Deborah J. Culley, M.D., Editor

Immunologic Consequences of Hypoxia during Critical Illness

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ABSTRACT

Hypoxia and immunity are highly intertwined at clinical, cellular, and molecular levels. The prevention of tissue hypoxia and modulation of systemic inflammation are cornerstones of daily practice in the intensive care unit. Potentially, immunologic effects of hypoxia may contribute to outcome and represent possible therapeutic targets. Hypoxia and activation of downstream signaling pathways result in enhanced innate immune responses, aimed to augment pathogen clearance. On the other hand, hypoxia also exerts antiinflammatory and tissue-protective effects in lymphocytes and other tissues. Although human data on the net immunologic effects of hypoxia and pharmacologic modulation of downstream pathways are limited, preclinical data support the concept of tailoring the immune response through modulation of the oxygen status or pharmacologic modulation of hypoxia-signaling pathways in critically ill patients. **(Anesthesiology 2016; 125:237–49)**

OPTIMIZATION of oxygenation to prevent tissue hypoxia is one of the cornerstones of critical care. Concurrently, in the majority of patients admitted to the intensive care unit (ICU), inflammatory processes take place, which may affect outcome. As hypoxia and immunity are highly interdependent at molecular, cellular, and clinical levels, immunologic effects of hypoxia may represent therapeutic targets in critically ill patients. At the cellular level, hypoxia activates distinct hypoxia-signaling pathways, including a group of transcription factors known as hypoxia-inducible factors and adenosine signaling. *In vitro* and animal studies have shown that these pathways are involved in modulation of inflammatory responses, and animal studies have demonstrated that these pathways are relevant to inflammatory conditions that are frequently encountered in critically ill patients, such as sepsis[1,2] and lung injury.[3,4] In addition, inflammatory conditions are frequently characterized by tissue hypoxia due to enhanced metabolic demand as well as decreased metabolic substrates resulting from edema, microthrombi, and atelectasis, in turn causing "inflammatory hypoxia."[5,6] As such, aiming for specific tissue oxygenation levels could be favorable in a range of inflammatory conditions in critically ill patients. Alternatively, these effects may also be achieved with pharmacologic interventions targeting hypoxia-signaling pathways.

In the current review, we provide an overview of the immunologic consequences of hypoxia. We focus on *in vitro*, animal, and human studies concerning inflammatory conditions relevant to critically ill patients, including a discussion of oxygen-dependent signaling pathways and intermediate signaling systems (*e.g.*, the hypoxia-inducible factor [HIF] system and adenosine metabolism).[2,7] Furthermore, we discuss the clinical potential of intervening in these mechanisms, including evidence on potential drawbacks of hyperoxia, feasibility of therapeutic *permissive hypoxia*, and pharmacologic therapies that act on oxygen-dependent pathways. The role of hypoxia and HIFs outside the scope of inflammatory conditions in critically ill patients is reviewed elsewhere.[2,7–9]

Immunologic Effects of Hypoxia

Evidence for immunologic effects of hypoxia has mainly been established in *in vitro* studies using myeloid cells (table 1).[10–12] Long-term hypoxia has been shown to represent an inflammatory stimulus in itself, as prolonged hypoxia results in production of cytokines in a human macrophage cell line.[14] In addition, hypoxia increases the production of proinflammatory cytokines upon stimulation with the toxins lipopolysaccharide or phytohemagglutinin in primary human mononuclear cells.[13,15] In contrast, other studies

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Table 1. *In Vitro* and (Pre)Clinical Studies on the Effects of Hypoxia on Immunity

	Reference	Model	Inflammatory Stimulus/Model	Oxygen Intervention	Timing Oxygen Intervention	Inflammatory Effect of Oxygen Intervention
In vitro	13	Primary human monocytes	Lipopolyssacharide or PMA	1% O_2	24 h	↑ TNFα and interleukin-1β
	14	Monocyte/macrophage cell line (THP-1)	—	1 or 9% O_2	Up to 24 h	↑ TNFα
	15	Primary human monocytes	Phytohemagglutinin	2% O_2	16 h and 40 h	↑ Interleukin-2, interleukin-4, interleukin-6, and IFNγ ↓ Interleukin-10
	16	Monocyte/macrophage cell line (U937)	—	2.8% O_2	24 h	↑ Adhesion of leukocytes to endothelium
	10	Primary human dendritic cells, monocytic (MM6), endothelial (HMEC-1), and intestinal epithelial (Caco-2) cell lines	—	2% O_2	6 h	↑ TLR2 and TLR6
	17	Murine bone marrow–derived dendritic cells	Lipopolyssacharide	1% O_2	24 h	↑ Costimulatory molecules, TNFα, and interleukin-6
	18	Rat alveolar macrophages	Lipopolyssacharide	1.3% O_2	1.5 h	↓ TNFα and interleukin-1β
	19	Murine peritoneal macrophages and monocytic cell lines (U937 and THP-1)	Lipopolyssacharide	< 0.3% O_2	24 h	↑ TNFα
	19	TG-elicited murine peritoneal macrophages and lipopoly-ssacharide-primed monocytic cell lines (U937 and THP-1)	Lipopolyssacharide	< 0.3% O_2	24 h	↓ TNFα
Animal model	20	Mice	Lipopolyssacharide intraperi-toneal at days 11 and 27	12% O_2	28 d	↑ TNFα
(Pre)clinical human studies	21	Healthy volunteers	None	Altitude hypoxia (4,350 m; Sa_{O_2}, 78.6 to 83.4%)	4 d	↑ Interleukin-6
	22	Healthy volunteers	None	Altitude hypoxia (3458–4559 m; Sa_{O_2}, 75 to 90%)	4 d	↑ Interleukin-6, interleukin-1RA, and CRP
	23	Healthy volunteers	None	Altitude hypoxia (4,500 m)	2 h per day for 7 consecutive days	Neutrophilia ↑ Neutrophilic superoxide production
	24	Healthy volunteers	*Ex vivo* stimulation of neutrophils with fMLP	12% O_2	2 h	↑ Chemotaxis, phagocytosis, and ROS production
	25	Healthy volunteers	*Ex vivo* stimulation of T cells and monocytes with PMA, phagocytosis of zymosan	Sa_{O_2}, 78%	2 h	= Cytokines ↑ Neutrophil phagocytosis
	11	Healthy volunteers	None	Sa_{O_2} 80%	1 h/day for 10 consecutive days	= Cytokines
	12	Healthy volunteers	None	11% O_2	30 or 60 min	= Cytokines

Control condition was room air unless specified otherwise and pressure is normobaric unless specified otherwise.

CRP = C-reactive protein; fMLP = *n*-formyl-Met-Leu-Phe; HMEC-1 = human microvascular endothelial cell; IFNγ = interferon γ; MM6 = mono mac 6 human monocytic cell; PMA = phorbol myristate acetate; ROS = reactive oxygen species; Sa_{O_2} = arterial oxygen saturation; TG = thioglycollate; TLR2 = toll-like receptor 2; TLR6 = toll-like receptor 6; TNFα = tumor necrosis factor alpha.

have demonstrated that hypoxia skews the proinflammatory character (M1-like) of macrophages toward an anti-inflammatory M2-like phenotype.[18,19] In addition to these contradictory findings, these *in vitro* studies are difficult to interpret, as the control condition is usually room air, which has a higher Pa_{O_2} compared to physiologic tissue Pa_{O_2}. Nevertheless, these *in vitro* studies demonstrate that oxygenation exerts immunologic effects, although the direction of this response may depend on the cell type and activation state.

Healthy volunteers subjected to hypoxia *in vivo* display enhanced *ex vivo* neutrophil chemotaxis, phagocytosis, and reactive oxygen species production[24] and increased activity of the key inflammatory transcription factor nuclear factor of kappa-light-chain-enhancer of activated B cells (NF-κB) in monocytes.[25] Furthermore, exposure of healthy subjects to high-altitude hypoxia (arterial oxygen saturation [Sa_{O_2}], 75 to 90%) for 4 days results in increased plasma levels of the proinflammatory interleukin-6,[21,22] while shorter periods of hypoxia do not induce such systemic responses[17,23] (table 1). Taken together, *in vivo*, prolonged hypoxia increases inflammatory responses of myeloid cells *ex vivo* and elicits a systemic immune response.

Concerning the underlying mechanisms, hypoxia *in vitro* induces an expansive cascade of cellular processes, regulated by oxygen-sensitive pathways consisting of prolyl hydroxylases (PHDs), the transcription factors HIFs and NF-κB, adenosine signaling pathways, and other oxygen-sensitive processes. These cellular mechanisms provide adaptation toward conditions of limited oxygen availability, and each pathway contributes in different ways to the immunologic effects of hypoxia. This may explain why hypoxia causes both pro- and antiinflammatory, as well as tissue-protective effects, as further detailed below.

Regulation of HIF-1α

HIFs represent a group of transcription factors that mediate a plethora of cellular adaptations in response to hypoxia.[26] HIFs are heterodimers consisting of HIF-β and one of the three oxygen-dependent transcriptionally active α subunits: HIF-1α, HIF-2α, and HIF-3α, of which HIF-1α is the most widely studied isoform. The cellular mechanisms responsible for the regulation of HIF-1α protein stabilization and signaling under normoxic, hypoxic, and inflammatory conditions are detailed in figure 1. Under normoxic conditions, the oxygen-dependent PHD-1, PHD2, and PHD3 and the asparaginyl-hydroxylase factor–inhibiting HIF (FIH) hydroxylate HIF-1α, after which hydroxylated HIF-1α binds to the Von Hippel–Lindau complex. Binding of HIFs to Von Hippel–Lindau ultimately results in ubiquitination and degradation in the proteasome. Under hypoxic conditions, the oxygen-dependent hydroxylases are inactive, which prevents degradation of HIF-1α. As such, hypoxia regulates HIF-1α in a posttranslational manner. A second, oxygen-independent, posttranslational mechanism of HIF-1α regulation involves heat shock protein (HSP) 90. HSPs are key players in the response to cellular stress, functioning as chaperone proteins that facilitate conformation, localization, and function of a diversity of proteins. HSP90 blocks the oxygen-independent degradation of HIF-1α and thereby results in stabilization of HIF-1α.[27–29] Furthermore, HSP90 binding to HIF-1α facilitates coupling with HIFβ and subsequent transactivation.[29]

Finally, the transcription and translation of HIF-1α are increased by inflammatory stimuli. Therefore, hypoxia, cellular stress, and inflammation (synergistically) enhance HIF-1α stabilization.[2,7]

HIF-1α stabilization facilitates transcription of more than 100 hypoxia-responsive genes,[30] many of which result in hypoxia adaptation, *e.g.*, erythropoietin and vascular endothelial growth factor.[31] Although the autoregulatory system of HIF-1α has not been fully elucidated, there appears to be a negative feedback system.[32] *In vitro*, hypoxia induces HIF-1α expression in a dose-dependent fashion, but prolonged hypoxia results in down-regulation of HIF-1α, mediated by a micro-RNA, which targets HIF (aHIF), of which levels increase over time under hypoxic conditions.[33] In contrast to *in vitro* data, where hypoxia has only been shown to prevent HIF-1α degradation, hypoxia *in vivo* stimulates transcription of HIF-1α, followed by a decrease to baseline levels, possibly resulting from the aHIF-mediated negative feedback.[34] Human studies revealed a large interindividual variability in leukocyte HIF-1α expression[35] and downstream target gene expression[36] in response to hypoxia, implicating phenotypical differences in HIF regulation.

Involvement of HIF-1α and Adenosine Signaling in the Immunologic Effects of Hypoxia

The Molecular Interplay among Hypoxia, HIFs, and NF-κB

The regulation of HIF-1α and NF-κB, the latter considered the master regulator of inflammatory responses, is highly intertwined.[37,38] In the inactivated state, NF-κB is bound to the inhibitory protein IκBα in the cytosol. Not only inflammatory stimuli but also other signals, activate the enzyme IκB kinase (IKK), resulting in phosphorylation of IκBα. Subsequently, NF-κB translocates into the nucleus, and an inflammatory response characterized by production of inflammatory cytokines is generated.[39] Another downstream effect of NF-κB activity is enhanced HIF-1α transcription.[40–42] Conversely, HIF-1α activity enhances NF-κB activity by increasing abundance of IKK and the NF-κB subunit p65.[41,43] Moreover, hypoxia prevents PHD-dependent IKK degradation.[44] *In vitro* studies confirmed this effect, as combined inhibition of PHD-1 and FIH enhanced basal NF-κB activity in a HIF-1α-independent fashion.[45] Paradoxically, PHD-1 and FIH inhibition suppress NF-κB activity under inflammatory conditions.[45] These data illustrate that there is extensive interplay between hypoxia, oxygen-dependent hydroxylases, HIF-1α, and NF-κB. Furthermore,

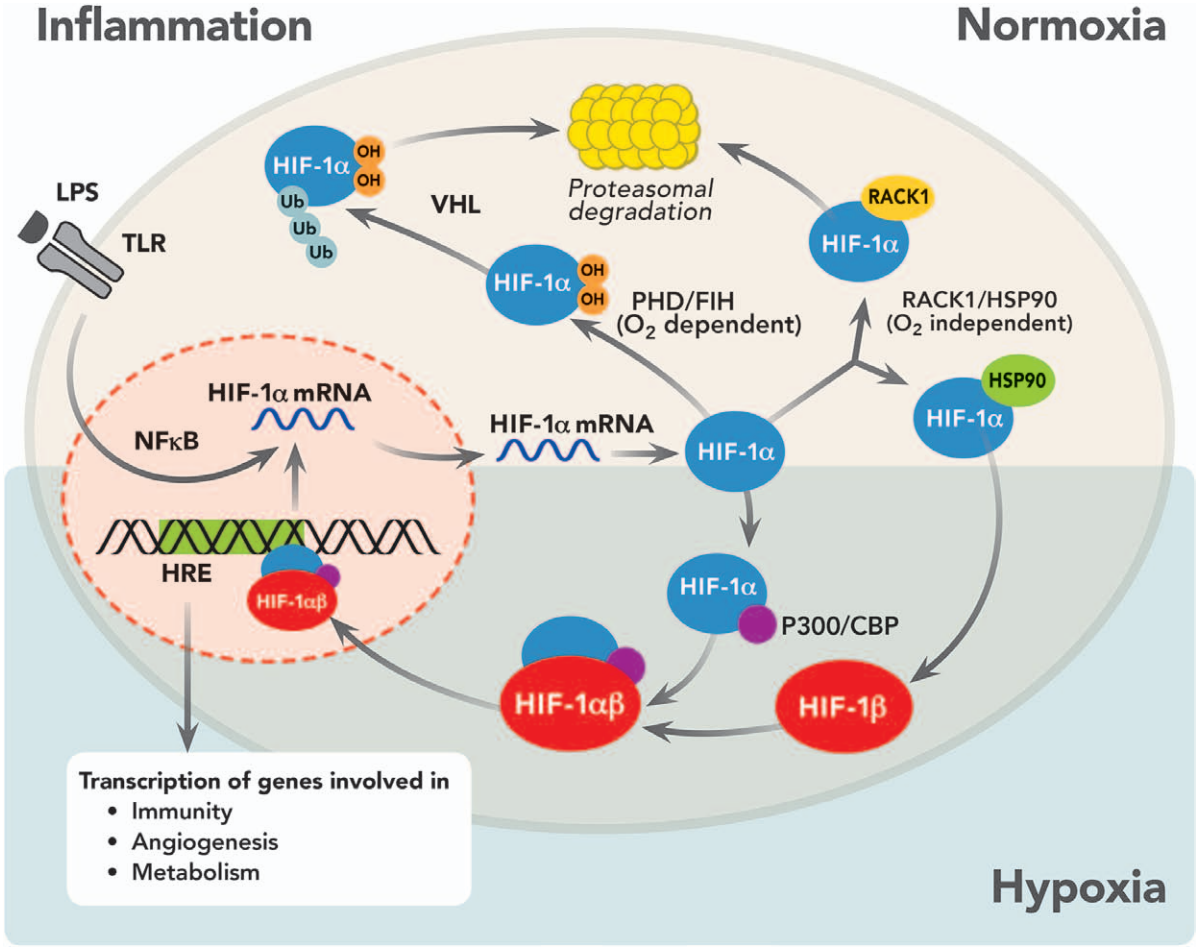

Fig. 1. Hypoxia-inducible factor (HIF)-1α regulation and signaling under normoxic, hypoxic, and inflammatory conditions. HIF-1α subunits are constantly produced but rapidly degraded under normoxic conditions. Several pathways of HIF-1α regulation have been described. First, under normoxic conditions, HIF-1α subunits are rapidly hydroxylated by oxygen-dependent prolyl hydroxylase domain enzymes (PHDs), which are subsequently captured by the ubiquitin ligase Von Hippel–Lindau (VHL) protein and degraded by the proteasome. Second, the oxygen-dependent asparaginyl hydroxylase factor-inhibiting HIF (FIH) hydroxylates a conserved asparaginyl residue, preventing the recruitment of coactivators P300 and cAMP-response element–binding protein (CBP), in turn inhibiting dimerization with HIFβ. During oxygen deficiency, PHD and FIH activities decrease, resulting in accumulation of HIF-1α subunits in the cytosol. The receptor for activated C kinase 1 (RACK1) and heat shock protein 90 (HSP90) regulate HIF-1α in an oxygen-independent manner: RACK facilitates oxygen-independent proteasomal degradation of HIF-1α, while HSP90 competes with RACK, thereby stabilizing HIF-1α, and facilitates its transactivation. Upon accumulation, HIF-1α is coactivated by P300/CBP and dimerizes with HIFβ to form stable HIF-1αβ dimers. These dimers translocate to the nucleus and bind to hypoxia response elements (HREs) in promoter enhancer regions of genes, resulting in transcriptional activity. HIF-1α stabilization results in transcription of many (greater than 100) hypoxia responsive genes. As FIH remains active at lower oxygen concentrations than PHDs, FIH suppresses the activity of HIF-1α proteins that escape destruction during moderate hypoxia. Not only hypoxia but also exposure to bacteria and bacterial products such as lipopolysaccharide (LPS) results in HIF-1α accumulation. NF-κB = nuclear factor of kappa-light-chain-enhancer of activated B cells; TLR = toll-like receptor.

as alluded to before, effects are dependent on the cellular activation state.

Cellular and In Vivo *Immunologic Effects of HIF-1α*

At the cellular level, HIF-1α stabilization in immune cells results in a differentiated response, highly depending on the cell type. In neutrophils, the induction of β_2-integrin involved in epithelial neutrophil binding,[16] regulation of pathogen-binding neutrophil extracellular traps, and antibacterial activity[46] are all HIF-1α dependent.[46] HIF-1α stabilization inhibits apoptosis of macrophages and neutrophils[43,47] and is involved in the differentiation of monocytes to macrophages as well as in macrophage maturation.[48] HIF-1α also results in increased expression of toll-like receptor 4[49] as well as in enhanced macrophage phagocytosis[50] and bacterial killing.[51]

A wide diversity of animal studies using cell-specific transgenic knockout mice and pharmacologic HIF-1α modulation also demonstrate the cell type–specific effects of HIF-1α. Myeloid HIF-1α knockout mice have a higher morbidity in

streptococcal skin infections than their wild-type littermates, which indicates that HIF-1α in myeloid cells is essential to mount an inflammatory response required to clear local infection.[51] In severe systemic inflammation induced by lipopolysaccharide (to mimic Gram-negative infection)[52] or lipoteichoic acid and peptidoglycan (to mimic Gram-positive infection),[53] myeloid HIF-1α–deficient mice display an attenuated inflammatory response, associated with less tissue damage and improved survival.[52] In accordance, HIF-1α gain of function results in an overwhelming inflammatory response in sterile and bacterial peritonitis, with aggravated organ damage and impaired survival.[1] As such, in myeloid cells, HIF-1α is essential for the generation of an effective inflammatory response to clear infections, while simultaneously, HIF-1α overexpression leads to the clinical picture of the early, proinflammatory phase of sepsis in mice.

In contrast to the proinflammatory effects observed in myeloid cells, HIF-1α activity induces antiinflammatory and tissue-protective effects in lymphocytes. For instance, HIF-1α induction results in increased numbers of regulatory T cells, with subsequent tissue protection due to attenuation of inflammation.[54] Furthermore, in a murine bacterial peritonitis model, T-cell–specific HIF-1α deficiency results in increased levels of proinflammatory cytokines.[55] Suggestive of antiinflammatory effects of HIF-1α in B cells, PHD inhibition with dimethyloxalylglycine before lipopolysaccharide administration in mice resulted in enhanced interleukin-10 production by B1 cells, which skewed macrophages toward an antiinflammatory M2-like phenotype.[56] Moreover, other studies demonstrate that the transcriptional program that drives antiinflammatory regulatory T-cell differentiation is under the control of HIF *via* the induction of the HIF-target gene *FoxP3*.[54]

Apart from effects in dedicated immune cells, HIF-1α stabilization also exerts immunologic effects in other cells, *e.g.*, intestinal and alveolar epithelium and myocytes. Pharmacologic stabilization of HIF-1α through PHD inhibition in murine chemical-induced colitis results in reduced levels of TNFα, interleukin-6, and interleukin-1β, while levels of antiinflammatory interleukin-10 increase[57] and clinical outcome improves.[58,59] Similarly, pharmacologic PHD inhibition in ventilator-induced lung injury results in HIF-1α–dependent reduced lung injury and prolonged survival, whereas HIF-1α inhibition aggravates lung injury and shortened survival.[4] The tissue-protective effects of HIF-1α are also involved in protection against ischemic injury. For instance, myocardial protection by remote ischemic preconditioning is dependent on increased interleukin-10 production mediated through HIF-1α,[60,61] and myocardial HIF-1α expression mediates a metabolic switch to glycolysis, which is crucial for adaptation to ischemia.[62] An overview of the immunologic effects of PHD inhibition in *in vitro* and animal studies is provided in table 2.[45,63–74]

Altogether, HIF-1α activity in myeloid cells is involved in the orchestration of immune responses aimed at pathogen clearance, whereas HIF-1α activity in lymphocytes, epithelium, and myocytes induces antiinflammatory and tissue protective effects (an overview is provided in fig. 2). Although these opposing effects may seem contradictory, studies in the field of oncology have shown that myeloid HIF-1α activity suppresses T-cell responses.[75] Therefore, it is conceivable that, in the context of inflammation and infection, local interplay between different immune cells is required to optimize infection control and simultaneously prevent tissue damage.[76]

HIF-1α in Sepsis

The role of HIF-1α in sepsis is of particular interest, as inflammation and tissue hypoxia often coexist, the latter due to a mismatch of oxygen demand and availability. The immunologic host response during early sepsis is characterized by (over)production of proinflammatory cytokines, which is aimed at pathogen clearance, but also results in the clinical syndrome of septic shock. However, an antiinflammatory reaction is mounted simultaneously, presumably to curtail the proinflammatory response and thereby prevent collateral tissue damage. When too pronounced and/or sustained, this antiinflammatory response results in a profoundly suppressed state of the immune system. It is increasingly recognized that this phenomenon, known as "sepsis-induced immunoparalysis," renders patients more vulnerable to secondary infections and is a major contributor to late mortality in septic patients.[77]

Based on the data described earlier, HIF-1α activity may enhance proinflammatory effects and innate immune functions, which could be beneficial in sepsis-induced immunoparalysis. This concept is supported by the observation that endotoxin tolerance, which bears similarities to sepsis-induced immunoparalysis, was partially reversed by chronic mild hypoxia in mice.[20] However, this single animal study does not fully reflect the complex dynamics of HIF-1α during human sepsis. Furthermore, it needs to be emphasized that the abovementioned studies on (the interplay between) inflammation and hypoxia have been conducted *in vitro* and in animals. The translation from animal studies to the human situation is an important topic of debate.[78,79] Fortunately, two recent observational studies in sepsis patients have increased our understanding of the dynamics of HIF-1α during sepsis. In one of these, samples were obtained within 2 to 4 h after admission, and HIF-1α mRNA expression in monocytes was increased.[80] Furthermore, HIF-1α induced the negative toll-like receptor regulator interleukin-1 receptor-associated kinase M, resulting in immunosuppression.[80] In contrast, the other study found reduced leukocytic HIF-1α protein and mRNA expression, but samples were obtained at later time points (*i.e.*, within 24 h after admission).[81] Although one has to be cautious when interpreting data from preclinical work in the context of clinical patient studies, it could be envisioned that the early proinflammatory response drives increased HIF-1α expression, resulting in the induction of negative regulators such as interleukin-1 receptor-associated kinase M to

Table 2. *In Vitro* and Preclinical Studies on the Effects of PHD Inhibitors on Immunity

	Reference	Model	Inflammatory Stimulus/Model	Intervention	Inflammatory Effect of PHD Inhibition
In vitro	63	Microgial cell line (BV2)	Lipopolysaccharide	EDHB	↓ mRNA, TNFα, and interleukin-6
	64	Keratinocyte cell line (HaCaT)	Lipopolysaccharide	AKB-4924	↑ VEGF, interleukin-6, interleukin-8
	65	Monocyte/macrophage cell line (U937) and neutrophils from healthy donors	Various Gram-positive and negative bacteria	AKB-4924	↑ Bactericidal activity
	66	Endothelial cell line (5A32)	TNFα	Dimethyloxalylglycine	↓ VCAM-1
	67	Macrophage cell line (RAW264.7)	Lipopolysaccharide	Dimethyloxalylglycine	↓ TNFα
	45	HeLa cell line	Interleukin-1β	Dimethyloxalylglycine	↓ NF-κB activity
Animal model	58	Mice	TNBS (chemical colitis)	FG-4497	↓ Colonic TNFα, weight loss, histologic inflammation
	59	Mice	DSS (chemical colitis)	Dimethyloxalylglycine	↓ Colonic interleukin-1β, TNFα, interleukin-12, interleukin-6, disease activity index, weight loss, histologic inflammation
	74	Rats	DNBS (chemical colitis)	Dimethyloxalylglycine	↓ Neutrophil infiltration
	68	Mice	TNBS and DSS (chemical colitis)	TRC160334	↓ Disease activity index, weight loss, histologic inflammation
	57	Mice	TNBS (chemical colitis)	AKB-4924	↓ Serum interleukin-1β, TNFα, interleukin-6, weight loss, disease activity ↑ Interleukin-10
	69	Mice	TNBS (chemical colitis)	AKB-4924	↓ Colonic interleukin-1β, TNFα, interleukin-12, interleukin-6, weight loss, histologic inflammation
	70	Mice	$TNF^{\Delta ARE/+}$ mice (spontaneous chronic terminal ileitis)	Dimethyloxalylglycine	↓ Histologic inflammation
	71	Mice	Lipopolysaccharide intraperitoneal (endotoxemic shock)	Dimethyloxalylglycine	↓ TNFα, mortality ↑ Interleukin-10
	4	Mice	Ventilator-induced lung injury	Dimethyloxalylglycine	↓ BAL MPO, pulmonary edema ↑ Gas exchange, survival time
	65	Mice	*Staphylococcus aureus* (cutaneous infection)	AKB-4924	↓ Lesion size, bacterial load, disease severity
	72	Mice	*Escherichia coli* (urinary tract infection)	AKB-4924	↓ Bacterial load, interleukin-1β, interleukin-6, KC, myeloperoxidase activity
	63	Mice	MPTP (neurotoxicity)	EDHB	↓ Striatal interleukin-6
	73	Rabbits	Lipopolysaccharide and methylprednisolone (osteonecrosis)	EDHB	↓ Osteonecrosis

BAL = bronchial alveolar lavage; DNBS = dinitrobenzene sulfonic acid; DSS = dextran sulfate sodium; EDHB = ethyl-3,4-dihydroxybenzoate; KC = keratinocyte-derived chemokine; MPO = myeloperoxidase; MPTP = 1-methyl-4-fenyl-1,2,3,6-tetrahydropyridine; NF-κB = nuclear factor of kappa-light-chain-enhancer of activated B cells; PHD = prolyl hydroxylase; TNBS = 2,4,6-trinitrobenzene sulfonic acid; TNFα = tumor necrosis factor alpha; $TNF^{\Delta ARE/+}$ mice = mice with gene targeted alterations in untranslated region of TNFα mRNA leading to development of severe ileitis; VCAM-1= vascular cell adhesion molecule-1; VEGF = vascular endothelial growth factor.

counteract excessive inflammation, ultimately resulting in reduced HIF-1α levels later in the course of sepsis.

Tissue-protective and Antiinflammatory Effects through the Adenosine Pathway

Hypoxia can also exert antiinflammatory and tissue-protective effects through the adenosine pathway, of which some elements have been reported to be HIF-1α dependent.[82,83]

Cellular distress (*e.g.*, hypoxia[84]) results in increased availability of the adenosine progenitors adenosine triphosphate and adenosine diphosphate.[85] Hypoxia leads to up-regulation of CD39 (ectoapyrase),[86,87] which converts adenosine triphosphate and adenosine diphosphate into adenosine monophosphate, and to HIF-1α–dependent up-regulation of CD73 (5′-ectonucleotidase), which converts adenosine monophosphate into adenosine.[82] The tissue-protective

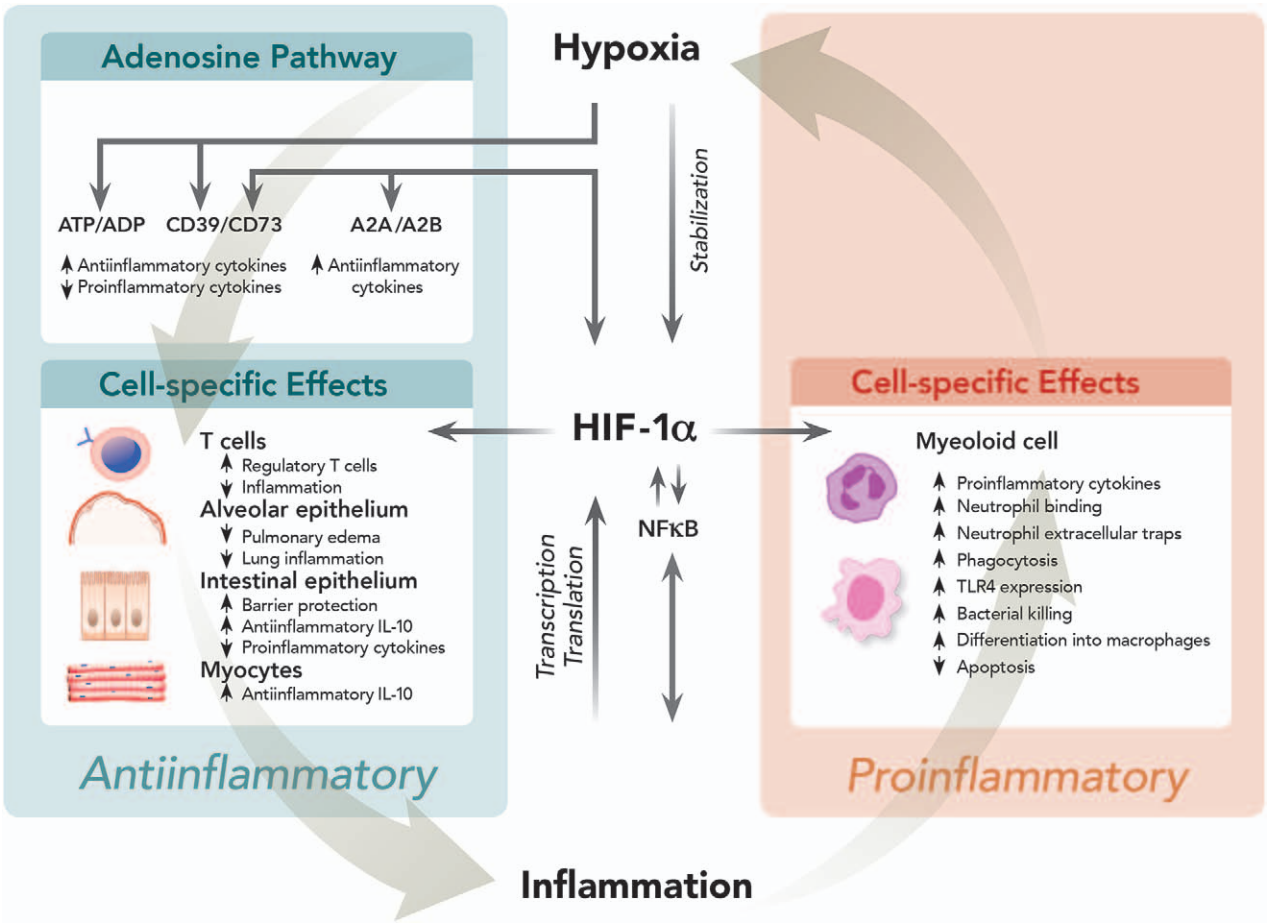

Fig. 2. The interaction between hypoxia and inflammation. Hypoxia enhances the immune response and is an inflammatory stimulus by itself. Hypoxia leads to cellular stabilization of hypoxia-inducible factor 1α (HIF-1α), resulting in a synergistic effect with the key inflammatory transcription factor nuclear factor of kappa-light-chain-enhancer of activated B cells (NF-κB). In addition, inflammation enhances transcription and translation of HIF-1α, leading to a synergistic effect in case of hypoxia and inflammation. In myeloid cells, such as neutrophils and monocytes, HIF-1α activity exerts proinflammatory effects, aimed at clearance of pathogens. Conversely, in many other cells, such as T cells, pulmonary and interstitial epithelium, and myocytes, HIF-1α activity has antiinflammatory effects. Furthermore, hypoxia exerts antiinflammatory effects through the adenosine pathway, as it increases the availability of adenosine progenitors adenosine triphosphate (ATP) and adenosine diphosphate (ADP), upregulates the converting enzymes CD39 and CD73 to enhance adenosine production, and increases the expression of the antiinflammatory adenosine 2A and 2B receptors (A2A and A2B). The up-regulation of CD73 and adenosine receptors is HIF-1α dependent. IL-10 = interleukin-10; TLR4 = toll-like receptor 4.

effects of these enzymes have been demonstrated in studies using knockout mice. For example, mice lacking either CD39 or CD73 display increased morbidity and mortality after inflammatory or ischemic injury.[88–90] Correspondingly, genetic overexpression of HIF-1α results in increased epithelial expression of CD73 and improves outcome in murine chemically induced colitis.[91] Finally, hypoxia increases the expression of the adenosine 2A (A2A) and 2B (A2B) receptors, the latter in a HIF-1α–dependent manner.[83] Stimulation of these receptors results in systemic antiinflammatory effects in murine models of ischemia–reperfusion,[89] hypoxia,[92] and inflammation.[93] Furthermore, permissive hypoxia (fraction of inspired oxygen [F_{IO_2}], 10%) attenuated lung damage and improved survival in a murine model of acute lung injury in an A2A receptor-dependent manner,[94] and induction of the A2B-receptor in type 1 alveolar cells during ventilator-induced lung injury was shown to be dependent on HIF-1α[3]. Similarly, hypoxic preconditioning protected mice from liver ischemia and reperfusion injury in an A2B receptor-dependent manner.[95]

The limited human data available substantiate that hypoxia results in enhanced adenosine availability. For instance, exposure to short-term hypoxia (20 min; Sa_{O_2}, 80%) in healthy volunteers increases plasma adenosine levels.[96] Furthermore, several experimental human studies have demonstrated antiinflammatory effects of adenosine signaling, as intravenous adenosine administration[97] as well as oral treatment with the adenosine uptake inhibitor

dipyridamole[98] attenuated the proinflammatory interleukin-6 response during experimental human endotoxemia, and dipyridamole treatment also augmented antiinflammatory interleukin-10 production.[98] However, increased adenosine availability in these latter studies was not induced by hypoxia. Finally, a proof-of-concept clinical study revealed that interferon-β-1a enhances CD73 expression in human lung tissue and that administration of this cytokine to acute respiratory distress syndrome (ARDS) patients is associated with reduced interleukin-6 and interleukin-8 levels as well as improved $Pa_{O_2}/F_{I_{O_2}}$ ratios and survival.[99]

In addition to HIF-1α, NF-κB, and adenosine metabolism and signaling pathways, other oxygen-sensitive transcription factors have been identified although the exact oxygen-dependent mechanisms and downstream effects are not fully elucidated (reviewed in Ref. [100]).

A schematic overview of the complex interplay between hypoxia and inflammation is depicted in figure 2.

Hypoxia in Critically Ill Patients

Hypoxic respiratory failure is a common condition in ICU patients, with an incidence of 22 to 33%,[101,102] depending on the definition (usually the need for mechanical ventilation and/or a $Pa_{O_2}/F_{I_{O_2}}$ ratio of less than 300 mmHg[101–103]), and is associated with a mortality of 31 to 52%.[101–103] A subcategory of hypoxic respiratory failure is ARDS, comprising 3 to 70% of patients with respiratory failure.[101–103] ARDS severity can be classified according to the Berlin definitions as mild (200 to 300 mmHg), moderate (100 to 200 mmHg), or severe (less than 100 mmHg), with mortality ranging from 32 to 65%.[103–109] It is important to differentiate between the diagnosis of hypoxic respiratory failure (*i.e.*, an indication for intubation and mechanical ventilation due to hypoxia) and actual hypoxia (*i.e.*, low Pa_{O_2}), as patients with hypoxic respiratory failure can have normal Pa_{O_2} levels. The occurrence of hypoxia (*i.e.*, Pa_{O_2} less than 80 mmHg) at ICU admission is frequent (40%),[110] and in a retrospective cohort study in Dutch ICU patients, hypoxia at ICU admission or during ICU stay was shown to be associated with increased mortality, even after correction for disease severity and other confounders.[110] The association between hypoxia at ICU admission and increased mortality was confirmed in a similar analysis in Australian and New Zealand ICU patients.[111] However, these studies are observational in nature, and although efforts have been made to eliminate bias, confounding factors may still play a role. Therefore, these studies cannot be used to guide oxygen therapy. Currently, oxygenation targets for critically ill patients are lacking. Since the landmark study on tidal volumes in ARDS, a target of 55 to 80 mmHg or Sa_{O_2} 88 to 95% is used in ARDS studies,[112] even though there is no solid evidence supporting these targets.[113]

Results of clinical trials on the effects of oxygenation in ICU patients are necessary to determine optimal oxygenation targets in diverse subsets of patients. Currently, the O2-ICU study randomizes ICU patients with systemic inflammation to either a target Pa_{O_2} of 120 or 75 mmHg (Clinicaltrials.gov Identifier NCT02321072). The Hyper2S study (Clinicaltrials.gov Identifier NCT01722422), in which patients with septic shock were randomized in a 2 × 2 fashion to normoxia (Sa_{O_2}, 88 to 95%) *versus* $F_{I_{O_2}}$ 100% for 24 h and resuscitation with isotonic saline *versus* hypertonic saline, was preliminary terminated because of a borderline significant increase in mortality in the hyperoxic/hypertonic group.[114] Additionally, the Air Versus Oxygen in ST-Segment Elevation Myocardial Infarction trial has shown that normoxic patients with ST-elevation myocardial infarction treated with supplemental oxygen exhibit increased creatine kinase levels and myocardial infarct sizes compared with normoxic patients who did not receive additional oxygen.[115] The putative harmful effects of hyperoxia have instigated further exploration of the safety and feasibility of conservative oxygenation targets. Two before-after studies in mechanically ventilated ICU patients applied Sa_{O_2} targets of 90 to 92%[116] and 92 to 95%,[117] respectively, which was not associated with adverse outcomes. The safety and feasibility of a conservative oxygenation strategy was recently affirmed by a randomized controlled pilot study comparing a liberal oxygenation strategy (SpO_2, greater than 96%) with a conservative strategy (SpO_2, 88 to 92%).[118]These results may pave the way for the exploration of a personalized oxygen target to influence inflammation in critically ill patients.

The Translation of Preclinical Data on Hypoxia and Inflammation toward Treatment in Critically Ill Patients

As illustrated by animal studies and the limited clinical data available, hypoxia and downstream signaling pathways may represent important and amendable factors in the pathophysiology of inflammatory conditions in critically ill patients, such as sepsis and lung injury. However, many hurdles still have to be taken before we can translate these insights into clinical practice. The host responses in inflammatory conditions in critically ill patients are complex, with considerable interindividual differences and changes over time. Nevertheless, it is conceivable that modulating the immune response toward a targeted, personalized, favorable immunologic phenotype, *e.g.*, immunostimulatory therapy in sepsis-induced immunoparalysis or antiinflammatory therapy in acute lung injury, may be of clinical benefit.[119] As many specific therapeutic target interventions have failed to show benefit in clinical trials,[120] it would be naive to assume that targeting hypoxia-dependent pathways is "the magic bullet." Nonetheless, optimization of all amendable parameters to tailor the inflammatory host response toward a more preferable profile should still be considered. As oxygen management is a daily practice in the ICU, the immunologic effects of oxygenation should therefore also be taken into account as a means of optimizing host responses.

Although grossly based on *in vitro* and animal data, oxygenation-dependent immunomodulatory strategies could be envisioned as either pursuing a nullification of hypoxia-induced immunologic effects by preventing hypoxia or enhancing immunologic effects of hypoxia by preventing hyperoxia or even permitting or inducing hypoxia. For example, animal data suggest that averting hyperoxia and even permitting hypoxia is beneficial in acute lung injury,[94] apart from prevention of direct oxygen toxicity. Naturally, intentional or permissive hypoxia as a therapeutic strategy is only expedient when safety margins are taken into account, especially as Pa_{O_2} targets would be at the steep part of the oxygen–hemoglobin dissociation curve. As previously proposed, a suitable oxygenation monitoring and control system should use real-time data on pulse oximetry, tissue oxygenation, and arterial oxygen tension to achieve a predefined oxygenation[121] and should naturally be extensively tested for safety, feasibility, and efficacy.

However, caution is warranted, as there is an association between long-term neurocognitive impairment and the amount of time that ARDS patients were hypoxic (*i.e.*, Sa_{O_2}, less than 90%).[122] Therefore, short-term benefits of hypoxia, *i.e.*, putative therapeutic effects in inflammation, and long-term effects, *i.e.*, neurocognitive impairment, need to be carefully weighed.

Alongside hypoxia, or if permissive hypoxia does not prove to be feasible, HIF-1α–mediated effects could also be pursued through pharmacologic inhibition of PHDs. The PHD inhibitor FG-4497 increased HIF-1α stabilization in mice, with subsequent resistance of stem cells to irradiation,[123] improved kidney transplantation survival,[124] and attenuated TNFα expression and weight loss during colitis.[58] A comparable PHD inhibitor (FG-2216) resulted in increased plasma erythropoietin levels in hemodialysis patients[125]; however, due to a case of fatal hepatic necrosis and other patients developing abnormal liver enzyme tests, the U.S. Food and Drug Administration suspended this clinical trial, and further development was discontinued.[126] Nonetheless, clinical trials with new drugs targeting PHDs for treatment of anemia in patients with chronic renal disease and dialysis are currently being performed.[26] Whether pharmacologic HIF stimulation affects the immune response in humans has not been established yet. Additionally, the frequently used PHD inhibitor dimethyloxalylglycine and the aforementioned FG compounds are pan-hydroxylase inhibitors and are not specific for HIF-1α stabilization, which may lead to undesired effects. For example, dimethyloxalylglycine also stabilizes HIF-2α, which results in increased erythropoietin levels[58,59] and could thus cause polycythemia. This can be circumvented by more specific PHD inhibitors, such as the selective PHD-1 inhibitor AKB-4924 and/or local instead of systemic drug delivery.[69]

Taken together, although the concept of tailoring the immune response through oxygenation or pharmacologic modulation of hypoxia-signaling pathways is tempting, the question remains if this approach is feasible and will result in clinical benefits for the patient. Therefore, studies assessing the putative therapeutic potential of these effects are highly warranted. Furthermore, immunomodulatory therapy in inflammatory conditions in the ICU still faces many challenges. For example, antiinflammatory strategies in sepsis have been unsuccessful in the past,[120] possibly because they render patients increased vulnerability to secondary infections, although it might also be due to the profound heterogeneity of this patient population. Immunostimulatory therapy to prevent and/or reverse immunoparalysis is currently under investigation for sepsis.[77] Meanwhile, a search for markers identifying the current "immune status" of ICU patients is ongoing and may result in better identification of patients who could benefit from immunomodulating therapy.[127]

Conclusion

There is extensive interplay between hypoxia and the immune system. Hypoxia and inflammation synergistically induce HIF-1α stabilization, resulting in cellular effects directed toward augmented pathogen clearance, of interest, simultaneously antiinflammatory and tissue-protective mechanisms occur, for instance through enhanced adenosine metabolism and signaling. The net effect of these effects is highly dependent on the cell type and activation state. Insights into these hypoxia-driven mechanisms promote the concept of personalizing oxygenation targets to tailor the immune response in inflamed critically ill patients. However, the development of such strategies requires exploration of the putative effects of hypoxia on the immune response in humans *in vivo*, as these data are currently lacking. Furthermore, additional studies on pharmacologic HIF-1α stabilizers and agents acting on the adenosine pathway are required. In any case, the optimal Pa_{O_2} and oxygen delivery in critically ill patients are likely to depend on diagnosis and comorbidities, and clinicians should be aware that their oxygen therapy may affect not only saturation but also the inflammatory host response. As clinical guidelines on optimal oxygenation are currently not present, ongoing clinical trials exploring the feasibility of liberal *versus* restrictive oxygenation are highly warranted and currently in progress; these could further pave the way toward individualized oxygenation therapy.

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Competing Interests

The authors declare no competing interests.

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