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REVIEW ARTICLE

# Hypoxia-Inducible Factor 1α and Its Role in Lung Injury: Adaptive or Maladaptive

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*Abstract*— Hypoxia-inducible factors (HIFs) are transcription factors critical for the adaptive response to hypoxia. There is also an essential link between hypoxia and inflammation, and HIFs have been implicated in the dysregulated immune response to various insults. Despite the prevalence of hypoxia in tissue trauma, especially involving the lungs, there remains a dearth of studies investigating the role of HIFs in clinically relevant injury models. Here, we summarize the effects of HIF-1α on the vasculature, metabolism, inflammation, and apoptosis in the lungs and review the role of HIFs in direct lung injuries, including lung contusion, acid aspiration, pneumonia, and COVID-19. We present data that implicates HIF-1α in the context of arguments both in favor and against its role as adaptive or injurious in the propagation of the acute inflammatory response in lung injuries. Finally, we discuss the potential for pharmacological modulation of HIFs as a new class of therapeutics in the modern intensive care unit.

**KEY WORDS:** HIF-1α; lung contusion; hypoxia; inflammation; apoptosis; alveolar epithelial cells.

## HYPOXIA-INDUCIBLE FACTORS

Hypoxia-inducible factors (HIFs) are a family of nuclear transcription factors that serve as the master regulator of the adaptive response to hypoxia. These transcription factors, including HIF-1, HIF-2, and HIF-3, control the transcription of numerous genes involved in metabolism, angiogenesis, erythropoiesis, and other adaptations to hypoxia. Hypoxia-inducible factor 1 (HIF-1) is composed of HIF-1 alpha and HIF-1 beta subunits. The basis of oxygen sensing for all three HIFs is the hydroxylation of proline residues in the oxygen-dependent degradation (ODD) domain by dioxygenase prolyl hydroxylase (PHD) [1–3] (Fig. 1). PHDs require an iron cofactor for their catalysis and, therefore, also function as sensors for intracellular iron [4]. Additionally, hydroxylation of the proline residues serves as an interaction scaffold for recognition of the Von Hippel–Lindau (VHL)-containing E3-ligase complex and the following degradation by the proteasome, but hydroxylation of the asparagine residue leads to the inhibition of Histone acetyltransferase p300 and cyclic adenosine monophosphate response element binding protein (p300/CBP) recruitment [5, 6].

In the setting of hypoxia, HIFs are stabilized and translocated to the nucleus, where they heterodimerize with the aryl hydrocarbon nuclear translocator (ARNT), also known as HIF-1β [7]. This heterodimer complex binds to the core DNA sequence 5′-TACGTG-3′ within the hypoxia response element (HRE) of target promoters

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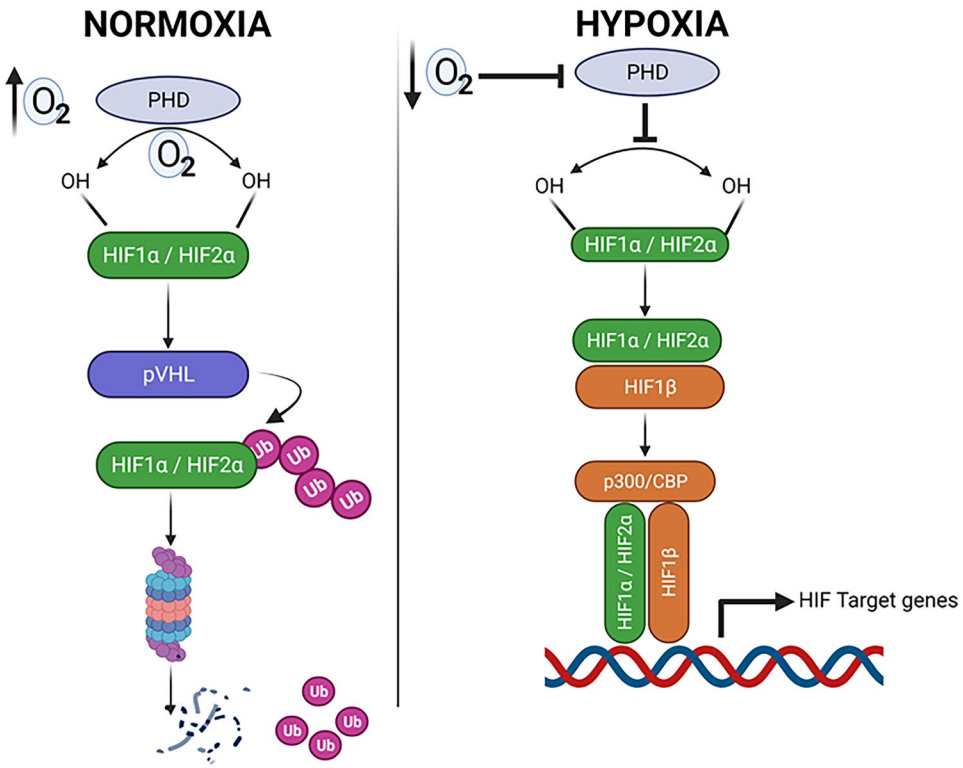


**Fig. 1** Hypoxia-inducible factors (HIFs) signaling pathway in normoxic and hypoxic conditions: under normoxia conditions, HIF1/2 are hydroxylated by prolyl hydroxylase domain (PHD)-containing enzymes. Hydroxylated HIFs are degraded in the proteasomes by von Hippel-Lindau tumor suppressor protein (VHL) via polyubiquitination. On the other hand, during hypoxic conditions, PHDs and FIH are unable to hydroxylate HIF-α subunits, which are translocated into the nucleus, resulting in dimerization of HIF-1α and HIF1β, recruitment of p300 and CBP, and ultimately, binding to HREs at target genes to cause activation. This complex thereby activates specific genes, which will further trigger pathological activities.

in conjunction with the p300/CBP complex and other co-activators [8, 9]. HIF-1α is the most prominent isoform implicated in the pathogenesis of inflammatory lung injury [10]. It binds to the core DNA sequence within the HRE of target promoters and causes the activation of over 200 genes involved in various pathways, including inflammation and angiogenesis [11].

## ROLE OF HIF IN SPECIFIC CELLULAR PROCESSES

### Vascular Growth and Remodeling

HIFs upregulate genes involved in oxygen delivery. This effect manifests in the rapid angiogenesis and vascularization promoted in hypoxic tissues. The arterial vasculature is comprised of three layers. The tunica intima is the innermost layer and is composed of endothelial cells. Hypoxia stimulates hypertrophy and sub-endothelial edema in the tunica intima [12, 13]. Hypoxic stress has also been associated with increased endothelial cell barrier permeability, possibly due to alterations of actin fibers and increased secretions of various vasoconstrictive and pro-mitogenic factors. Vascular endothelium growth factor (VEGF), a prototypical pro-mitogenic factor, is a potent angiogenic agent excreted in response to hypoxia by endothelial and non-endothelial cells including alveolar epithelial cells (AEC) and alveolar macrophages (AM) [14–16]. HIF-1α in endothelial cells regulates the production of stromal-derived factor (SDF)-1, which recruits stem cells to areas of hypoxia and vascularization [17]. Recent evidence also suggests a role for HIFs in

releasing the factors thrombospondin-1 and endothelin-1, which are involved in vasoconstriction and vascular remodeling [18, 19].

Furthermore, HIFs promote vascular remodeling and alveolarization in various models of lung injury and prolonged hypoxia [20–24]. These changes are also stimulated by inflammatory cytokines such as interleukin-6 (IL-6) and the recruitment of cells of monocytic lineage, both of which have been shown to act synergistically with hypoxia [25–27].

## Cellular Metabolism

HIFs curtail functions associated with oxygen usage, shunting metabolism towards the glycolytic pathway. It was previously believed that the glycolytic pathway was employed under hypoxic conditions because oxygen is limiting. However, studies show that during hypoxia (1% $O_2$), HIF-1α do not finish oxidative phosphorylation. These cells eventually undergo apoptosis due to excessive reactive oxygen species (ROS) [28, 29]. Notably, HIFs reduce ROS production formed as a byproduct of the electron transport chain (ETC). The aerobic glycolysis reaction favored by HIF signaling is called the Warburg effect.

Glycolysis is modulated under hypoxic conditions through HIF-controlled upregulation of the glycolytic enzymes aldolase A, phosphoglycerate kinase 1, enolase 1, phosphofructokinase 2, and pyruvate kinase, all of which have been found to contain HREs within their promoter regions [30–32]. HIF-1α also upregulates pyruvate dehydrogenase kinase and lactate dehydrogenase [33]. GLUT1, a vital glucose transporter, is upregulated by HIF-1α under hypoxic conditions to promote glycolysis further [34]. Inflammation has also been shown to trigger the switch to aerobic glycolysis through an AKT-mTOR-HIF-1α pathway mediated by the α-glucan receptor dectin-1 in response to immunogenic challenge [35]. In addition, Eckle *et al*. demonstrated, with models of ventilator-induced acute lung injury (ALI), that HIF-1α is stabilized even in normoxia, promoting glycolysis, the tricarboxylic acid (TCA) cycle, and preventing worsening of lung injury [36].

PHD activity is blocked by succinate and fumarate, stabilizing HIF-1α activity [37]. Succinate, specifically in macrophages, stabilizes HIF-1α, and is a predominant regulator of acute inflammation, mediated by IL1β [38]. Plasma level of succinate is reported to predict mortality in critically injured trauma patients [39]. Finally, HIFs downregulate the biosynthesis of mitochondria while simultaneously increasing mitophagy [40, 41].

## Bidirectional Relationship of HIF-1α and Acute Inflammation

There is a well-known link between hypoxia and inflammation. Prominent among factors other than hypoxia that activate HIF-1α is nuclear factor kappa B (NF-κB). This transcription factor is controlled through the IkB (inhibitor of NF-κB) kinases, IKKα, and IKKβ. Once these kinases are phosphorylated, which occurs under hypoxic conditions, they phosphorylate IkBα-β, causing its degradation and the release of NF-κB [42, 43]. NF-κB, in turn, can upregulate the transcription of HIFs [43–45]. HIF-1α participates in a negative feedback loop by inducing the TAK-TAB complex and CDK6 to sequester NF-κB [46]. In addition to the IKK/NF-κB pathway, HIFs also modulate the PI3K/AKT pathway, of which NF-κB is a downstream effector [47]. HIF-1α, as a result, is directly involved in the regulation of a wide range of proinflammatory proteins, including interleukin-1β (IL-1β), IL-6, MIP-1, TNF-α, hydrogen peroxide, and prostaglandins in AM [38, 48–51]. A bidirectional relationship, therefore, exists between HIF-1α and NF-κB.

Our lab and others have characterized the role of the alveolar epithelium in hypoxic inflammation. Type II AECs are a significant source of chemotactic factors, such as CCL20 (chemokine ligand 20), CCL2, and CXCL1, which serve as recruitment signals for circulating leukocytes and adhesive factors for leukocyte extravasation, such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1) [52–55]. Like AM, type II AECs produce many proinflammatory mediators, including MIP-2, GM-CSF, IL-6, and IL-1β [53, 55, 56]. Interestingly, recent work has revealed an anti-inflammatory mechanism involving HIFs in regulating extracellular adenosine, a metabolite involved in dampening the inflammatory response. HIF-1α regulation of heme oxygenase-1 (HO-1) has also been identified as an important anti-inflammatory pathway [57].

## Apoptosis

The role of HIFs in apoptosis is complex. Multiple studies report that HIFs can stimulate or suppress apoptosis [58, 59]. Indeed, the function of HIFs in both the intrinsic and extrinsic apoptotic pathways seems to

depend on the specific cell type, environmental factors, and particular pathology.

Broadly, apoptosis involves two separate regulatory pathways. In the intrinsic pathway, damage to DNA leads to the release of three interacting subgroups of Bcl-2 family proteins. The first group consists of proteins such as Bcl-2 and Bcl-xL, which have anti-apoptotic properties. The second group, including the proteins Bax and Bak, is crucial to apoptotic signaling and mediates mitochondrial outer membrane permeabilization and the release of cytochrome c into the cytosol [60, 61]. The third group includes proteins such as Bid and Bim, which regulate group 2 proteins and cause oligomerization of Bax and Bak [62]. Cytosolic cytochrome c binds to Apaf-1 and pro-Caspase 9 to form the apoptosome complex, ultimately activating caspase 3 and caspase 7 to execute apoptosis [63]. In the extrinsic pathway, a death ligand binds to a death receptor on the outer leaflet of the plasma membrane. Much of the research on the relationship between HIFs and apoptosis in the context of AEC, including from our group, suggests a generally pro-apoptotic relationship [64].

Several studies have also characterized the link between HIFs and p53 [65–67]. This subject has spawned significant interest because of the role of p53 as a master regulator of proliferative genes, tumor suppressor genes, and apoptotic signaling pathways [68, 69]. It has been proposed that direct protein–protein –HIFs ODD domain lead to the stabilization of p53 [65, 70, 71]. Other interactions between HIF-1α and the p53 ubiquitin ligase Mdm2 and between the VHL complex and p53 suggest different association mechanisms and induction between HIFs and p53 [66, 72].

Much of the body of evidence demonstrating the anti-apoptotic role of HIFs has been found in studies of cancer cell lines [73, 74]; the specific relevance to lung injury requires further investigation. In one such study, an inhibitor of a PHD was used to show that increased HIF-1α activity was associated with lower expression of Fas and caspase 3 [75]. Finally, in more clinically relevant studies, HIF-1α has been shown to downregulate the expression of Mcl-1 in hypoxic bronchial epithelial cells [76].

## ROLE OF HIF-1A IN SPECIFIC ETIOLOGIES OF ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a clinical condition in which bilateral inflammation in the lung leads to the development of progressive respiratory failure. The clinical situation is characterized by the development of hypoxia, acute onset bilateral infiltrates, and reduced compliance of the lung. Despite advances in critical care that include low tidal volume ventilation [77], restrictive fluid strategies, and therapy directed at early identification and treatment of risk factors, ARDS-related mortality remains at 30–46% (increasing with ARDS severity) [78] with considerable morbidity [79, 80]. Prominent risk factors for ARDS development among direct insults to the lung include bacterial pneumonia, lung contusion, and aspiration-induced lung injury. Indirect lung insults include sepsis and pancreatitis. The broad impact of the response to hypoxia and HIF-mediated pathways on the progression of lung injuries is becoming better defined. The role of HIFs and the possible effects of HIF modulation is complex and primarily dependent on the clinical context [81, 82].

### Lung Contusion

Lung contusion (LC) describes an injury caused most frequently by blunt force trauma to the chest, damaging the alveolar capillaries without ripping or tearing the lung tissue. Most injuries occur due to two underlying mechanisms: lighter alveolar tissue shearing from hilar tissue due to differential densities and rapid implosion and then expansion of air in alveolar spaces in the wake of a shock wave. These result in the accumulation of alveolar injury, accumulation of blood, and pulmonary edema. LC often presents with hypoxemia, reduced lung compliance, and tachycardia. There are currently no specific pharmacological treatments. Management is purely supportive, focusing on providing supplemental oxygen and mechanical ventilation. Importantly, LC is an independent risk factor for acute respiratory distress syndrome (ARDS), a condition characterized by fluid buildup in alveolar spaces and widespread inflammation associated with significant morbidity and mortality [83].

Using a standardized sterile unilateral model of LC, our lab has recently reported that hypoxic type II AEC is the primary driver of inflammation through the activation of HIF-1α. Using a chimeric HIF-1α with the ODD domain fused to luciferase, we demonstrated that LC results in profound global hypoxia with HIF-1α activation and subsequent upregulation of proinflammatory mediators, including IL-1β and IL-6. Following conditional knockout (cKO) of HIF-1α in type II AEC through a Cre-lox system, there were significant reductions in permeability injury, proinflammatory cytokines and chemokines, and AEC apoptosis. HIF-1α cKO mice

were also found to have decreased activation of NF-κB, NLRP-3, caspase 1, and IL-1β. This data suggests that HIF-1α mediates inflammation by propagating NF-κB and the NLRP-3 inflammasome [53, 67]. HIF-1α cKO mice were also found to have diminished intra-alveolar hemorrhage, proteinaceous deposits, and infiltration of macrophages and neutrophils consistent with better preservation of lung tissue following LC [53]. Histologic evaluation confirmed that both inflammation and injury were mediated through HIF-1α. These results ultimately show that HIF-1α in AEC directly regulates the nature of the acute inflammatory response following LC. A summary of the findings is illustrated in Fig. 2. Importantly, these results indicate that blockade of HIF-1α activation with compounds represents a targeted therapy for blunt force trauma resulting in pulmonary contusion.

## Aspiration-Induced Lung Injury

Aspiration is defined as the inhalation of foreign particles into the airways. The particles are highly variable depending on the situation and commonly consist of blood, bacteria, or ingested substances. Aspiration-induced injury can be challenging to diagnose as it is not uncommon for micro-aspiration events to occur sub-acutely in sedation, endotracheal intubation, and trauma. Aspiration injuries can be categorized as either aspiration pneumonitis (i.e., chemical pneumonitis) or aspiration pneumonia, characterized by infection secondary to the aspiration event. The severity of the aspiration-induced injury can vary from mild subclinical pneumonitis to progressive respiratory failure and ARDS [84, 85].

Our lab has recently published data on the crucial role of HIF-1α through type II AEC in hypoxia-mediated inflammation and injury following the aspiration of gastric acid (GA) and the combination of acid and small gastric particles (CASP) [55]. Using our previously mentioned murine models with luciferase-linked HIF-1α and type II AEC-specific HIF-1α cKO, we demonstrated hypopharyngeal injection of a suspension of gastric particles in hydrochloric acid produced significant hypoxia in the lungs and globally. There was diminished proinflammatory cytokine and chemokine production, including IL-1β and KC, in knockout mice and decreased histological injury with minor intra-alveolar hemorrhage, neutrophil infiltration, and edema. As with LC, reductions in aspiration-induced swelling and inflammation also appeared linked to attenuation in hypoxia-induced NF-kB activity [55].

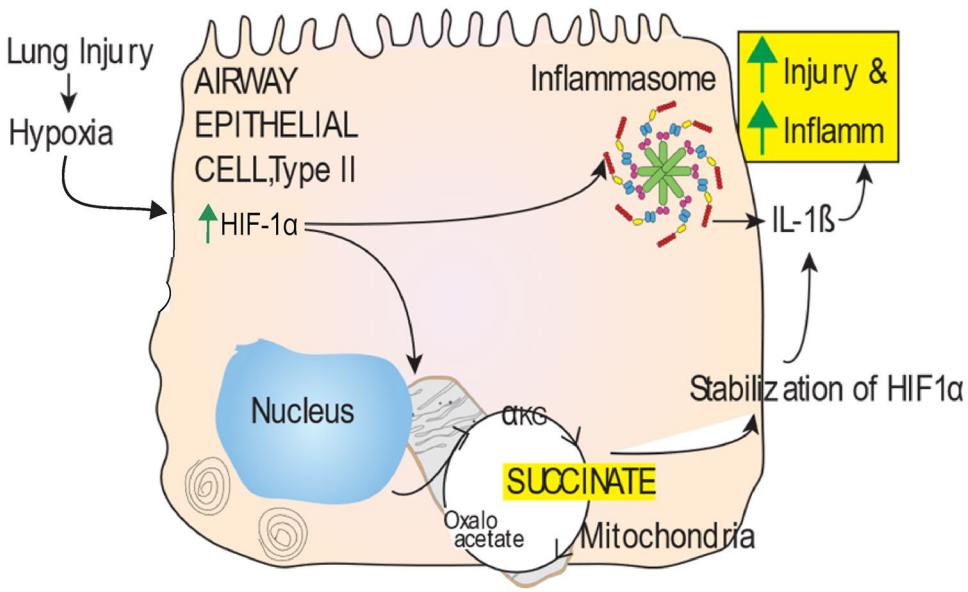


**Fig. 2** Alveolar epithelial cell (type II) regulation of HIF-1α promotes lung injury and inflammation. Mechanisms of activation include succinate dehydrogenase (SDH) accumulation due to mutation that further stabilizes HIF1. There is both direct and indirect (through NF-kB) mechanism of inflammasome activation leading to further injury and inflammation. HIF-1α is a nuclear transcription factor and regulates gene expression, and its role in lung injury and inflammation is transcription-dependent.

Zhang *et al.* have also made significant contributions to our understanding of the role of HIFs in aspiration-induced injury. In their injury model, rats are anesthetized with sodium pentobarbital, and the prepared sea water is injected into the trachea. In this model, HIF-1α was shown to upregulate endothelial cell adhesion factor semaphorin 7A, resulting in a wide range of effects, including neutrophil infiltration, the release of proinflammatory cytokines, loosening of the barrier, and increased VEGF expression [86, 87].

## Bacterial Pneumonia

Bacterial pneumonia is a significant cause of morbidity and mortality in the modern ICU and remains one of the most common nosocomial infections [88]. In a recent epidemiological study of ventilator-associated pneumonia (VAP), the most common bacterial pathogens identified were *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Enterobacter* species [89]. It is well-known that HIFs, particularly HIF-1α, are involved in responses to various human pathogens both *in vitro* and *in vivo* under hypoxic and normoxic conditions [90, 91]. HIF-1α has been reported to promote the innate immune response through myeloid cell lines, modulating the expression of primary proinflammatory mediators such as TNF-α [92]. In macrophages, HIF-1α improves phagocytosis and bactericidal capacity and is linked to the expression of immunologic surface markers, including TLR-4 and antigen-presenting structures [93–95].

*P. aeruginosa* (*PA*), the next most common pathogen implicated in VAP, also has varied interactions with HIFs. HIF-1α has been found to play a protective role in the immune response of airway epithelial cells to *PA*. Polke *et al*. demonstrated that the production of proinflammatory molecules, including IL-6, KC, and MIP-2, following exposure to *P*A and TLR ligands was reduced under hypoxia or in the presence of dimethyloxalylglycine (DMOG) *in vitro* with human bronchial epithelial cells (HBEC) and human lung cancer cell line (Calu-3) [96]. The administration of siRNA targeting HIF-1α resulted in the upregulation of proinflammatory molecules. Gil-Marques *et al*. illustrated another mechanism by which hypoxia and HIF-1α are potentially protective against infection with *PA in vitro* using A549 cells and RAW 264.7 murine macrophages and *in vivo* with a murine model of pneumonia. In vitro, HIF-1α expression in hypoxia was associated with improved bactericidal capacity, and a similar response was observed following DMOG administration under normoxic conditions. Bacterial burden *in vivo* in the lungs of mice was also reduced, although the levels of HIF-1α were found to be decreased compared to controls [97].

*KP*, *Klebsiella pneumoniae*, has been found to stimulate the epithelial–mesenchymal transition (EMT), the pathological process by which epithelial cells become undifferentiated and develop mesenchymal characteristics. In vitro, with A549 airway epithelial cells, Leone *et al*. have described that *KP* induces intracellular ROS production, thereby upregulating HIF-1α expression and leading to EMT. This process was found to be reversed by the administration of the antioxidant resveratrol, suggesting that this process is mediated upstream by ROS [98]. *KP* also employs siderophores, which function as iron chelators and improve virulence in a murine model of pneumonia with alveolar epithelial cell-specific HIF-1α cKO mice.

## LPS-Induced Lung Injury

Lipopolysaccharide (LPS) is often used as a surrogate for bacterial pneumonia. It is used to illustrate the effects of LPS, a product constituent of the bacterial wall in gram-negative infections, in animal models to illustrate the effect of bacterial products without the impact of bacterial growth. Studies have linked HIF to NF-κB activity while observing marked reductions in proinflammatory cytokine production in response to an LPS challenge [99]. Xu *et al*. found that HIF-1α translation through the PI3K/AKT and MAPK pathways was blocked, and HIF-1α breakdown was increased with tanshinone IIA treatment following LPS exposure. Therefore, the improvement in inflammation following the administration of tanshinone IIA points to the upregulation of HIF-1α as a mechanism of LPS-mediated inflammation [100]. In myeloid cells, a synergistic effect with Toll-like receptor 4 (TLR-4), the LPS-sensitive pattern recognition receptor, was proposed in which HIF-1α directly upregulates proinflammatory cytokines and TLR-4 gene expression (101). Further experiments corroborated the detrimental effect of HIF-1α in myeloid cells, demonstrating worse edema, leukocyte infiltration, and cytokine release [102].

Interestingly, there exist conflicting reports regarding the role of HIF-1α in the setting of LPS-related lung injury. Tang *et al*. examined the alveolar–capillary interface in an LPS model of ALI [103]. They found that upregulation of the TNF-α/HIF-1α pathway reduced the expression of vasodilator-stimulated phosphoprotein, which is involved in maintaining cytoskeleton integrity. HIF-1α upregulation was associated with higher permeability of the alveolar–capillary barrier. There is also

evidence for a protective metabolic effect of HIF-1α. In a recent report, Tojo *et al*. investigated the efficacy of the PHD inhibitor dimethyloxalylglycine (DMOG) in an LPS model of ARDS. They found both *in vitro* with MLE12 alveolar epithelial cells and *in vivo* with a murine model that cell viability was improved, likely through the HIF-1α mediated preference for glycolysis [104]. In another study, Hu *et al*. investigated the outcome of isoflurane treatment following an LPS model of ALI [105]. They found that the inhibitory microRNA miR-155 levels were decreased by isoflurane, thereby increasing the expression of HIF-1α and HO-1.

## Role of HIF in SARS-CoV-2 (COVID-19)

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel virus first identified in China and is responsible for the unprecedented 2019–2022 pandemic [106]. Andrey *et al*. reported that the first step of viral invasion is the interaction of SARS-CoV-2 with the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface [107]. ACE2 is the surface receptor for SARS-CoV-2, directly interacting with the spike glycoprotein (S protein) [108]. Previous studies demonstrated increased ACE2 expression in the setting of hypoxia [109, 110]. Several reports suggest that COVID-19 infection induces severe hypoxic conditions [107]. Hypoxia, in turn, activates HIF-1α with subsequent inflammatory cytokine production and glycolysis enhancement. Therefore, the COVID-19 hypoxic conditions and the following HIF-1α-dependent gene expression likely potentiate and exacerbate M1 polarization.

On the contrary, Endika Prieto-Fernández *et al*. reported that hypoxia decreases the attachment of the receptor-binding domain (RBD) and the S1 subunit (S1) of the spike protein to epithelial cells. However, hypoxia also inhibits the binding of the spike to human lung epithelial cells lacking ACE2 expression, indicating that hypoxia modulates the expression of additional binding partners of SARS-CoV-2 [111, 112]. Ultimately, hypoxia acts to prevent SARS-CoV-2 infection, suggesting that the hypoxia signaling pathway might offer therapeutic opportunities for treating COVID-19. In this context, elucidating the role of the HIF signaling pathway might unlock novel therapeutic targets that, when modulated, reduce the initial virus–host interaction and viral load [111].

Notably, the SARS-CoV-2 virus primarily attacks pulmonary tissues and impairs gas exchange, leading to acute respiratory distress syndrome (ARDS) and systemic hypoxia [113] Tian *et al*. reported that during SARS-CoV-2 infection, the viral ORF3a protein elevates the production of HIF-1α, which, in turn, promotes SARS-CoV-2 disease and inflammatory responses. Therefore, HIF-1α is a crucial activator for SARS-CoV-2 infection and inflammatory responses [114]. RNA sequencing shows that HIF-1α signaling, immune response, and metabolism pathways are dysregulated in COVID-19 patients [114]. Clinical analyses indicate that HIF-1α production, inflammatory responses, and high mortalities occur in elderly patients. HIF-1α and proinflammatory cytokines are elicited in patients and infected cells. HIF-1α plays an essential role in promoting SARS-CoV-2 infection and inducing proinflammatory responses to COVID-19 [114]. Zoya *et al*. speculated in their review article that the activation of the HIF-1α signaling pathway under mild hypoxic conditions would decrease ACE2 and TMPRSS2 and increase ADAM17 levels on the surface of alveolates and, therefore, decrease the invasiveness of SARS-CoV-2 [113]. On the contrary, the protein targets of HIF-1α are involved in the severe hypoxia-induced activation of proinflammatory cytokine expression and the subsequent inflammation process and cytokine storm phase of COVID-19 [113].

Finally, COVID-19 results in inflammatory solid response and ARDS in severe disease cases. Based on the available data, HIF-1α is a crucial factor that responds to the hypoxic microenvironment at the site of inflammation [19]. HIF-1α is an essential activator for SARS-CoV-2 infection and inflammatory response, serving as a potential therapeutic target for virus-induced inflammatory diseases and COVID-19. A summary of the current understanding of the role of HIF-1α in the pathogenesis of SARS-COV-2 is outlined in Fig. 3. HIF-1α inhibition through pharmacological strategies might provide a new approach to aid the treatment of patients affected with COVID-19.

## IS HIF IN LUNG INJURY ADAPTIVE OR MALADAPTIVE?

In models of LC and gastric aspiration (ACID and ACID + particulate), we have reported that hypoxia is seen as early as 30 min following insult. This coincides with increased nuclear activity of HIF-1α (confirmed by western blots and luciferase activity in ODD-Luc mice) [53]. Furthermore, direct abrogation of HIF-1α led to significant reductions in permeability injury and acute inflammatory responses. Post-mortem human samples of

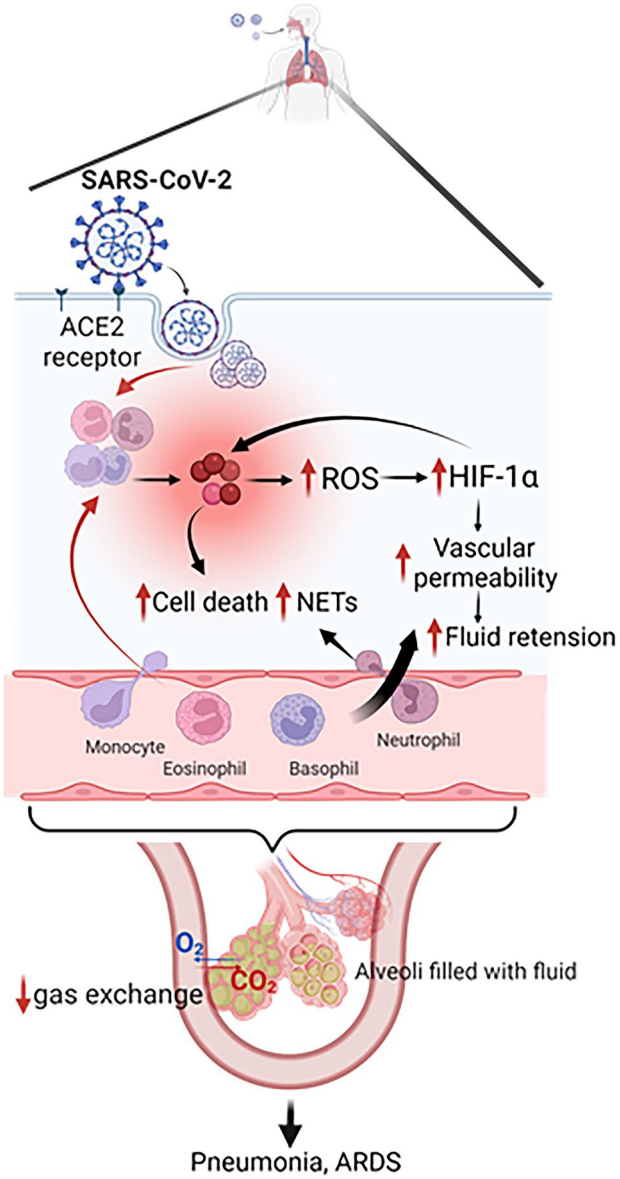


**Fig. 3** Proposed pathological mechanisms of COVID-19 involve hypoxia and HIF-1α-dependent detrimental cell signaling pathways. SARS-CoV-2 attaches to the ACE2 receptor on the cell surface of type II alveolar epithelial cells. Moreover, HIF-1α induction in the hypoxic and inflammatory conditions increases the recruitment of inflammatory cells to the infection site and increases fluid accumulation leading to pneumonia and ARDS. Increasing the recruitment of inflammatory cells to the infection site and increased fluid accumulation leads to pneumonia and ARDS.

lungs from patients who died with LC show important HIF1-α protein localization in alveolar macrophages and airway epithelial cells. Notably, similar findings were discovered in acid aspiration [55]. Alveolar epithelial cells (AEC), including type II AEC, constitute the physical and functional barrier in the lung. Once considered innocent bystanders in ARDS, they are now understood as stem cells with a specific role in the reparative processes. Our lab and others have identified AEC to have a particular role in initiating and progressing certain forms of inflammatory lung injury (LC, ACID, and ACID + particulate aspiration) [53, 55]. Specifically, we have shown that the

**Table 1** A Complete List of Potential Therapeutic strategies, Based on Their Mechanism of Action

| Drug | Mechanism | References |
|---|---|---|
| EZN-2968 | Antisense oligonucleotide inhibiting HIF-1α mRNA expression | **Greenberger *et al.*** (2008). A RNA antagonist of hypoxia-inducible factor-1alpha, EZN-2968, inhibits tumor cell growth. Mol Cancer Ther 7, 3598–3608 |
| Acriflavine | Inhibits HIF-α/HIF-1β dimerization and disrupts HIF transcriptional activity | **Lee *et al.*** (2009). Acriflavine inhibits HIF-1 dimerization, tumor growth, and vascularization. Proc Natl Acad Sci USA 106,17910–17915 |
| Topotecan | Causes decreased HIF-1α protein expression and HIF-1α translation | **Rapisarda *et al.*** (2002). Identification of small molecule inhibitors of hypoxia-inducible factor 1 transcriptional activation pathway. Cancer Res 62, 4316–4324<br>**Rapisarda *et al.*** (2004). Schedule-dependent inhibition of hypoxia-inducible factor-1alpha protein accumulation, angiogenesis, and tumor growth by topotecan in U251-HRE glioblastoma xenografts. Cancer Res 64, 6845–6848<br>**Kummar *et al.*** (2011). Phase I study of PARP inhibitor ABT-888 in combination with topotecan in adults with refractory solid tumors and lymphomas. Cancer Res 71, 5626–5634 |
| Echinomycin | A cyclic oligopeptide that disrupts HIF-1 α binding to HRE | **Kong *et al.*** (2005). Echinomycin, a small-molecule inhibitor of hypoxia-inducible factor-1 DNA-binding activity. Cancer Res 65, 9047–9055 |
| Camptothecin | Topoisomerase I inhibitor that inhibits HIF-1α translation | **Bertozzi *et al.*** (2014). The natural inhibitor of DNA topoisomerase I, camptothecin, modulates HIF-1alpha activity by changing miR expression patterns in human cancer cells. Mol Cancer Ther 13, 239–248 |
| 2-Methoxyestradiol (2ME2) | A microtubule inhibitor that strongly inhibits HIF-1α translation, nuclear translocation, and related angiogenic activity | **Mabjeesh *et al.*** (2003). 2ME2 inhibits tumor growth and angiogenesis by disrupting microtubules and dysregulating HIF. Cancer Cell 2003, 3(4), 363 – 375 |
| Geldanamycin (GA) | An HSP-90 inhibitor that increases proteasomal degradation of HIF-1α in both normoxic and hypoxic conditions | **Isaacs *et al.*** (2002). Hsp90 regulates a von Hippel Lindau-independent hypoxia-inducible factor-1alpha degradative pathway. J. Biol. Chem. 2002, 277(33), 29936 – 29944 |
| EC154 | An HSP-90 inhibitor that disrupts HIF-1α protein stability | **Bohonowych *et al.*** (2011). Comparative analysis of novel and conventional Hsp90 inhibitors on HIF activity and angiogenic potential in clear cell renal cell carcinoma: implications for clinical evaluation. BMC Cancer 11, 520 |
| Triptolide | An HSP-70 inhibitor that increases HIF-1α levels in normoxic and hypoxic conditions | **Zhou *et al.*** (2010). Increased accumulation of hypoxia-inducible factor-1alpha with reduced transcriptional activity mediates the antitumor effect of triptolide. Mol Cancer 9, 268 |

**Table 1** (continued)

| Drug | Mechanism | References |
|---|---|---|
| Vorinostat/romidepsin | HDAC inhibitors that promote HIF-1α degradation. Vorinostat may work through HIF-1α translational inhibition or Hsp-90 inhibition | **Hutt *et al*.** (2014). The histone deacetylase inhibitor, Vorinostat, represses hypoxia-inducible factor 1 alpha expression through translational inhibition. PLoS One 9, e106224<br>**Keith *et al*.** (2012). HIF1alpha and HIF2alpha: sibling rivalry in hypoxic tumor growth and progression. Nat Rev Cancer 12, 9–22 |
| YC-1 | Activator of platelet guanylate cyclase that enhances factor inhibiting HIF (FIH) binding to HIF-1α | **Chun *et al*.** (2001). Inhibitory effect of YC-1 on the hypoxic induction of erythropoietin and vascular endothelial growth factor in Hep3B cells. Biochem Pharmacol 61, 947–954 |
| PX-478 | Small-molecule inhibitor that decreases HIF-1α mRNA level, protein stability, and translation of HIF-1α in hypoxic cancer cells | **Koh *et al*.** (2008). Molecular mechanisms for the activity of PX-478, an antitumor inhibitor of the hypoxia-inducible factor-1alpha. Mol Cancer Ther 7, 90–100 |
| PX-12, Pleurotin, AJM290 and AW464 | Trx-1 inhibitors often decrease HIF-1α expression but can increase HIF-1α stability | **Ramanathan *et al*.** (2011). A randomized phase II study of PX-12, an inhibitor of thioredoxin in patients with advanced cancer of the pancreas following progression after a gemcitabine-containing combination. Cancer Chemother Pharmacol 67, 503–509 |
| Ouabain, proscillaridin A, and digoxin | Cardiac glycosides that reduce HIF-1α protein expression but increase mRNA levels | **Zhang *et al*.** (2008). Digoxin and other cardiac glycosides inhibit HIF-1alpha synthesis and block tumor growth. Proc Natl Acad Sci U S A 105, 19579–19586 |
| FM19G11 | Inhibits HIF-1α transcriptional activity and degrades HIF-1α mRNA in tumor and stem cells | **Moreno-Manzano *et al*.** (2010). FM19G11, a new hypoxia-inducible factor (HIF) modulator, affects stem cell differentiation status. J Biol Chem 285, 1333–1342 |
| Polyamides | Synthetic oligomers that target HRE's, including binding of HIF-1 to the VEGF HRE | **Olenyuk *et al*.** (2004). Inhibition of vascular endothelial growth factor with a sequence-specific hypoxia response element antagonist. Proc Natl Acad Sci U S A 101, 16768–16773 |
| Wortmannin | Inhibits HIF-1α protein expression through P13k inhibition in prostate cancer cells | **Dial *et al*.** (2003). Three conformational states of the p300 CH1 domain define its functional properties. Biochemistry 2003, 42(33), 9937 – 9945 |
| KC7F2 | Inhibits HIF-1α protein expression through mTOR1 inhibition with increased effectiveness in hypoxic conditions | **Chan *et al*.** (2015). Structural elucidation and synthesis of eudistidine A: an unusual polycyclic marine alkaloid that blocks interaction of the protein binding domains of p300 and HIF-1alpha. J. Am. Chem. Soc. 2015, 137(16), 5569 – 5575 |
| Rapamycin | Inhibits HIF-1α protein expression through mTOR1 inhibition | **Goey *et al.*** (2016). Screening and biological effects of marine pyrroloiminoquinone alkaloids: potential inhibitors of the HIF- 1alpha/p300 interaction. J. Nat. Prod. 2016, 79(5), 1267 – 1275 |
| LY-294002 | Inhibits BCR/ABL dependent HIF-1α protein expression and subsequent VEGF gene expression | **Block *et al.*** (2009). Direct inhibition of hypoxia-inducible transcription factor complex with designed dimeric epidithiodiketopiperazine. J. Am.Chem. Soc. 2009, 131(15), 18078 – 18088 |
| Gefitinib | EGFR inhibitor that increases HIF-1α proteasomal digestion and decreases its biosynthesis | **Dubey *et al*.** (2013). Suppression of tumor growth by designed dimeric epidithiodiketopiperazine targeting hypoxia-inducible transcription factor complex. J. Am. Chem. Soc. 2013, 135(11), 4537 – 4549 |

**Table 1** (continued)

| Drug | Mechanism | References |
|---|---|---|
| Genistein | Completely blocks HIF1-a subunit biosynthesis and HIF-1 dimer binding to DNA | **Jayatunga *et al*.** (2015). Inhibition of the HIF1α-p300 interaction by quinone- and indandione mediated ejection of structural Zn(II). Eur. J. Med. Chem. 2015, 94, 509 – 516 |
| PD-98059 | A MEK pathway inhibitor that Inhibits HIF-1-dependent gene activation | **Cassin *et al*.** (2006). Use of Thiazolidinone Derivatives as Antiangiogenic Agents. WO2006066846A1 |
| NS-398 | COX-2 inhibitor with an unknown mechanism decreasing HIF-1α protein levels | **Kwon *et al*.**, 2012. Inhibition of VEGF transcription through blockade of the hypoxia-inducible factor-1α-p300 interaction by a small molecule. Bioorg. Med. Chem. Lett. 2012, 22 (16), 5249 – 5252 |
| NSC-609699 | A topoisomerase 1 inhibitor that decreases HIF-1α gene expression in an unknown manner | **Shin *et al.*** (2008). Bortezomib inhibits tumor adaptation to hypoxia by stimulating the FIH-mediated repression of hypoxia-inducible factor-1. Blood 111, 3131–3136 |
| 17-AAG; 17-DMAG | HSP-90 inhibitors that increase HIF-1a ubiquitination | **Wu *et al*.** (2013). A novel function of novobiocin: disrupting the interaction of HIF 1α and p300/CBP through direct binding to the HIF1α C-terminal activation domain. PLoS One 2013, 8 (5), No e62014<br>**Kushal *et al*.** (2013). Protein domain mimetics as *in vivo* modulators of hypoxia-inducible factor signaling. Proc. Natl. Acad. Sci. U. S. A. 2013, 110 (39), 15602 – 15607 |
| RITA | A p53-MDM2 inhibitor that disrupts HIF-1α protein stability through a PHD-dependent pathway | **Lee *et al*.** (2009). Acriflavine inhibits HIF-1 dimerization, tumor growth, and vascularization. Proc Natl Acad Sci U S A 106, 17910–17915 |
| KRH102053/KRH102140 | PHD activators that disrupt HIF-1α protein stability in hypoxic cancer cells | **Miranda *et al*.** (2013). A cyclic peptide inhibitor of HIF-1 heterodimerization that inhibits hypoxia signaling in cancer cells. J. Am. Chem. Soc. 2013, 135 (28), 10418 – 10425<br>**Erbel *et al*.** (2013). Structural basis for PAS domain heterodimerization in the basic helix–loop–helix-PAS transcription factor hypoxia-inducible factor. Proc. Natl. Acad. Sci. U. S. A. 2003, 100 (26), 5504 – 15509 |
| R59949 | HIF prolyl hydroxylase activator that causes PHD-dependent HIF-1α protein stability disruption | **Scheuermann *et al*.** (2013). Allosteric inhibition of hypoxia-inducible factor-2 with small molecules. Nat Chem Biol 9, 271–276 |
| LW6 | Decreases HIF-1α protein stability and by binding and degrading it | **Key *et al*.** (2009). Principles of ligand binding within a completely buried cavity in HIF2alpha PAS-B. J. Am. Chem. Soc. 2009, 131 (48), 17647–17654 |

**Table 1** (continued)

| Drug | Mechanism | References |
|---|---|---|
| Isonicotinic acid derivatives, benzimidazole derivatives, and (E)-phenoxyacrylic amide derivative | Disrupts HIF-1α protein stability and facilitates degradation | **Scheuermann *et al.*** (2015). Isoform-selective and stereoselective inhibition of hypoxia-inducible factor 2. J. Med. Chem. 2015, 58 (15), 5930 – 5941<br>**Wehn *et al.*** (2018). Design and activity of specific hypoxia-inducible factor 2alpha (HIF-2alpha) inhibitors for the treatment of clear cell renal cell carcinoma: discovery of clinical candidate (S)-3-((2,2-difluoro-1-hydroxy-7-(methylsulfonyl)-2,3-dihydro-1H-inden-4-yl) oxy)-5-fluorobenzonitrile (PT2385).J. Med. Chem. 2018, 61 (21), 9691 – 9721<br>**Wallace *et al.*** (2016). Genistein decreases A549 cell viability via inhibition of the PI3K/AKT/HIF1 alpha/VEGF and NF-kB/COX-2 signaling pathways. Mol. Med. Rep. 2017, 15 (4), 2296 – 2302<br>**Courtney *et al.*** (2018). Phase I dose-escalation trial of PT2385, a first-in-class hypoxia-inducible factor-2alpha antagonist in patients with previously treated advanced clear cell renal cell carcinoma. J. Clin. Oncol. 2018, 36 (9), 867 – 874 |
| N-(benzofuran-5-yl)-aromatic sulfonamide derivatives | Increases HIF-1α protein degradation | **Xie *et al.*** (2017). Activation of intestinal hypoxia-inducible factor 2alpha during obesity contributes to hepatic steatosis. Nat. Med. 2017, 23 (11),1298 – 1308 |

regulation of HIF-1α in type II AEC directly regulates the progression of the acute inflammatory response leading to hypoxia, diminished lung compliance, and robust inflammation [53, 55].

It is entirely possible that HIF-1α plays the role of an adaptive molecule by driving the metabolic pathway towards glycolysis in certain etiologies of lung injury. A body of evidence shows enhancement of glycolysis by inhibition of PHD and thereby activation of HIF-1α to protect alveolar epithelial cells [104]. Alveolar stretch is a phenomenon seen in ventilator-induced lung injury following the development of refractory hypoxia in lung injury. Eltzschig and colleagues have reported that, in a model of alveolar stretch-induced inflammation, HIF-1α plays a protective role [115]. Similarly, McClendon *et al*. concluded that HIF-1α is activated in ATII cells after lung injury and promotes proliferation and spreading during repair [116]. These results are contradictory to our experimental data. In our models of lung injury, HIF1-α increases lung injury and inflammation and is, therefore, maladaptive [53, 55].

It is highly likely that HIF-1α has disparate roles that depend on the cell type, nature of the inflammatory response, and timing of injury-acute versus chronic. For example, hypoxia is a direct consequence of LC and acid aspiration that prompts some patients to require mechanical ventilation.

## THERAPEUTIC STRATEGIES FOR MODULATION OF HIF

Several recent reviews [74, 117–119] demonstrate mechanisms of pharmacological HIF modulation. In cases of sterile injury, HIF inhibitors acriflavine, 4-hydroxyphenyl acetic acid, and 3,5,4′-tri-O-acetyl resveratrol reduce inflammation with beneficial effects. By contrast, HIF inducers such as PHD inhibitors have been tested as therapeutic agents in non-sterile injury. Most PHD inhibitors are 2-oxoglutarate analogs, such as DMOG and mimosine, which induce HIFs [120]. PDH inhibitors represent a promising new drug class, and multiple recent reviews discuss their potential effectiveness [120–122]. Such compounds may constitute an original, desperately needed approach to lung injuries, especially as the increasing prevalence of antibiotic-resistant pathogens and conditions like ARDS continues to challenge the modern ICU (Table1).

## AUTHOR CONTRIBUTION

MVS, SB, SA, and KR wrote the main manuscript text, SS prepared Figs. 1–3. YS and KC edited the manuscript text. All authors reviewed the manuscript.

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## DATA AVAILABILITY

All data collected and analyzed within this study are available from the corresponding author on request.

## DECLARATIONS

**Ethics Approval and Consent to Participate** The review was written following the ethical standards and appropriate guidelines on consent to participate.

**Consent for Publication** All authors consent for publication.

**Competing Interests** The authors declare no competing interests.

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