University of Colorado School of Medicine, Aurora, CO, USA. 3Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA.
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Inflammation in hypoxic conditions

- Carotid body
- High altitude sickness
- Organ transplantation
- Ischemia driven inflammation

Inflammation in inflammatory conditions

- Cancer
- Acute lung injury
- Alveolus
- Colitis
- Infections with pathogens

Fig. 1. Potential role for PKA-dependent HIF-1α stabilization at the interface of hypoxia and inflammation. HIF stabilization during hypoxic or ischemic tissue conditions can dampen hypoxia-driven inflammation during organ transplantation, high-altitude illness, and ischemia-driven inflammation. On the other hand, inflammatory conditions are associated with HIF-1α stabilization and HIF-elicited alterations in gene expression, including colitis, ALI, or infections with pathogens. During cancer, hypoxia-driven inflammation and inflammatory hypoxia can occur simultaneously. PKA-dependent HIF-1α stabilization may have an impact in many of these disease processes and could be a therapeutic target to drive HIF1-dependent tissue protection.

REFERENCES AND NOTES


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