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Involvement of Hypoxia-Inducible Factors in the Dysregulation of Oxygen Homeostasis in Sepsis

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Abstract: Sepsis is a state of infection with serious systemic manifestations, and if severe enough, can be associated with multiple organ dysfunction and systemic hypotension, which can cause tissues to be hypoxic. Inflammation, as part of the multifaceted biological response to injurious stimuli, such as pathogens or damaged tissues and cells, underlies these biological processes. Prolonged and persistent inflammation, also known as chronic inflammation, results in progressive alteration in the various types of cells at the site of inflammation and is characterized by the simultaneous destruction and healing of tissue during the process. Tissue hypoxia during inflammation is not just a simple bystander process, but can considerably affect the development or attenuation of inflammation by causing the regulation of hypoxia-dependent gene expression. Indeed, the study of transcriptionally regulated tissue adaptation to hypoxia requires intense investigation to help control hypoxia-induced inflammation and organ failure. In this review, I have described the pathophysiology of sepsis with respect to oxygen metabolism and expression of hypoxia-inducible factor 1.

Keywords: Chemokine, cytokine, hypoxia, hypoxia-inducible factor, inflammation, NF-κB, sepsis.

INTRODUCTION

"Sepsis" is historically derived from the Greek word for the state of putrefaction or decay in a body. Today, it is recognized and referred to as the disseminated inflammatory response primarily induced by microbial, and sometimes viral, infection [2, 3]. However, sepsis is a complicated syndrome [3, 4]. It comprises a layer of clinical conditions caused by the response of body to mainly bacterial infection. In a severe form, sepsis is accompanied by organ dysfunction or failure. In fact, it is a major cause of mortality. It is estimated that more than one thousand people die daily from sepsis [2, 5, 6]. Although mortality rates from sepsis have dropped in recent years, patients suffering from severe sepsis are graded on a scale similar to that of cancer, and is one of the leading causes of death in the intensive care units and (ICU) and high care units around the world [3, 6-8].

Sepsis is caused by the multi-system responses to a serious infection, most commonly caused by bacteria in the blood, lungs, urinary tract, biliary tract, or other organs and tissues [6, 9, 10]. However, the site of original infection cannot always be identified, and the type of infective organism may provide no additional clues [3]. Sepsis confers a line of symptoms. Common symptoms are not only a specific infection, but also usually accompanied by high fever, tachycardia, hyperventilation, altered mental status, and hypotension or "septic shock." However, the pattern of symptoms may be atypical (e.g., hypothermia) and lacking an easily localizable infection, especially in immunocompromised patients [3].

According to the American College of Chest Physicians and the Society of Critical Care Medicine, sepsis can be defined in different ways [3, 11]:

> "•Systemic inflammatory response syndrome (SIRS) is the presence of two or more of the following: abnormal body temperature, heart rate, respiratory rate or blood gas, and white blood cell count.
>
> •Sepsis is defined as SIRS in response to an infectious process, which can be triggered by many things other than sepsis.
>
> •Severe sepsis is defined as organ dysfunction due to an infection, while septic shock is severe sepsis plus persistently low blood pressure following the administration of intravenous fluids."

Due to rapid endothelial dysfunction, microthrombi may occur by activation of the coagulation system, resulting in drastic changes in blood rheology and causing organ failure due to hypoperfusion or misperfusion. These phenomena also lead to lack of oxygen supply in the tissues or organs due to hypoperfusion of blood. Moreover, proinflammatory cytokines suppress the oxygen utilization of mitochondria, resulting in a change of metabolic pathway from oxidative phosphorylation to glycolysis, thus causing cells to change their mode of metabolism to glycolytic or anaerobic.

In this review, I have described the pathophysiology of sepsis from the perspective of oxygen metabolism and the activation of the transcription factor hypoxia-inducible factor 1 (HIF-1).

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SYSTEMIC INFLAMMATORY RESPONSE IN THE PATHOPHYSIOLOGY OF SEPSIS

Inflammation consists of a multifaceted biological response to pathogens or damaged tissue and cells. Four fundamental or rather classical signs: dolor (pain), calor (heat), rubor (redness), and tumor (swelling), historically characterize it [12, 13].

Inflammation is one of the initial or primitive responses that is triggered by pathogens, and is considered one of the common mechanisms of innate immunity.

Inflammation can be classified as being either acute or chronic based on its time span [14]. Acute inflammation is the initial and rapid response of the body to pathogens and injurious stimuli. The increased movement of plasma and leukocytes from the blood stream into the injured or affected interstitial tissues accompanies it. A cascade of biological processes induces the inflammatory response in the vascular and immune systems [12]. In contrast, chronic inflammation is a prolonged and persistent process. It results in a progressive shift in the type of cells present at the sites of inflammation, and is characterized by concomitant remodeling of the injured tissues [12].

VASCULAR AND ENDOTHELIAL DYSFUNCTION IN SEPSIS

One of the distinctive features of sepsis is the modification of microvascular function. Septic status induces rapid and profound changes in the function of endothelial cells (ECs), with the widespread damage and apoptosis of ECs playing a critical role in the pathophysiology of sepsis [6, 7, 15].

The immune and coagulation systems are critically regulated by ECs. Furthermore, because ECs consist the inner most surface of blood vessels, they regulate the blood flow to the solid organs and tissues; thus, endothelial activation and damage are closely related to organ dysfunction [16]. ECs mediate multiple biological functions and provide a connection between the local and systemic immune response. Thus ECs are not only a source of, but also a target for inflammation. Local activation of ECs is crucial for terminating infection. On the other hand, systemic activation of ECs may result in capillary leakage, micro thrombosis resulting in tissue or organ hypoxia, and multiple organ dysfunction [12, 16-18].

The release of multiple cytokines and chemokines in large quantities by the immune system (referred to as an excessive surge of cytokines, or a cytokine storm) and endotoxin from bacteria has an adversely disruptive effect on the host's EC functions [17]. Inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin-1 beta (IL-1β), destabilize interactions between ECs and disable vascular barrier function [19, 20]. Due to rapid changes in the function of ECs, microthrombi occur by activation of the clotting system, resulting in changes in blood rheology and causing organ failure due to hypoperfusion [7, 21]. Disruption of blood perfusion also confers hypoxia on the tissues or organs [5, 6]. Moreover, proinflammatory cytokines suppress the oxygen utilization of mitochondria, resulting in conversion from oxidative phosphorylation to glycolysis (metabolic switch).

THE INTERDEPENDENCE OF HYPOXIA AND INFLAMMATION

Tissue hypoxia in the presence of inflammation is not just a consequence of decreased blood supply. It can significantly influence the development or termination of inflammation by the regulation of expression of hypoxia-dependent genes [22].

Increased oxygen demands of infiltrated immune cells, reduced supply of metabolic substrates by blood clots and compression of blood vessels, and atelectasis of lung contribute to tissue hypoxia during inflammation. Inflamed tissue commonly constitutes hypoxia, hypoglycemia, acidosis, and increased production of free radicals and reactive oxygen species (ROS) [23, 24]. Thus, at the site of tissue inflammation, dysregulation of oxygen metabolism modulates the environment of the tissue by regulating hypoxia-induced gene expression.

The concept that hypoxia by itself can elicit inflammation has been generally accepted through a line of studies of the hypoxia-induced signaling pathway [22, 23, 25, 26]. The development of inflammation in response to tissue hypoxia is frequently observed in the clinical setting. In fact, it is reported that ischemia in organ grafts increases the risk of inflammation and graft failure or rejection [27]. The relationship is also observed in acute respiratory distress syndrome (ARDS), in which tissue hypoxia and systemic inflammation are typically seen [28]. In the case of obesity, an imbalance between the supply of, and demand for, oxygen causes hypoxia and increase inflammatory adipokines in adipose tissue [29]. The infiltrated macrophages and chronic low-grade systemic inflammation promote insulin resistance. Exposure to ambient hypoxia, as seen during high-altitude mountaineering, is associated with edema of the lungs or brain, and systemic inflammatory responses (like acute mountain sickness) in humans [30, 31]. Similarly, short-term exposure of mice to environmental hypoxia leads to elevated concentration of inflammatory chemokines and cytokines and pulmonary edema [30, 32, 33]. Taken together, the evidence indicates that hypoxia promotes inflammation.

Pathogen invasion is aided by destruction of the lining layers of epithelia and endothelial cells by mechanical or inflammatory injury. Through the damaged barriers, neutrophils invade the site of inflammation, followed by the infiltration of innate immune cells such as macrophages and activation of dendritic cells. Inflammatory responses consist of ROS and/or reactive nitrogen species formation, cytokine production, and activation of adaptive immune cells. The inflammatory responses elicited by pathogens occur in the interstitial space that is hypoxic. Blood supply to the site is restricted because vessels are clogged with immune cells and thrombi, damaged by primary injury, or constricted by proinflammatory cytokines and chemokines. Moreover, at

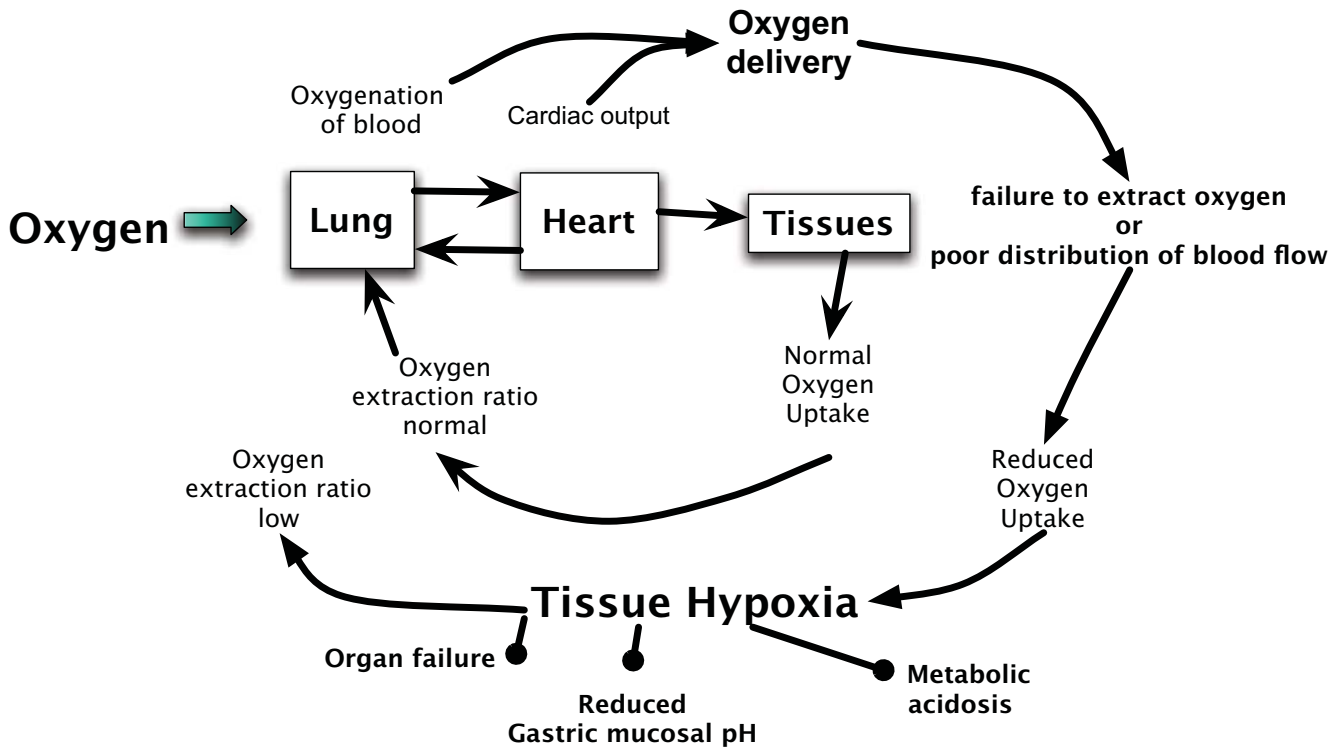

Fig. (1). Regulation of oxygen delivery. In sepsis or a systemic inflammatory response, distribution of blood flow is largely abnormal. Moreover, tissues and organs fail to use oxygen. Responses to hypoxia induce dysregulation in organ function. Original plan of this figure was based on [5, 79].

sites of inflammation, O_2 consumption is elevated. The eradication of pathogens demands immune cell surveillance and requires the adaptation of immune cells to reduced oxygen availability (Fig. **1**). The cellular hypoxic response, including sense and coordination responses, is largely carried out by the transcription factor hypoxia-inducible factor (HIF) [34] (Table **1**).

INDUCTION OF HIF ACTIVATION BY CONTINUOUS HYPOXIA

HIF-1 was identified and purified as a nuclear factor that was induced in hypoxic cells and bound to a cis-acting hypoxia response element (HRE). Although HREs were initially identified in the 3′-flanking region of the human EPO gene, which encodes erythropoietin [35, 36], they were also later found in the regulatory region consisting of more than 1,000 hypoxia-inducible genes [37].“HIF-1 is a heterodimeric transcription factor composed of an HIF-1αand an HIF-1β subunit. Both HIF-1 subunits are members of the basic helix-loop-helix PER-ARNT-SIM domain (bHLH-PAS) family of transcription factors. The HLH and PAS domains mediate heterodimer formation between HIF-1αsubunits and HIF-1β subunits, which is necessary for DNA binding by the basic domains” [35, 38].

In humans, as well as other mammals, the *HIF1A*, *EPAS1*, and *HIF3A* genes have been shown to encode HIF-1αand the structurally related proteins HIF-2α and HIF-3α, respectively. HIF-1α and HIF-2α are similar to each other in structure and the function. Intracellular expression of these proteins is hypoxia-induced, and these proteins dimerize with HIF-1β and mediate HRE-dependent transcriptional activity. However, HIF-1 and HIF-2 regulate distinct groups of target genes *in vivo*. In contrast, HIF-3α appears to function as an inhibitor that is involved in the negative regulation of transcriptional responses to hypoxia [38].

Whereas HIF-1βproteinalso known as ARNT is constitutively expressed in the cells regardless of oxygen tension, HIF-1α protein expression increases exponentially in response to reduced O_2 concentration. For rapid response to hypoxic insults, cells continuously produce and degrade HIF-α including HIF-1α and HIF-2α proteins in an ubiquitin system-dependent manner even under non-hypoxic conditions. During hypoxic conditions, the degradation of HIF-αis inhibited, resulting in accumulation of the protein, dimerization with HIF-1β, binding to HREs within target genes, and activation of transcription *via* recruitment of the coactivators, p300 and CBP (CREB-binding protein; Fig. **2**).

Hydroxylation of evolutionally well-conserved two prolyl residues of HIF-α (Pro402 and Pro564 in human HIF-1α) facilitate interactions between HIF-α and the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex that conveys HIF-1α (as well as HIF-2α and HIF-3α) to the proteasome complex for degradation [39, 40]. “These hydroxylated residues are present within a conserved motif that is recognized by HIF-1αprolyl hydroxylases, which utilize O_2 as a substrate with a Michaelis constant (K_m) that is slightly

Table 1. Inflammatory mediators activating HIF.

Mediators and Pathogens	Mechanism	Reference
Hypoxia	Inhibition of PHD	[41]
Intermittent hypoxia	Inhibition of PHD by ROS	[47]
	Induction of HIF-1α transcription	[50]
ROS	Oxidative modulation of PHD	[56]
	Oxidation of Fe (II)	[56]
NO	Increase of HIF-1α translation	[54]
	Inhibition of PHD	[93]
	S-nitrosylation of HIF-1α	[94]
Cytokines (TNF-α, IL-1β)	Increase of HIF-1α translation	[51]
Chemokines (MIF, SDF-1)	Increase of HIF-1α translation	[95]
	Stabilization of HIF-1α	[96]
Thrombin	Increase of HIF-1α translation	[97]
PGE_2	Increase of HIF-1α translation	[98]
LPS	Increase of HIF-1α translation	[53]
	Induction of HIF-1α transcription	[53]
Monocyte differentiation	Increase of HIF-1α translation	[69]
	Induction of HIF-1α transcription	[69]
Bacteria	Inhibition of PHD	[9]
	Increase of HIF-1α translation	
Acidosis	Increase of HIF-1α stabilization	[99]

ROS: reactive oxygen species, NO: nitric oxide, TNF: tumor necrosis factor, MIF: macrophage inhibitory factor, SDF: stromal cell-derived factor, PHD: prolyl hydroxylation domain-containing protein

above atmospheric concentration, such that enzymatic activity is modulated by changes in O_2 concentration under physiological conditions [1]". A family of three human HIF-1α prolyl hydroxylases (prolyl hydroxylase domain-containing proteins (PHDs),) were identified. Those are encoded by the *EGLN2*, *EGLN1*, and *EGLN3* genes, respectively [41]. Factor-inhibiting HIF-1 (FIH-1) also hydroxylates an asparaginyl residue in the transactivation domain of HIF-1α (Asn803 in human HIF-1α). Hydroxylation of Asn803 inhibits the interaction of the HIF-1αtransactivation domain with the transcriptional coactivators CBP and p300 [42, 43].

The hydroxylation reactions require O_2, Fe (II), and α-ketoglutarate (also known as 2-oxoglutarate) as substrates and generates succinate and CO_2 as side-products. The PHDs and FIH-1 possess a double-stranded α-helix core and Fe (II)-binding residues that are also present in other members of the dioxygenase family, such as the procollagen prolyl 4-hydroxylases [38, 44].

It is reported that HIF-1 is responsible for over hundred genes transccriptional induction in response to hypoxia [25]. In addition, a study of global gene expression analysis adopting DNA microarrays indicates that more than 2% of all human genes expression is under direct or indirect regulation of HIF-1 in human umbilical endothelial cells [37, 45, 46].

INDUCTION OF HIF-1 ACTIVITY BY INTERMITTENT HYPOXIA

Systemic hypoxia can be either continuous or intermittent. Systemic intermittent hypoxia (IH) is a commonly observed and life-threatening condition that occurs in many different diseases and situations, including obstructive sleep apnea syndrome and surgical operations (Fig. **2**). IH increases HIF-1α protein levels and consequent gene expressions. The mechanisms of HIF-1α increase are considered to be different from that of continuous hypoxia and still to be investigated. But a line of studies indicates that the mechanism may involve increased translation of HIF-1αprotein from activation of the mammalian target of rapamycin (mTOR). IH also increases activity of the rate-limiting enzyme of catecholamine tyrosine hydroxylase (TH). This effect is mediated by calcium/calmodulin-dependent protein kinase (CaMK). Under IH, Ca^{2+}-dependent activation of CaMK stimulates HIF-1 transcriptional activity by phosphorylation of p300 [47]. These studies suggest that IH stimulates transcriptional, as well as post-translational, mechanisms. Interestingly, treatment with antioxidants or

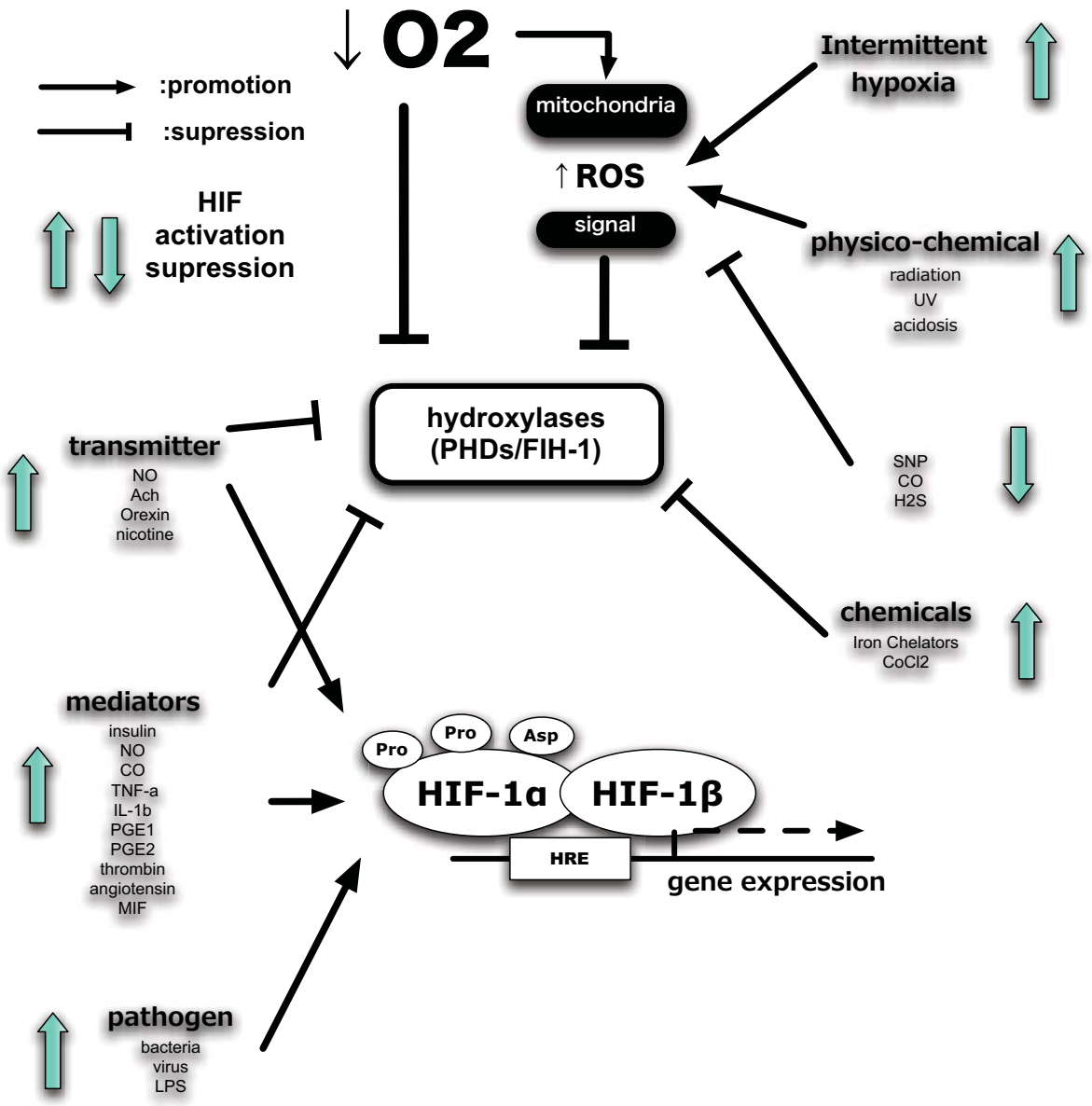

Fig. (2). Regulation of HIF-1 in sepsis. Under normoxic conditions, the prolyl hydroxylases (PHDs) hydroxylases hypoxia-inducible factor 1α (HIF-1α) usign molecular O_2 at amino acid residues 402 and 564. Hydroxylated proryl residues are target for polyubiquitylation of the HIF1α protein by von Hippel–Lindau (VHL) tumor suppressor protein. The uniqutined HIF1α are transported to the proteasomes and degradated. The asparaginyl hydroxylase factor inhibiting HIF-1 (FIH-1; also known as HIF1AN) functions in conjunction with the prolyl hydroxylation. The asparagine residue is located in the HIF-1α carboxy-terminal domain, which serves as a strong transcription facilitator. As all of these post-translational events depend on intracellular oxygen, they are inhibited by intracellular oxygen deprivation. In addition to hypoxia, HIF-1 can be activated by a microenvironment affected by sepsis and systemic inflammation. HRE: hypoxia response element, PHD: prolyl hydroxylation domain, FIH-1: factor-inhibiting HIF-1, SNP: sodium nitroprusside, ROS: reactive oxygen species, LPS: lipopolysaccharide

ROS scavengers suppresses the IH-induced HIF-1 activation, indicating a critical involvement of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-derived ROS in this process [47-50].

INDUCTION OF HIF-1 ACTIVITY UNDER NON-HYPOXIC CONDITIONS

Cytokines and chemokines are mediators of inflammation (Fig. **2**). They are involved in the regulation of phagocyte activity, and in the recruitment of leukocytes; they also cause fever, which is a typical symptom of local and systemic inflammation. Both the proinflammatory cytokines TNF-α and IL-1β are reported to activate HIF-1 [51]. TNF-α and IL-1βactivate HIF-1 *via* multiple pathways, including ROS and nitric oxide (NO) production and phosphoinositide 3-kinase (PI3K) and/or nuclear factor κB (NF-κB) activation [51]. Moreover, mediators of the inflammatory micro-environment, including adenosine and lipopolysaccharide

(LPS), also activate HIF-1. Expression of HIF-1αproteinis induced after stimulation of the adenosine receptor and toll-like receptor 4 (TLR-4) in a PI3K-dependent, ROS-dependent/ROS-independent, manner [14, 52, 53]. Increase in protein translation shifts the balance by overwhelming the degradation system, resulting in HIF-1α; the steady state of HIF-1α expression is mainly determined by the hydroxylation-mediated degradation system in proteasomes.

Accumulating evidence indicates that NO, regardless of exogenously added or endogenously produced, accumulates HIF-1α protein and causes transactivation of HIF-1 under normoxic conditions (20% O_2) [51, 54] (Fig. **2**). NO decreases PHD activity and inhibits HIF-1αubiquitination, suggesting that hypoxia and NO adopt synergistic intracellular pathways to stabilize and increase HIF-1αprotein [51]. Another study report using the NO donor NOC-18 has also proposed that NO increases PI3K activity and HIF-1αprotein translation in a mTOR-dependent manner even under normoxic conditions [54]. In contrast, when HIF-1αexpression is analyzed under 1% O_2conditions, treatment by a NO donor (DETA/NO) suppresses accumulation of HIF-1αprotein by affecting the mitochondrial electron transfer chain [55]. This paradox can be explained by an observation that NO competes with O_2 for binding to mitochondrial cytochrome oxidase, which consumes most of the oxygen within the cell [55]. Inhibition of PHDs by NADPH oxidase-mediated ROS production is proposed as the underlying regulatory principle. In fact, exogenous H_2O_2 also induces expression of HIF-1α protein and increases HIF-1 activity. It is reported that ROS oxidize Fe (II) at the catalytic site of PHDs, thus blocking the activity [56]. Another possibility is that ROS inhibits the PHDs by oxidation of active site amino acids. These possibilities imply that an increase in ROS during inflammation may contribute to HIF-1αaccumulation and its activation.

INTERACTION BETWEEN NF-κB AND HIFs

HIFs play a crucial role in the cellular hypoxic response. However, these are not the only molecules that regulate sensitivity to environmental oxygen concentrations. So far, more than twenty different transcription factors have been reported to mediate different kinds of hypoxic response directly and indirectly [57] (Fig. **3**).

Members of the NF-κB family of transcription factors are identified to be one of the main regulators of biological processes, such as inflammation and immune responses, and

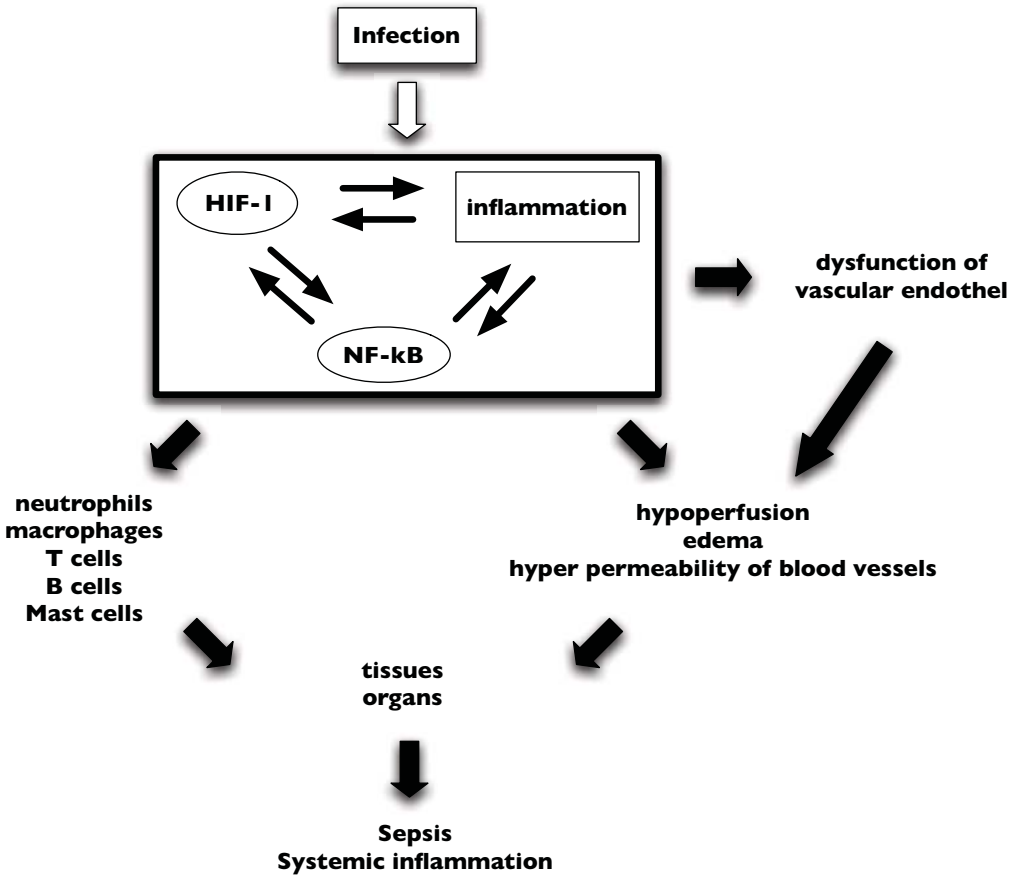

Fig. (3). Interdependence of HIF-1 and NF-κB. The transcription factors HIF-1 and NF-κB interdependently act on each other involving in intracellular regulation of inflammation. Thus, the interaction between the transcription factors, which are under regulation by oxygen metabolism of the inflammation site, plays an essential role in the progress of sepsis. The evidence strongly suggests that the oxygen homeostasis can be a therapeutic target of sepsis.

serve as a regulator of tissue oxygen homeostasis. It has recently become apparent that HIF and NF-κB crosstalks with each other in hypoxic inflammation. Studies using *in vitro* systems have generated results that show that HIF-1α activates NF-κB that controls HIF-1α transcription from the genome. HIF-1α activation may occur concurrently with the inhibition of NF-κB [58, 59].

Activity of NF-κB is tonically regulated by IκB kinases (IKKs). IKKβ mediates degradation of IκB in response to inflammatory insults. Hypoxia inhibits prolyl hydroxylases that negatively modulate IKK β catalytic activity and activates NF-κB. It is also reported that HIF-1 mediates NF-κB activation in neutrophils under hypoxic conditions and promotes the expression of NF-κB-regulated cytokines in macrophages stimulated by LPS in a TLR4-dependent manner [58, 59].

It is reported that NF-κB contributes to increase *HIF1A* mRNA transcription under hypoxic conditions [60]. The activation of *HIF1A* transcription by LPS under normoxic, as well as hypoxic, conditions has been recently confirmed in a study adopting mice deficient in IKKβ. A marked defect in HIF1αexpression in macrophages is observed in mice harboring deletion of gene encoding IKKβ even when the mice are exposed to Gram-positive or Gram-negative bacteria and hypoxic conditions. The evidence clearly indicates that transcriptional activation of *HIF1A* by IKKβ is a crucial precursor to posttranscriptional stabilization and accumulation of HIF-1α [60] (Fig. **3**).

HIF-1 AND IMMUNE CELLS

Accumulating evidence indicates that HIFs are key regulators of the intrinsic immune and inflammatory responses [9, 61]. Effector cells, which play a crucial role in the innate immune system, must preserve their viability and maintain their physiologic functions in microenvironments with low oxygen levels [62]. Monocytes circulating in the bloodstream differentiate into macrophages at the site of inflammation. During this process, cells must acquire the ability to perform or exert effects at the hypoxic inflammatory sites such as interstitial tissue [62, 63] (Table **2**).

Neutrophils are one of the key players in innate immunity. Because these cells largely rely on glycolysis to generate ATP for their killing activity, they must adapt to hypoxic microenvironments at sites of inflammation. Cramer *et al.* created conditional knockout mice, which allowed specific deletion of HIF-1α in a myeloid cell lineage [64]. They analyzed the role of HIF-1α and the transcription factor HIF-1 in myeloid cell function *in vivo* by adopting this mice model. The mice have a normal phenotype and viability. However, the mice without HIF-1α displayed a significant reduction in cellular ATP concentration and a severe myeloid cell dysfunction including cell aggregation, motility, invasiveness, and reduced bacterial killing [64, 65]. Importantly, the ATP shortage is observed under normoxic conditions, suggesting that activation of HIF-1is essential for the maintenance of energy metabolism in myeloid cells, even in physiologically oxygenated environments.

The role of HIF in regulating neutrophil apoptosis at the site of inflammation *in vivo* is another issue. Apoptosis itself has been implicated in the resolution of inflammation, and excessive neutrophil activation and prolonged survival have been described in several disease settings, including ARDS and non-resolving pneumonias [59]. Considering the exaggerated oxygen gradient that exists at many inflamed sites, it is probable that a role for HIF in the regulation of neutrophil apoptosis in these settings [61, 66, 67].

A lack or deficiency of oxygen and the dramatic recruitment of immune cells such as macrophages and neutrophils characterizes inflammatory regions. The recruitment of myeloid cells to sites of inflammation is mediated by the β2 integrin family of adhesion receptors [68]. The β2 integrins are heterodimeric glycoproteins. β2 integrin subunits expression is regulated by HIF-1 [68]. Analysis of these mutant mice demonstrated that HIF-1α is critically important for successful inflammatory responses mediated by myeloid cells. However, the disruption of HIF-1α did not influence myeloid cell differentiation or development. As described, HIF-1αdeletion did result in significant metabolic defects manifested as profound impairment of myeloid cell motility, bacterial phagocytosis, and aggregation [64]. Interestingly, these functional responses are also dependent on β2 integrin expression [64, 68].

Increased expression of both HIF-1α and HIF-1β, as well as increased HIF-1 transcriptional activity are observed during the differentiation of human acute monocytic leukemia cell line THP-1 cells or monocytes from peripheral

Table 2. Immune cells involved in innate and adaptive immunity.

	Innate Immunity	Adaptive Immunity
Type of Cells	PMN, macrophage, DC	T cell, B cell, NK cell
Activation Cue	Differentiation, recruitment	Proliferation
Metabolic Regulator	HIF, mTOR, Akt	HIF, mTOR, Akt
Mitochondria	Few	Many
Primary Energy Source	Glycolysis	Oxidative phosphorylation

PMN: polymorphonuclear leukocyte

blood to macrophage [69]. The activation of HIF-1 in differentiated or activated THP-1 cells results from the combined effect of increased HIF-1α mRNA and protein levels [53, 69]. Differentiation-induced HIF-1αprotein and mRNA and HIF-1-dependent gene expression, but not differentiation by itself, was blocked by treating cells with an inhibitor of protein kinase C or mitogen-activated protein kinase (MAPK) signaling pathways.

Dendritic cells (DCs) are specialized antigen presenting cells that act as a critical mediator bridging innate and adaptive immunity. External signals such as stimulation of TLR agonists induce maturation of DCs, leading to an adaptive immune response mediated by T-cells. The stimulation to TLR4 and TLR2 induce the expression of HIF-1αin human monocyte-derived DCs (MoDCs) under normoxic conditions [70, 71]. On a functional level, inhibition of the transcription factor HIF-1 using HIF-1α-inhibitors such as YC-1 and digoxin leads to no consistent effect on MoDC maturation or cytokine secretion as in the case of macrophages [69, 70]. In addition, TLR stimulation resulted in an increase of HIF-1α-dependent vascular endothelial growth factor (VEGF) secretion [53].

The differentiation of T cells into distinct functional effectors and inhibitory subsets is also regulated by the microenvironment. Several studies demonstrate that HIF-1 regulates the balance between regulatory T cell (Treg) and T helper 17 cell (Th17) differentiation [72]. HIF-1 induces Th17 development through direct transcriptional activation of RORγt and *via* tertiary complex formation with RORγt and p300 recruitment to the IL-17 promoter [72]. At the same time, HIF-1 suppresses Treg development by binding Foxp3 and targeting it for proteasomal degradation. Interestingly and importantly, this regulation is not dependent on oxygen environment. Together, the findings indicate the significance of metabolic triggers in T cell fate determination and suggest that metabolic modulation could ameliorate certain T cell-based immune pathologies [73, 74].

Peripheral T lymphocytes undergo activation by antigenic stimulation, and function in hypoxic inflammatory circumstances. CD3-positive human T cells accumulating in inflammatory environment express HIF-1α. The evidence indicates a critical role of hypoxia-mediated signals in regulation of T cell function [75]. The mechanism of HIF-1α stabilization in T cells appears to be similar to that in myeloid cells, as engagement of T cell receptors (TCRs) by foreign antigens up-regulates HIF-1α *via* PI3K/mTOR signaling pathway. "Together, these reports demonstrate that stabilization of HIF-1αin the context of inflammation and immunity can occur through multiple signaling cascades in both normoxic and hypoxic environments. Accumulation of HIF-1αin human T cells required not only hypoxia but also TCR/CD3-mediated activation [76]. Moreover, hypoxia repressed activation-induced cell death by TCR/CD3 stimulation, resulting in increased cell survival" [14, 75, 76].

Mast cells are granulocytic cells that localize in the skin and the mucosa of the respiratory and gastrointestinal tracts. It is demonstrated that activation of HIF-1 in human mast cells is followed by release of proinflammatory cytokines including IL-8 and TNF-α [77]. It is also shown that HIF-1 activation in mast cells of the bronchial epithelium stimulates VEGF expression, leading to increased vascular permeability, protein extravasation into the alveolar space, and airway edema [78]. Moreover, HIF-1 activation induces histidine decarboxylase gene expression catalyzing the formation of histamine [77].

OXYGEN METABOLISM AND SEPSIS

The monitoring of the transportation of oxygen, the regulation of its distribution between and within organs or tissues, and cellular metabolism are essential in the clinical management of critically ill patients [5, 79]. Patients with sepsis have a hemodynamic disturbance characterized by an increased cardiac output and reduced systemic vascular resistance [5]. Although delivery of oxygen may be maintained or even increased by pharmacological means, most patients have poor peripheral uptake of oxygen. The cause of this phenomenon remains still to be examined. Sepsis and SIRS are associated with damage to the vascular endothelium, which normally produces vasoactive substances that regulate microvascular blood flow to ensure that all organs are adequately oxygenated. The microcirculation may therefore be disrupted. This is one of the explanation of poor oxygen extraction in septic patients. In addition, inflammatory mediators may directly modulate the intracellular mechanisms that regulate the availability of oxygen (Fig. **1**).

"In clinical settings, each patient's response to the activation of inflammatory cascades can be determined by abnormalities of gene transcription and regulation that modulate the release of vasoactive substances such as NO, endothelins, and cyclooxygenase products, such as thromboxanes and prostaglandins. Additionally, changes in the effectiveness of endogenous defense systems, such as cellular antioxidant protection, repair, and apoptosis may be relevant in determining outcomes. In any event, the clinical result of these disturbances is tissue hypoxia [1]".

Plasma lactate, which is recognized as an end product of glycolysis, is routinely used as a marker of tissue hypoxia in states of shock [80, 81], as well as in the prediction of patient outcomes. However, plasma lactate concentrations are influenced by both the production and clearance of lactate, which can be a limitation for the interpretation of plasma lactate concentrations at the bedside. Several studies have demonstrated an increased expression of HIF-1αin patients' whole blood with shock from sepsis, hemorrhage, and cardiac dysfunction [80, 82, 83].

LPS increases the level of the transcriptional regulator HIF-1αin macrophages, increasing HIF-1α and decreasing prolyl hydroxylase mRNA production in a TLR4-dependent fashion. Murine conditional gene targeting of HIF-1α in the myeloid lineage model demonstrates that HIF-1α is a critical determinant of the sepsis phenotype [84]. It is demonstrated that the deletion of HIF-1α in the myeloid lineage reduced

LPS-induced hypothermia. Resistance against LPS-induced hypotension was also observed in the myeloid-specific HIF-1α null mice compared to the controls of wild type. With improvement in this hemodynamic parameter, the shock index was significantly decreased in HIF-1αmyeloid null mice compared with the WT controls [84].

"HIF-1α promotes the production of inflammatory cytokines (including TNF-α, IL-1, IL-4, IL-6, and IL-12) that reach harmful levels in the host during early sepsis. HIF-1α deletion in macrophages is protective against LPS-induced mortality and blocks the development of clinical markers, including hypotension and hypothermia [1]". Thus it is probable that inhibition of HIF-1α activity represents a novel therapeutic target for LPS-induced sepsis [85].

HIF ACTIVITY IMPACT OF DRUGS USED AT THE SITE OF CRITICAL CARE

Synthetic glucocorticoids (GCs) are drugs that are widely used to suppress the development of the cardinal symptoms of inflammation such as local heat, redness, swelling, and tenderness. However, in addition to these beneficial effects, synthetic GCs including dexamethas one cause side effects, such as delayed wound healing and local and systemic immunosuppression. In fact, dexamethasone attenuates HIF-1 activity in a glucocorticoid receptor-dependent manner [86]. HIF-1α increased in the cytosol after dexamethasone treatment under hypoxic conditions instead of accumulating in the nucleus [86].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are believed to suppress prostaglandin synthesis and delay healing of ulcers [87]. However, the mechanisms of this inhibition are not completely understood at time moment. A various types of NSAIDs including nonselective type (Indomethacin and Ibuprofen) and COX-2-selective type (Celecoxib) inhibit hypoxia-induced *in vitro* angiogenesis in gastric microvascular endothelial cells [88-90].

The intravenous anesthetic propofol reversibly inhibits HIF-1 activity and the gene expression mediated by HIF-1 by blocking the synthesis of the HIF-α subunit under 20% or 5% O_2 conditions, but not under 1% O_2 conditions [91]. In addition, it has been reported that propofol prolonged survival, attenuated acute lung injury, and decreased the expression of HIF-1α, IL-6, keratinocyte-derived chemokine, and TNF-αin the lungs of endotoxemic mice. HIF-1αknockdown in A549 cells results in suppression of LPS-induced TNF-α and IL-6 secretion and the pro-apoptotic BNIP3 expression and then reduction of apoptosis were observed. The intravenous anesthetic propofol, but not an inhibitor of NF-κB, reduced HIF-1αproteinexpression in LPS-stimulated A549 cells. Propofol also down-regulated the expression of IL-6, IL-8, TNF-α, and BNIP3 and apoptosis of A549 cells [92].

CONCLUSION

The transcription factor HIF and the biological processes that are dependent on it are vitally involved with the pathways of sepsis pathophysiology. The significance of these findings is that host bactericidal and inflammatory activities are deeply dependent on oxygen metabolism in the local tissue or niche microenvironment. HIF controls energetic and gene expression pathways of immune cells. Through the control, defensive activities against infection can be focused and amplified at the foci of tissue infection or inflammation, where oxygen and nutrients are limiting and concentration of chemokines and cytokines are high. A detailed understanding of the relationship between HIF, the pathways of innate and acquired immune signal transduction including TLR-NF-κB and antigen-TCR signaling, and the distribution of various immune effector cellsa and molecules will provide amore comprehensive understanding of sepsis which a systemic manifestation of infectious and inflammatory. Advances in understanding the role of these oxygen sensors in hypoxia tolerance and inflammation would create new opportunities for pharmacological interventions for sepsis [85].

DISCLOSURE

Part of this article has been previously published in "Chronic Inflammation Molecular Pathophysiology, Nutritional and Therapeutic Interventions CRC Press 2012 Pages 51-66 [1]."

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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