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REVIEW

Hypoxia-Inducible Factor (HIF) as a Pharmacological Target for Prevention and Treatment of Infectious Diseases

Tamara Bhandari · Victor Nizet

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ABSTRACT

In the present era of ever-increasing antibiotic resistance and increasingly complex and immunosuppressed patient populations, physicians and scientists are seeking novel approaches to battle difficult infectious disease conditions. Development of a serious infection implies a failure of innate immune capabilities in the patient, and one may consider whether pharmacological strategies exist to correct and enhance innate immune cell function. Hypoxia-inducible factor-1 (HIF-1), the central regulator of the cellular response to hypoxic stress, has recently been recognized to control the activation state and key microbicidal functions of immune cells. HIF-1 boosting drugs are in clinical development for anemia and other indications, and could be repositioned as infectious disease therapeutics. With equal attention to opportunities and complexities, we review our current understanding of HIF-1 regulation of microbial host–pathogen interactions with an eye toward future drug development.

Keywords: Bacteria; Dendritic cells; Hypoxia-inducible factor; Innate immunity; Macrophages; Neutrophils; T cells; Virus

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T. Bhandari · V. Nizet (✉)
Center for Immunity, Infection and Inflammation, Department of Pediatrics and Biomedical Sciences Graduate Program, University of California, San Diego, La Jolla, USA
e-mail: vnizet@ucsd.edu

V. Nizet
Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, USA

V. Nizet
Center for Immunity, Infection and Inflammation, Medical Sciences Research 4113, University of California, San Diego, 9500 Gilman Drive, MC 0760, La Jolla, CA 92093-0760, USA

INTRODUCTION

The golden age of antibiotics may be nearing its end, as more and more pathogens acquire resistance to an ever-widening range of antibiotics. New ways to prevent and treat infectious diseases are urgently needed. One possible solution is to focus on the other side of

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the host–pathogen equation—not killing the invaders, but strengthening the defenses. Just as vaccines harness the power of the adaptive immune system to prevent infectious disease, treatments that activate the innate immune system could potentially help to cure acute infections. Hypoxia-inducible factor (HIF)—a transcriptional regulator that controls the key aspects of the immune response—is a promising target for such immune-boosting treatments. HIF regulates the energy generation and production of multiple microbicidal effectors of phagocytic cells including neutrophils and macrophages, and established pharmacological strategies exist to increase cellular HIF levels. But one must proceed prudently, since a growing body of research reveals that HIF plays multiple roles in immune regulation, with differing effects in different cell types. Strategies to modulate HIF levels for infectious disease therapy must take these complexities into consideration.

HIF BIOLOGY AND REGULATION

Hypoxia-inducible factor is a basic helix–loop–helix transcription factor [1] first identified for its role in erythropoietin regulation [2], but later discovered to also regulate genes involved in glycolysis, angiogenesis, cell differentiation, apoptosis, and other cellular pathways [3]. HIF is a heterodimer composed of a HIF-α subunit and HIF-1β subunit. *Hif-a* is actually a family of three genes: *Hif1a*, *Hif2a*, and *Hif3a*. HIF-3α is distantly related to HIF-1α and HIF-2α and little is known about its function, although it may inhibit the activity of HIF-1α and HIF-2α [4]. The HIF-1α and HIF-2α subunits are closely related, sharing 48% overall amino acid identity [5]. The two subunits are very similar in their DNA binding and dimerization domains but differ in their transactivation domains, implying that they may regulate unique sets of target genes [5]. Whereas HIF-1α is ubiquitously expressed, HIF-2α is most abundantly expressed in vascular endothelial cells during embryonic development and in endothelial, lung, heart [6], and bone marrow cells [7] in the adult. HIF-2α levels are closely correlated with vascular endothelial growth factor (VEGF) mRNA expression [6] and are frequently elevated in solid tumors [7], suggesting that its most important functions may lie in vascularization [6]. Since only a small fraction of published research focuses specifically on HIF-2α or HIF-3α, this review will be restricted primarily to HIF-1α.

In the presence of oxygen and the absence of inflammatory stimuli, the level of HIF-α is kept low by two mechanisms. In one, HIF-α is hydroxylated by prolyl hydroxylases [8]. The hydroxylated HIF-α is recognized by the ubiquitin ligase von Hippel–Lindau factor (vHL), which ubiquitinates HIF-α, targeting it for destruction via the proteasome [9]. In the second mechanism, factor inhibiting HIF (FIH) hydroxylates HIF-α, blocking its ability to associate with p300-CREB binding protein (CREB-BP), which in turn inhibits the ability of the HIF complex to bind DNA and promote transcription [10]. When oxygen tension is low, neither hydroxylation event occurs, HIF-α and HIF-1β dimerize, combine with CREB-BP and bind to hypoxia-response elements (HRE) in the promoter regions of over a hundred target genes [3].

The NF-κB pathway appears to be crucial for the induction of HIF in response to hypoxia [11]. The human HIF-1α promoter contains a canonical NF-κB binding site −197/−188 base pairs upstream of the transcriptional start site, the mutation of which leads to a loss of hypoxic HIF-1α upregulation [11]. There is evidence that NF-κB family members bind to the HIF-1α promoter [12], and the endogenous inhibitor

of NF-κB, IκBα, derepresses HIF-1 by sequestering FIH [13]. Basal NF-κB activity is required for HIF-1α protein accumulation under hypoxia in cultured cells and in the liver and brain of hypoxic animals [11]. IKK-β deficiency results in defective induction of HIF-1α target genes including VEGF. IKK-β is also essential for HIF-1α accumulation in macrophages during the response to bacterial infection. Hence, IKK-β is an important physiological contributor to the hypoxic response, linking it to innate immunity and inflammation [11].

Though HIF was first identified and named for its role in hypoxia, later work showed that a variety of molecular signals of infection and inflammation may increase HIF activity even under normoxic conditions. Growth hormones such as insulin-like growth factor [14], cytokines such as interleukin-1β (IL-1β) [15] and viral proteins [16] all activate HIF. This regulation can occur at the transcriptional, translational, or post-translational levels. For example, lipopolysaccharide (LPS) induces *Hif1a* mRNA expression in a toll-like receptor 4 (TLR4)-dependent manner that involves members of the NF-κB, mitogen-activated protein kinase (MAPK), and extracellular signal-regulated kinase (ERK) pathways [17–19]. TLR7/8 ligation also leads to *Hif1a* transcript accumulation [20] and to protein stabilization in macrophages [20, 21].

Cytokines, on the other hand, often increase HIF activity by post-translational mechanisms. TGF-β1 enhances HIF-1α protein stability by inhibiting the expression of prolyl hydroxylase 2 (PHD2), which hydroxylates HIF and targets it for proteolytic destruction [22]. Tumor necrosis factor-α (TNF-α) [23] and IL-1β [15, 24] induce HIF-1α protein stabilization in an NF-κB-dependent mechanism without affecting its mRNA level.

HIF AS A REGULATOR OF IMMUNE FUNCTION

Why should a ubiquitous transcription factor be induced by both hypoxia and molecular signals of infection? Tissue foci of inflammation represent hypoxic microenvironments, with oxygen tensions measured under 1% [25]. Hypoxia reflects increased metabolic demands due to a high density of inflammatory cells and microorganisms, and limited perfusion because of thrombosis, damage to the vasculature, or compression of blood vessels due to interstitial hypertension. Immune cells, therefore, need to be able to carry out their functions under conditions of reduced oxygen tension, a situation made even more challenging since many leading bacterial pathogens proliferate readily even in anaerobic microenvironments. Since infection and hypoxia are so often encountered together, it perhaps stands to reason that HIF would be induced not only by hypoxia but also in response to a broad range of infections: viral, bacterial, protozoan, and fungal [26, 27].

HIF IN REGULATION OF INNATE IMMUNITY

Hypoxia-inducible factor has been proposed as a master regulator of innate immunity [28]. HIF expression in epithelial cells can control the release of chemoattractants that recruit neutrophils to the site of infection or inflammation. Dendritic cells (DCs) exposed to hypoxia upregulate genes coding for proteins chemotactic for neutrophils such as chemokine (C-X-C motif) ligand (CXCL)2, CXCL3, CXCL5, and CXCL8 [29]. HIF induces β2 integrin expression in neutrophils [30], and Cdc42 and Rac1 expression in macrophages [31],

enhancing migration of both cell types to the site of infection. Hypoxia also increases CXC chemokine receptor (CXCR)4 [32] and inhibits CC chemokine receptor (CCR)5 [33] expression in macrophages in a HIF-dependent manner, which increases retention of macrophages at the site of infection.

Not only are more immune cells recruited and retained, but those cells live longer. HIF extends the functional neutrophil lifespan by inhibiting apoptotic pathways in an NF-κB-dependent manner [34, 35]. People with mutations in vHL—and therefore constitutively elevated HIF levels—have neutrophils with longer lifespans. Hypoxia also promotes survival of monocytes and macrophages [36]. HIF transcriptional regulation also supports other phenotypes related to immune cell activation. Hypoxia leads to TLR-2, TLR-4, and TLR-6 upregulation in a HIF-dependent manner [37, 38], enhancing the detection of pathogen-associated molecular patterns. Hypoxic myeloid cells from mice exhibit increased phagocytosis [39], and those from humans who have mutations in vHL have increased phagocytic capacity as well [40].

In an in vivo model of innate infection, mice lacking HIF-1α in myeloid cells had diminished capacity to fight off a skin infection with the pathogen group A *Streptococcus* (GAS) [41]. *Hif1a* knockdown by siRNA also led to more severe corneal disease in mice infected intraocularly with *Pseudomonas aeruginosa,* and this effect was due to impaired neutrophil function [42]. Conversely, mice in which HIF was elevated by drug treatment were better able to control skin infection by methicillin-resistant *Staphylococcus aureus* (MRSA) [43, 44]. Overall, augmenting HIF in macrophages increases bactericidal activity by increasing the production of a wide range of antimicrobial factors [43, 44]. Hypoxia leads myeloid cells to release more nitric oxide (NO), granule proteases, antimicrobial peptides, and proinflammatory cytokines [41, 45]. One notable exception is superoxide generation via the oxidative burst, which appears to transpire with equal efficiency in wild type and *Hif1a* null macrophages [41]. It is perhaps logical that the enzymatic pathway for superoxide generation is not elevated during hypoxia, given that it requires the presence of oxygen, which is by definition in short supply. HIF has also been recognized to promote the production of neutrophil [46] and mast cell [47] extracellular traps, a specialized process whereby nuclear DNA and histones are released at tissue foci of infection to help ensnare and kill bacteria.

DENDRITIC CELLS AND PRIMING THE ADAPTIVE IMMUNE RESPONSE

Some innate immune cells' also play a crucial role in priming the adaptive immune response through their antigen-presenting functions. Dcs, closely related to the macrophage, serve a pre-eminent role as antigen-presenting cells (APCs). As such, they provide three signals to T cells: the antigen, presented in the context of major histocompatibility complex (MHC)-I or MHC-II; co-stimulatory signals through ligation of surface molecules; and cytokines and other soluble mediators. The combination of signals alerts the T cells to the foreign antigen, activates them, and modulates the strength and polarization of the adaptive immune response. DCs are a functionally and phenotypically diverse group of cells. They can be derived from the myeloid or lymphoid lineages [48]. Myeloid DCs can be classified as pre-dendritic cells (pre-DCs), conventional dendritic cells (cDCs), and inflammatory dendritic cells

(iDCs); cDCs can be further divided into migratory and lymphoid tissue-resident dendritic cells.

Pre-DCs are cells without the classic dendritic form and antigen-presenting function, but with a capacity to develop into DCs with little or no division. An inflammatory or microbial stimulus might be required. For example, monocytes can be considered pre-DCs because they can give rise to inflammatory DC upon exposure to inflammatory stimuli [49]. cDCs already have DC form and function. Migratory DCs fit the profile of the textbook DCs, and can be immature or mature. Lymphoid tissue-resident cDCs collect and present foreign and self-antigens in their home organ; these cells play crucial roles in maintaining tolerance to self-antigens, harmless environmental antigens, and commensal microorganisms. iDCs are specialized for antigen capture and processing and have limited ability to stimulate T cells. Under steady-state conditions, iDCs mostly reside at sites of contact between the host and the environment, such as the skin and the respiratory or gastrointestinal mucosa. These sentinel cells continuously scan the surroundings for the presence of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). Upon antigen uptake and activation by proinflammatory cytokines and DAMPs or PAMPs, iDCs undergo phenotypic and functional changes called maturation.

Maturation prepares the DC to fulfill the second half of their sentinel duty: to take the antigens they had previously captured while immature to the lymph nodes and present them to T cells. At the molecular level, maturation manifests as increased expression of MHC antigens and co-stimulatory molecules (such as CD83, CD80, CD86, and CD40), decreased expression of phagocytic/endocytic receptors, and a switch in the chemokine receptor repertoire to downregulate receptors for inflammatory chemokines (e.g., CCR1, CCR2, CCR5, CCR6, and CXCR1) and upregulate receptors for chemokines required for homing to secondary lymphoid organs, namely CCR7 and CXCR4.

DENDRITIC CELLS AND HIF

Research into the role of HIF in DCs is complicated by the fact that DCs are a rare cell type and it is difficult to obtain adequate numbers of primary cells for experimentation. Consequently, much of the in vitro work on DCs and HIF has been performed on human peripheral blood monocytes or mouse bone marrow cells differentiated into DCs by treatment with granulocyte–macrophage colony stimulating factor (GM-CSF) and IL-4 for periods of 7–11 days. Both methods produce DCs most similar to iDCs [50], and not the migratory cDCs that are likely to play an important sentinel role in vivo.

Previous attempts to determine the role of HIF in DC maturation have yielded contradictory results. Various investigators have produced data indicating that hypoxia promotes DC maturation both alone [51, 52], and in combination with LPS stimulus [53, 54], as measured by decreased phagocytosis [55, 56], increased migration [57, 58], and increased expression of MHC and co-stimulatory molecules [54, 56, 57, 59]. Others have come to exactly the opposite conclusion, namely, that hypoxia inhibits DC maturation [55], migration [60, 61] (possibly by reducing expression of MMP-9, which helps DC migrate [62, 63]), and expression of co-stimulatory molecules [60, 64, 65].

When it comes to the effect of hypoxia and HIF on the ability of APC to prime T cells, the literature is no less mixed. Some groups have shown that hypoxia and HIF increase the ability of APCs to stimulate a T-cell response [53, 56, 66, 67] and lead to the expression of more proinflammatory cytokines [53, 59, 60, 64, 65, 68, 69] that bias toward a T_H1 response [66], and type I interferons [70], which are essential for the ability of DC to induce T_H1 differentiation [71]. Others have found the opposite [55, 72]. Still others have reported a mixed phenotype among the DC in their in vitro model system [60].

From the above literature survey, the jury is still out on the role of HIF in priming the adaptive immune response. Some of the variation in reported results may be due to differences in stimuli. Critically, the context within which HIF is activated (hypoxia versus inflammation) affects the results of HIF activation. When HIF is activated by hypoxia, it enhances transcription from a different set of target genes than when it is activated by a TLR ligand such as lipopolysaccharide (LPS) [73]. Hypoxia and LPS stabilize HIF through different pathways; LPS-induced HIF stabilization requires both NF-κB and MyD88, while hypoxia-induced HIF stabilization is independent of NF-κB [73]. Furthermore, when hypoxia is used as a stimulus in the antigen presentation readouts, it affects not only the APC but the T cells themselves, further influencing the results of the experiments.

HIF REGULATION IN T CELLS

Intriguingly, HIF appears to have certain opposing effects on lymphoid cells of the adaptive immune system when compared to the properties it exhibits with myeloid cells of the innate immune system. Hypoxia and HIF-1α elevation reduces T-cell survival [74, 75] and proliferation [75, 76]. Hypoxia also inhibits T-cell activation by upregulating the inhibitory isoform I.1 of HIF-1α [77]. When isoform I.1 was deleted in T cells, the overall ability to fight infection was improved, with reduced bacterial load, increased resistance to sepsis, enhanced M1 macrophage polarization, and the release of more proinflammatory cytokines and less of the anti-inflammatory IL-10 [78]. Other researchers showed that loss of HIF-1α in T cells led to an increase in IFNγ secretion by both $CD4^+$ and $CD8^+$ T cells [79].

Hypoxia and HIF play an important role in tipping the balance between regulatory T cells (T_{reg}) and T_H17 cells towards the T_{reg} lineage. T_{regs} and T_H17 cells derive from naïve $CD4^+$ T cells, with T_{regs} characterized by expression of the transcription factor Foxp3 [80] and T_H17s characterized by the expression of RORγT [81]. Hypoxia leads to induction of Foxp3 in a HIF-dependent manner [82] and increased numbers of T_{regs} in vivo [82] and more potent T_{regs} in vitro [83]. Knockout of *Hif1a* in $CD4^+$ T cells leads to an increase in the numbers of T_H1 and T_H17 cells [84]. Others have found that differentiating naïve $CD4^+$ T cells under hypoxia followed by re-oxygenation increases the number of T_H17 cells [85], and that *Hif1a* knockout in $CD4^+$ T cells results in increased T_{regs} and fewer T_H17 cells [86], possibly by transcriptional activation of RORγT and degradation of Foxp3 [86]. However, these latter studies looked at the effect of HIF in the presence of IL-6, which biases toward a T_H17 response, or using the autoimmune disease model of experimental autoimmune encephalomyelitis, which creates the same bias [86, 87]. In the absence of conditions that bias toward the development of T_H17, T_{regs} are produced [82].

COMPLEX EFFECTS OF HIF IN THE IMMUNE RESPONSE TO INFECTION

Taken together, the research suggests that HIF positively regulates the activity of innate immune cells but negatively regulates the activity of T cells, with effects on APCs that still require experimental clarification. Kominsky et al. [88] have argued that the differential HIF response mechanisms in myeloid cells versus T cells has to do with the fundamental metabolism exhibited by each cell type. Myeloid lineage cells tend to glycolysis, whereas lymphoid lineage cells tend to oxidative phosphorylation [88]. HIF, which promotes glycolysis in the absence of sufficient oxygen for oxidative phosphorylation, would therefore be most important for supporting glycolysis in myeloid cells, which are best adapted for taking advantage of increased glycolysis. Conversely, supporting glycolysis in lymphoid cells may be a less-effective way of increasing their metabolic activity. DC can belong to either lineage; the sometimes contradictory research studies discussed above have all been performed using experimental models of myeloid DC. The hypoxia-induced reduction in T-cell activity and increase in the development of T_{regs} may aid in preventing an uncontrolled immune response that provokes autoimmunity or pathological tissue damage.

MANIPULATION OF HIF BY PATHOGENS

Hypoxia-inducible factor induction is a general part of the host response to infection. HIF is induced in response to both Gram-positive and Gram-negative bacteria [11, 41], as well as by viruses [89, 90], protozoa [27], and fungi [27]. Given the centrality of HIF in the immune response, it should come as no surprise that some pathogens have developed immune evasion strategies to counteract HIF. For example, oncolytic reovirus can prevent accumulation of HIF-1α in a proteasome-dependent manner, without affecting *Hif1a* transcription [91]. Moloney murine leukemia virus is able to prevent HIF-1α protein accumulation in infected mice without affecting *Hif1a* gene transcription by reducing the levels of the HIF-stabilizing host protein Jab1 [92]. *Chlamydia pneumoniae* degrades HIF by secreting the chlamydial protease-like activity factor into the cytoplasm of infected cells [93]. *Pseudomonas aeruginosa* expresses alkyl quinolones that target the HIF-1α protein for proteasomal degradation [94].

Infections by certain other viral pathogens may increase HIF levels or activity, perhaps exerting an anti-apoptotic effect that promotes survival of the host cell they are infecting. The carboxy terminus of HBx from hepatitis B virus was shown to enhance the transactivation of HIF-1α by enhancing its association with CREB-BP [95]. The Kaposi's sarcoma-associated herpesvirus (KSHV) expresses a protein known as latency-associated nuclear antigen (LANA), which targets vHL for degradation via ubiquitination, thereby increasing HIF protein levels [96], and another part of LANA promotes HIF nuclear accumulation [96]. Epstein–Barr virus (EBV) oncoprotein latent membrane protein 1 (LMP1) activates HIF-1α by upregulating Siah1 E3 ubiquitin ligase by enhancing its stability, which allows it to increase the proteasomal degradation of prolyl hydroxylases 1 and 3 that normally mark HIF-1α for degradation [97]. As a result, LMP1 prevents formation of the vHL/HIF complex, and HIF is not degraded.

Other viral and parasitic organisms are able to subvert HIF activity to their own benefit. HIF-1α stimulates the transcription of HIV-1 genes by associating with HIV-1 long terminal repeat [98], and the JCV polyomavirus genes by binding to the early promoter of the virus [99]. Other viruses may be sensing HIF as a marker of cellular stress to indicate when it is appropriate to exit the cell. Murid herpesvirus 4 [100] and EBV [101] switch from lysogenic to lytic when HIF levels are high. High levels of HIF lead to the expression of platelet-activating factor, which some pathogens then use to increase translocation across the intestinal epithelium [102]. *Toxoplasma gondii* survives better when HIF is elevated [103]. *Toxoplasma* induces HIF stabilization via activin-like receptor kinase signaling [104]. *Leishmania,* too, survives better when HIF is elevated, and HIF inhibition reduces survival of the parasite [105, 106].

HIF FOR PREVENTION AND TREATMENT OF INFECTIOUS DISEASE

As a master regulator of innate immunity, HIF stands as a promising target for fine-tuning the immune response. In most infections, increasing HIF levels could be expected to boost diverse myeloid cell antimicrobial activities and promote clearance of infection. Under certain conditions, particularly among viral pathogens, HIF stabilization may promote the extended survival of infected cells, therefore care must be taken in determining when HIF augmentation can be a beneficial strategy.

Along with in vitro work showing that HIF increases the bactericidal capacity of immune cells, it has also been found that treating mice with the HIF stabilizers mimosine [43] or AKB-4924 [44] improves their ability to fight skin infections. While HIF-boosting agents (prolyl hydroxylase inhibitors) are in advance clinical trials for anemia due to their ability to boost erythropoietin production [107], no trials in humans have been initiated to date in which drugs that upregulate HIF are used to treat acute bacterial infection. Nonetheless, such a strategy could be effective for difficult clinical scenarios such as opportunistic bacterial infections in patients with weakened immune systems or with pathogens exhibiting multidrug resistance to conventional antibiotics. Theoretically, HIF boosting may also have an advantage in reducing the likelihood of drug resistance; it would be prohibitively difficult for bacteria to evolve resistance to the whole arsenal of antimicrobial factors that are increased when HIF activity increases [3].

For those scenarios in which bacteriologic control is easily achievable by conventional antibiotics and in which pathology is being driven by an overactive immune response to bacterial components, HIF induction would have unclear utility. In noninfectious experimental LPS-induced sepsis, for example, which provokes an immunopathological cytokine storm, knocking out HIF in either myeloid cells [108] or T cells [109] reduces the severity of disease. This is in agreement with clinical research showing that septic patients exhibit reduced levels of HIF-1α mRNA with an inverse relationship between mRNA level and disease severity [110].

Inflammatory bowel disease, which involves a complex interaction between epithelial barrier function, mucosal immune response and the normal colonic flora, has emerged as a promising therapeutic target for HIF-1 boosting. Treatment of mice with HIF-boosting agent AKB-4924 provided protection from

chemical-induced colitis [111]. Treatment was associated with a 50-fold decrease in serum endotoxin in this model, along with reduction in cytokines proinflammatory cytokines IL-1β, IL-6, and TNF-α, while increasing the anti-inflammatory cytokine IL-10; such protection was not seen in colonic epithelial-specific HIF-1-deficient mice, implicating epithelial HIF-1 as the tissue target for AKB-4924-mediated protection. Intestinal inflammation involves a rapid accumulation of neutrophils at the colonic mucosa. The transmigrating neutrophils rapidly deplete oxygen in the local microenvironment, stabilizing intestinal epithelial HIF levels. Mice with chronic granulomatous disease, deficient in reactive oxygen species (ROS) generation, have exaggerated neutrophil recruitment and colitis, but pharmacological HIF stabilization with AKB-4924 protected these animals from severe colitis [112].

For viral infections, the landscape may be more complicated. On the one hand, HIF is a positive regulator of key immune response effectors against viral infections, just as against bacterial ones. On the other hand, since high HIF levels encourage certain lysogenic viruses to become lytic, activating HIF may potentially influence reactivation phenotypes. Also, HIF treatment in vivo could influence the antiviral activity of plasmacytoid DCs (pDCs), and one group has shown that HIF-1α is a negative regulator of pDC development in vitro and in vivo [113].

The work in APCs suggests that HIF elevation could be effective not only in treating but also in preventing disease, through examination of adjuvant characteristics. To take advantage of the positive role of HIF in innate immune cells and avoid the negative effect of HIF on T cells, a HIF-stabilizing agent would have to be effective in the first hours of the immune response, but be exhausted by 24–48 h after immune stimulation when T cells begin activating. We have recently reported [114] proof-of-concept experiments using the HIF stabilizer AKB-4924 to strengthen the response to vaccination with ovalbumin, a model antigen. In this work, DC of mice treated with AKB-4924 showed increased MHC and co-stimulatory molecule expression and induced greater T-cell proliferation, and higher titers of antibodies were generated in mice provided the HIF-1 stabilizing agent. Further research must be done to determine whether a HIF–1 boosting drug could be developed fruitfully as a vaccine adjuvant.

It is important to recognize that both HIF-1α and HIF-2α are expressed in myeloid cells, and many drugs, including iron-chelating agents such as mimosine and desferioxamine, that target HIF-1 would affect HIF-2 similary. A potential exception to this rule is AKB-4924, which appears to preferentially stabilize HIF-1α [44]. The conclusions in this review were drawn based mostly on work that exclusively analyzed HIF-1α without specific analysis performed to ascertain changes in HIF-2α level. While HIF-1 and HIF-2 have different tissue expression patterns and play distinct roles in several processes such as embryonic development and iron homeostasis [115], but their roles in the immune response to infection appear to be very similar (our own unpublished data and [115, 116]). One way in which HIF-1 and HIF-2 are known to have different effects on the immune response is in regulation of the neutrophil chemoattractant IL-8. Overexpression of HIF-2α increases IL-8 expression in endothelial cells [117], and siRNA knockdown of *Hif2a* reduces IL-8 expression [118], while HIF-1α overexpression decreases IL-8 expression [119]. Researchers have shown, however, that hypoxia, which

stabilizes both HIF-1 and HIF-2, results in reduced IL-8 expression [117], suggesting that the HIF-1 response is more influential than HIF-2 in IL-8 regulation and that a pharmacological agent targeting both isoforms would predominantly mirror the HIF-1 effect.

SUMMARY

Hypoxia-inducible factor, which exerts transcription control over immune cell energy generations and key effectors of the innate and adaptive immune response, represents a molecularly accessible and intriguing target for immune-boosting therapeutics. HIF stabilization in macrophages, neutrophils and epithelial cells can increase levels of key antibacterial factors including antimicrobial peptides, nitric oxide and proinflammatory cytokines. HIF-stabilizing agents also boosts DC antigen presentation and T-cell priming and provide barrier protective and immunomodulatory functions in inflammatory colitis. Yet differing effects of HIF modulation in T lymphocytes may pose complexities in the arena of antiviral therapy. Further exploration of the disease spectrum for which application of HIF modulation could serve as an adjunctive therapy to classical anti-infective therapeutics is warranted.

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Compliance with ethics. This review is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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