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HIF-1α as a central mediator of cellular resistance to intracellular pathogens

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Hypoxia-inducible transcription factor-1α (HIF-1α) was originally identified as a master regulator of cellular responses to hypoxia. More recently, HIF-1α has emerged as a critical regulator of immune cell function that couples shifts in cellular metabolism to cell type-specific transcriptional outputs. Activation of macrophages with inflammatory stimuli leads to induction of the metabolic program aerobic glycolysis and to HIF-1α stabilization, which reinforce one another in a positive feedback loop that helps drive macrophage activation. This activation of aerobic glycolysis and HIF-1α is important both for production of inflammatory cytokines, such as IL-1β, and for cell intrinsic control of infection. Here, we review the importance of HIF-1α for control of bacterial, fungal, and protozoan intracellular pathogens, highlighting recent findings that reveal mechanisms by which HIF-1α is activated during infection and how HIF-1α coordinates antimicrobial responses of macrophages.

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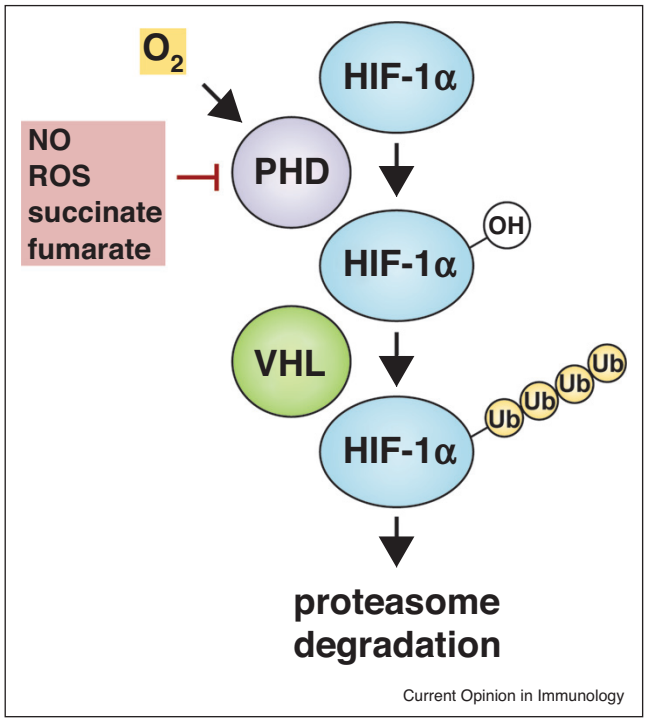
Introduction

Originally discovered as a master regulator of cellular responses to hypoxia [1], the transcription factor Hypoxia inducible factor-1α (HIF-1α) has recently emerged as a key player in macrophage-based immune responses. Over the last five years, there has been significant progress in our understanding of HIF-1α's regulation in macrophages, and an increasing awareness of its central role in defense against intracellular pathogens. Here, we review mechanisms of HIF-1α regulation, including key studies that demonstrate links between HIF-1α and the shifts in macrophage metabolism that accompany activation and differentiation. In addition, we review recent studies that reveal a role for HIF-1α in defense against intracellular bacterial, fungal, and protozoan pathogens. Interestingly, although the majority of these studies find that HIF-1α promotes classical inflammatory responses and cell intrinsic control of intracellular pathogens, a few studies point to HIF-1α as a factor that downregulates immune responses and impairs control of infection. We also discuss important unanswered questions related to HIF-1α and immunity to intracellular pathogens, including the need to elucidate context-dependent roles for HIF-1α during infection with different pathogens *in vivo*, and to determine cell type-specific responses regulated by HIF-1α in macrophages, dendritic cells, neutrophils, and epithelial cells. Finally, the seeming importance of HIF-1α in defense against a wide variety of pathogens suggests that pharmacological agents that activate HIF-1α represent interesting targets for the development of host targeted therapeutics for fighting drug resistant infections, an area that despite a small number of interesting studies, remains largely unexplored.

HIF-1 transcription factor regulation

The HIF-1 transcription factor is a heterodimer consisting of two protein subunits, HIF-1α and HIF-1β [2]. Whereas HIF-1β is constitutively expressed in cells, HIF-1α protein levels are highly regulated, both by O_2 and by specific metabolites. HIF-1α protein is constitutively transcribed and translated but is rapidly targeted for degradation via hydroxylation of HIF-1α by prolyl hydroxylases (PHDs) [3–5]. O_2-dependent hydroxylation facilitates HIF-1α interaction with the Von Hippel–Lindau tumor suppressor protein (VHL), a component of an E3 ubiquitin ligase that ubiquitinates HIF-1α, leading to its degradation by the proteasome [6,7]. Under conditions of low O_2, PHD proteins are unable to hydroxylate HIF-1α, leading to a rapid increase in protein levels and transcriptional activation of HIF-1α target genes, a phenomenon known as HIF-1α stabilization (Figure 1). Importantly, HIF-1α stabilization also occurs under normoxic conditions in response to fluctuating levels of metabolites. For example, increased levels of the TCA cycle intermediates succinate and fumarate stabilize HIF-1α protein by direct inhibition of PHDs, or through promotion of reactive oxygen species production [8–10]. In addition, HIF-1α stabilization can be induced by nitric oxide (NO), which stabilizes HIF-1α directly via S-nitrosylation and indirectly by inhibition of PHDs [11–13]. Although metabolic mechanisms for HIF-1α stabilization were initially

Figure 1



In an O_2-dependent manner, prolyl hydroxylases (PHDs) hydroxylate HIF-1α, leading to ubiquitination by the Von Hippel–Lindau tumor suppressor protein (VHL) and targeting of the protein for degradation by the proteasome. HIF-1α protein stabilization can occur as a result of low O_2 conditions inhibiting hydroxylation by PHDs. In addition, PHDs can be inhibited by ROS, NO, and metabolites including succinate and fumarate.

discovered in the context of cancer [14], the same mechanisms are operative in activated macrophages, where normoxic HIF-1α stabilization is promoted by succinate, lactate, and NO [15–17].

HIF-1α and metabolic regulation of macrophage function

In response to activation by TLR ligands or IFN-γ, macrophages alter their metabolism by downregulating oxidative phosphorylation and increasing flux through glycolysis to maintain ATP production [18]. This metabolic event, known as aerobic glycolysis, occurs even under normoxic conditions and is promoted by several factors, including mTOR, AKT, and downregulation of AMPK [19]. Increased glycolytic flux and the accompanying rewiring of central metabolism that accompanies aerobic glycolysis lead to HIF-1α stabilization, a phenomenon observed in macrophages stimulated with TLR ligands as well as in macrophages infected with intracellular pathogens [15,20••,21]. Once activated, HIF-1α increases the expression of numerous glycolytic genes, reinforcing glycolytic flux and setting up a positive feedback loop for macrophage activation [18,20••].

Why do activated M1 macrophages induce aerobic glycolysis? One possibility is that a switch to aerobic glycolysis enables macrophages to meet the bioenergetic demands of activation [22]. In addition, relying on glycolysis for ATP generation may prepare macrophages to enter hypoxic tissues and areas of inflammation. Indeed, early studies reported that HIF-1α deficient macrophages were defective for ATP production, resulting in profound migration defects to sites of sterile inflammation [23]. However, other studies found no differences in ATP production, or in the numbers of macrophages recruited to sites of inflammation during infection [20••,24]. Furthermore, the fact that M2 macrophages, which also have increased biosynthetic demands and migrate into inflamed tissues, do not activate aerobic glycolysis suggests that bioenergetics alone do not explain the switch to aerobic glycolysis in M1 macrophages. Indeed, it has subsequently become clear that the importance of aerobic glycolysis during macrophage activation is in large part due to the activation of HIF-1α, which induces a gene expression program in macrophages that includes expression of inflammatory cytokines and chemokines, as well as inducible nitric oxide synthase (iNOS) and antimicrobial peptides. The specific effectors induced by HIF-1α that contribute to functional control of infection differ depending on the pathogen and cellular context. However, an emerging principle is that HIF-1α couples metabolic cues with immune responses required for control of infection.

HIF-1α and bacterial infections

The importance of HIF-1α for antibacterial-immunity was initially discovered in the context of infection with *Streptococcus* spp. Macrophages lacking HIF-1α were found to be defective for killing both Group B and Group A Streptococci (GAS) [23,24]. Furthermore, mice lacking HIF-1α in macrophages and neutrophils (*Hif1a*$^{fl/fl}$-*LysMcre*) were more susceptible to infection with GAS in a soft tissue infection model. Susceptibility was correlated with a decrease in production of NO and TNF-α by macrophages, and a defect in production of both granule proteases and the antimicrobial peptide CRAMP by neutrophils. These seminal studies established a critical role for HIF-1α in regulating both inflammatory and antimicrobial responses in response to bacterial infection.

Macrophage HIF-1α expression has also been shown to be important for control of intracellular bacterial pathogens that replicate in the macrophage niche. Mice lacking HIF-1α in macrophages are impaired in their ability to control infection with *Listeria monocytogenes* in the liver, a finding that correlated with decreased production of TNF-α and decreased induction of glycolytic flux by macrophages in infected mice [23]. Interestingly, *Francisella tularensis* (Ftt) appears to actively impair HIF-1α stabilization in order to facilitate intracellular growth in macrophages. WT Ftt infections do not lead to HIF-1α activation, a result of the immuno-modulatory effect of the Ftt capsule. Capsule deficient mutants

induce HIF-1α and are largely attenuated for intracellular growth [25].

The importance of HIF-1α for host immunity to intracellular bacterial pathogens is best understood in the context of infection with pathogenic mycobacterial species. In a granuloma necrosis model of *Mycobacterium avium* infection, *Hif1afl/flLysMcre* mice had increased bacterial burden in livers relative to wild-type, and a more rapid formation of necrotic granulomas [26]. This was originally attributed to HIF-1α deficient macrophages being incapable of adaptation to hypoxia, but more recent studies have implicated a role for HIF-1α during normoxic mycobacterial infections. HIF-1α was found to be important for control of *Mycobacterium marinum* infections of zebrafish, due to HIF-1α-dependent induction of IL-1β in macrophages resulting in enhanced NO production by neutrophils (Figure 2) [27,28]. In this context, HIF-1α stabilizers enhance control of mycobacterial infection, raising the intriguing possibility that exogenous HIF-1α stabilization may enhance immune responses to infection. In the context of infection with *Mycobacterium tuberculosis*, HIF-1α is a critical mediator of IFN-γ-dependent immunity [20••]. During Mtb infection, HIF-1α deficient macrophages exhibit decreased IFN-γ-dependent expression of iNOS, numerous cytokines and chemokines, genes required for lipid droplet and eicosanoid production, and genes required for induction of aerobic glycolysis [20••,29]. As a result, *Hif1a$^{fl/fl}$LysMcre* mice are very susceptible to disease and succumb to infection far earlier than WT [20••]. Intriguingly, recent work has found that during Mtb infection HIF-1α stabilization requires NO, establishing a positive feedback loop for macrophage activation [16]. Furthermore, NO has been found to inhibit inflammatory cytokine production both by inhibiting transcription of IL-1β and by inhibiting IL-1β processing by the inflammasome [30,31]. Importantly therefore, HIF-1α simultaneously helps drive NO production to reduce excess inflammation and regulates cell intrinsic antibacterial effectors, many of which remain to be defined [16].

In addition to its role in myeloid cells, several studies suggest that HIF-1α is also important for defense against infection of epithelial cells with intracellular bacteria. HIF-1α-dependent expression of iNOS, β-defensin, and cathelicidins in keratinocytes contributes to defense against uropathogenic *Escherichia coli* (UPEC) infection in human bladder epithelial cells and in a mouse model of bladder infection (Figure 2) [32••]. Indeed, HIF-1α is a key regulator of constitutive β-defensin production in colonic epithelial cells [33]. Importantly, pharmacologic stabilization of HIF-1α was shown to increase control of UPEC infection, suggesting that HIF-1α stabilizers may have therapeutic applications across a range of bacterial infections [32••]. HIF-1α was also found to be required for autophagic control of invasive *E. coli* in intestinal epithelial cells. Furthermore, mice lacking HIF-1α in intestinal epithelial cells were found to be significantly more susceptible to oral challenge with *Yersinia enterolitica* than wild-type mice [34]. Finally, it was reported that *Chlamydia pneumoniae* produces a virulence factor that actively degrades HIF-1α during late stages of epithelial cell infection, and that this destabilization of HIF-1α is required for efficient growth of *C. pneumoniae* under hypoxic conditions [35].

HIF-1α and fungal infections

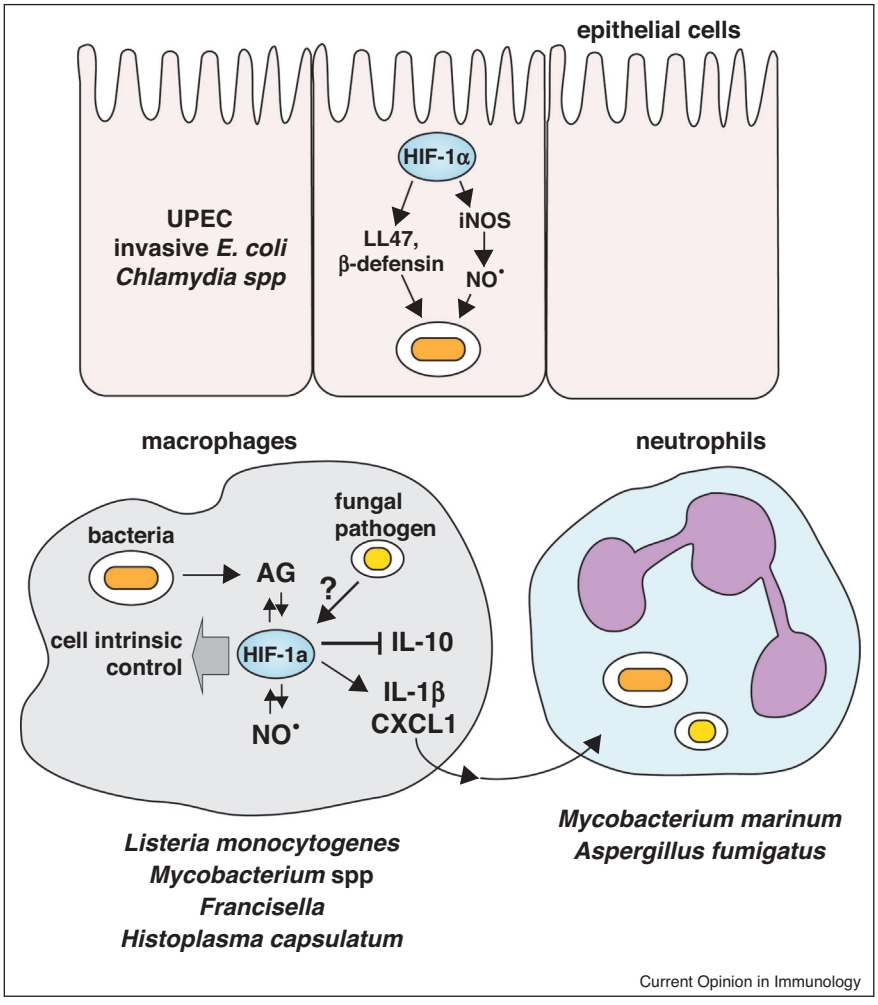
Similar to its role in bacterial infections, HIF-1α appears to support immune responses to fungal pathogens. C57BL/6 mice are more susceptible to infection with *Coccidioides immitis* than DBA/2 mice. This susceptibility correlates with greater HIF-1α-dependent gene expression patterns in the resistant DBA/2 mice [36–38]. Furthermore, *Hif1a$^{fl/fl}$LysMcre* mice are highly susceptible to infection with *Aspergillus fumigatus*. Interestingly, hyphal damage assays and FACS analysis of conidial viability during *ex vivo* infections indicated that HIF-1α deficient macrophages and neutrophils are not impaired in fungal killing. Instead, *Hif1a$^{fl/fl}$LysMcre* mice displayed a neutrophil recruitment defect, resulting specifically from reduced production of CXCL1 by HIF-deficient macrophages *in vivo* [39]. *Hif1a$^{fl/fl}$LysMcre* mice are also highly susceptibility to *Histoplasma capsulatum* infection. In this case, no defect in cell recruitment was observed; however, *Hif1a$^{fl/fl}$LysMcre* mice displayed elevated production of the anti-inflammatory cytokine IL-10. Administration of an anti-IL-10 neutralizing antibody reduced fungal burden in *Hif1a$^{fl/fl}$LysMcre* mice and extended survival [40••]. Taken together, these data demonstrate that HIF-1α plays an important role in mediating protective inflammatory responses to fungal pathogens by distinct mechanisms (Figure 2).

Although there is a limited research on manipulation of HIF-1α for treating fungal disease, it was shown that pharmacological stabilization of HIF-1α during *Candida albicans* infection of murine and human macrophages resulted in decreased fungal burden. Conversely, treating the media with 2-ME to inhibit HIF-1α increased fungal burden [41]. These results suggest that manipulation of HIF-1α *in vitro* and *in vivo* could impact cell intrinsic control of fungal infection, and that HIF-1α stabilization is a promising area of research for the development of novel antifungals.

HIF-1α and protozoan infections

In contrast to the importance of HIF-1α to bacterial and fungal immunity, the role of HIF-1α during protozoan infections is less clear. It was initially reported that *Leishmania amazonensis* benefits from HIF-1α during infection of murine macrophages, as inhibition of HIF-1α nuclear translocation resulted in decreased pathogen burden in murine macrophages [42]. Similarly,

Figure 2



HIF-1α contributes to cell intrinsic control of epithelial cells infected with invasive UPEC or *Chlamydia* by inducing expression of iNOS and antimicrobial peptides. In macrophages, HIF-1α, aerobic glycolysis, and NO can promote each other through positive feedback mechanisms that provide host protection to intracellular bacterial pathogens. In the context of infection with the fungal pathogen *Histoplasma capsulatum* stabilization of HIF-1α results in inhibition of anti-inflammatory cytokine IL-10, while upregulating production of inflammatory cytokines and chemokines like IL-1β and CXCL1 which can promote neutrophil migration to sites of infection.

silencing *Hif1a* using siRNA in the J774 macrophage cell line reduced parasite load whereas overexpressing HIF-1α promoted parasite growth during infection with *Leishmania donovani* [43]. It was subsequently reported that expression of HIF-1α in dendritic cells (DCs) weakened host immunity to visceral *L. donovani* infection by suppressing CD8 T cell expansion [44] and by promoting M2 macrophage differentiation during infection [45•]. As a consequence, *Hif1a*$^{fl/fl}$*-Cd11c-cre* mice, deficient for HIF-1α in DCs, are resistant to visceral *L. donovani* infection [44]. Conversely, however, *Hif1a*$^{fl/fl}$*LysMcre* mice suffer a non-resolving cutaneous infection with *Leishmania major*, whereas WT mice are able to recover [46•]. One possible explanation for this apparent discrepancy is the use of different Cre drivers (*CD11c-cre* versus *LysMcre*) which create a HIF-1α deficiency in overlapping but distinct populations of myeloid cells [47]. In addition, differences could be attributed to tissue site-specific differences in the immune function of HIF-1α, or differences in immune responses to *Leishmania spp*. Further research is required to elucidate the role of HIF-1α in cells and tissues of the innate immune system, and how this influences the overall inflammatory milieu during infection.

Conclusions

HIF-1α is an important regulator of immunity to bacterial, fungal, and protozoan pathogens. Here, we have summarized how HIF-1α activation in myeloid and epithelial cells influences immune responses to intracellular pathogen. However, there are still significant gaps in our understanding of HIF-1α mediated immunity. It has

been clearly established that HIF-1α controls expression of inflammatory cytokines and chemokines, and induces iNOS and various antimicrobial peptides that clearly contribute to microbial killing both *in vitro* and *in vivo*. However, many additional HIF-1α-dependent cell intrinsic antimicrobial effectors, particularly in the context of mycobacterial and fungal infections, remain to be discovered. Interestingly, although most studies focus on the pro-inflammatory activities of HIF-1α, several studies also suggest that HIF-1α can promote downregulation of excessive inflammatory responses, as has been reported for sepsis [48]. HIF-1α appears to influence polarization of some cells towards antimicrobial activation states, and skew others away from microbicidal capabilities. HIF-1α's complicated and sometimes contradictory roles in these myeloid cell populations requires further investigation. Furthermore, HIF-1α influences the function of lymphocytes, promoting activation and differentiation [49–51], and likely impacts adaptive as well as innate immune responses to intracellular pathogens. Finally, although HIF-1α likely plays a role in immune responses to viruses, this area of HIF-1α biology has been largely unexplored. Nonetheless, the emergent understanding of HIF-1α's importance to host immunity suggests that HIF-1α manipulation may lead to the development of novel therapies to bolster our increasingly limited arsenal of effective antimicrobial treatments.

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Conflict of interest statement

Nothing declared.

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- •• of outstanding interest

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