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Current Opinion in Physiology

Hypoxia and reprogramming of host pathogen interactions

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Upregulation of key transcriptional pathways in response to hypoxia enables host responses to readily adapt to hypoxic environments, with preservation of key immune functions. Recent discoveries have highlighted the ability of hypoxia and its master regulator, the HIF hydroxylase pathway, to reprogramme the immune response with long lasting effects on host pathogen outcomes. Pathogens can also sense and adapt to areas of low oxygen availability with new evidence emerging of a direct oxygen sensing pathway in the *Pseudomonas* spp. Thus the determinants of success in hypoxic host pathogen interactions are a dynamic summation of adaptations to hypoxia, in both the host and infiltrating pathogens.

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Current Opinion in Physiology 2019, **7**:15–20

This review comes from a themed issue on **Hypoxia**

Edited by **Hesham Sadek** and **Gregg Semenza**

For a complete overview see the Issue and the Editorial

Available online 27th November 2018

https://doi.org/10.1016/j.cophys.2018.11.004

Introduction

Hypoxia, or oxygen deficiency, exists in both health and disease in mammals. However, in areas of inflammation and infection this relative lack of oxygen is further amplified [1–3]. Impaired blood supply and the high oxygen requirement of large numbers of infiltrating cells can lead to profound hypoxia or even anoxia at these sites [4,5].

Thus the host response must be equipped to respond effectively and efficiently to pathogens in areas of lower PaO_2 than the physiological norm. Hypoxic regulation of the immune response is mediated by a number of pathways and metabolite availability [6,7], of which HIF (hypoxia inducible factor) is the best characterised and considered to be the master regulator of the host response to hypoxia.

In normoxia, the prolyl hydroxylase family (PHDs) and factor inhibiting HIF (FIH), hydroxylate HIF, tagging it for degradation via the Von Hippel Lindau (VHL) ubiquitin ligase system and preventing it from binding to necessary co-factors, respectively. In addition to oxygen, HIF hydroxylases require α-ketoglutarate, a tricarboxylic acid cycle intermediate, and Fe^{2+}, thus enabling metabolic regulation of HIF activity [8,9]. In its active stable form, HIF binds hypoxic response elements, upregulating transcription of genes with diverse functions such as erythropoiesis, metabolism and control of proliferation and apoptosis [10].

Emphasizing the importance of hypoxic adaptation, the HIF/hydroxylase pathway is highly conserved across species. Moreover, pathogens such as *Pseudomonas* are now recognised to contain an oxygen sensing domain, enabling direct adaptations to oxygen availability [11]. Consequently, at sites of tissue injury in the context of infection, hydroxylase activity is regulated in both the host and infiltrating pathogens. Thus the determinants of success in host pathogen interactions, are the net balance between hypoxic activation of the immune system, both via HIF and HIF independent pathways, and pathogen adaptations to hypoxia.

Host response

Many reviews have extensively assessed the effects of hypoxia on the innate and adaptive immune responses [12–14]. We will briefly discuss some key findings here but primarily focus on the new and emerging field of immune response reprogramming via hypoxia/HIF activation.

Innate immunity

Key innate immune functions are preserved in hypoxic environments. Hypoxia enhances neutrophil survival via HIF and NFκB activation [15]. HIF1α is essential for myeloid mediated inflammation with reduction in motility, invasiveness and bactericidal ability in HIF1α knock out macrophages [16]. Macrophage phagocytosis is not only preserved in hypoxic conditions, the quantity of particles ingested by each macrophage increases [17]. In keeping with this, silencing of PHD3 (with subsequent increased HIFα activity) also results in increased macrophage phagocytosis [18]. Studies of human neutrophils cultured in hypoxia show a significant increase in uptake of heat inactivated *Streptococcus pneumoniae* and preserved *Escherichia coli* phagocytosis.

Bacterial killing is, however, less well preserved in hypoxia than other innate functions. This likely reflects reliance on the respiratory burst to kill certain pathogens. This rapid release of reactive oxygen species (ROS) is

mediated by the oxygen requiring NADPH oxidase. *In vitro* experiments confirmed impaired generation of ROS in hypoxic neutrophils and resulting reduction in *Staphylococcus aureus* killing [19]. *In vivo* experiments by Wiese *et al.* revealed impaired macrophage killing of *E. coli* and *S. aureus* in hypoxia, which was largely due to reduced NADPH oxidase and NO synthase activity [20].

Immunometabolism plays a pivotal role in macrophage activation states. Inflammatory activated macrophages are preferentially glycolytic, regardless of oxygen availability [21]. A seminal paper by Cramer *et al.* showed that HIF regulated macrophage glycolytic capacity [16]. More recently, work by O'Neill *et al.* observed that LPS induced macrophage activation is mediated, in part, by increased glycolysis and subsequent succinate accumulation. Succinate stabilised HIF, which induced expression of the pro inflammatory cytokine, IL1β. This effect was lost when glycolysis was blocked [22].

Adaptive immunity

The adaptive immune response must be similarly well equipped to function in hypoxic environments. However, the role of hypoxia and HIF activation is less well defined in this system. Hypoxia reduces T cell proliferation and, as in other immune cells, HIF induces a key metabolic switch from oxidative phosphorylation to glycolysis, though it is not indispensable for this switch in all T cell subsets [23]. Contrasting findings for the role of HIF activation in T Cells suggest it may serve as both a negative and positive regulator of function. In a model of peritonitis using HIF1α deficient T cells, mutant mice had improved survival and decreased bacterial load. This was mediated by increased cytokine release—namely IL-2 and IFNγ [24]. A similar phenomenon has also been demonstrated in a model of vascular injury suggesting that HIF may limit T Cell inflammatory responses [25]. In contrast to these findings, two studies found that HIF 1α stabilization promoted T Cell differentiation to pro-inflammatory TH17T cells, with a reduction in quantity of Treg cells [26,27]. This apparent divergence in the role of HIF1α may be explained by the degree and mechanism of activation of HIF, but this remains to be explored.

Comparable to its role in T cells, hypoxia increases glycolytic rate in germinal centre (GC) B cells, by inhibiting the metabolic checkpoint kinase mTORC1. Inhibition of mTORC1 leads to reduced proliferation, increased apoptosis, and impaired class-switching. HIF stabilisation via deletion of VHL decreases antigen-specific GC B cells and impairs the generation of high affinity IgG, with a specific reduction in class switching to the pro inflammatory IgG2c isotype [28]. Hence, similar to one of its described roles in T Cells, HIF appears to function as a negative regulator in B Cells, impairing the humoral response.

Hypoxic reprogramming of the host response

Trained immunity and hypoxia

Recent studies have challenged the traditional dogma classifying host defences into two branches-specific the rapid, non-specific response of the innate immune system, incapable of memory versus the slow, but highly specific adaptive immune response, which builds immunological memory over time. Recent studies have contested this concept with evidence of immunological memory existing also in innate immune cells. The term 'trained immunity' is now used to describe how adaptations in innate immunity, following challenge by pathogens, lead to enhanced immune responses on restimulation. This immunological memory, though in the early stages of its characterisation, is generally accepted to be mediated by epigenetic changes [29].

Early epidemiological studies suggested that BCG vaccination protected against unrelated pathogens [30]. A seminal study by Van Wout *et al.* confirmed that prior BCG vaccination lead to superior control of systemic candidiasis, specifically via augmented macrophage function [31]. However, until recently, the mechanism behind enhanced immunity following vaccination, remained poorly explored in humans. Netea *et al.* demonstrated that BCG vaccination protects against experimental viral infection in humans. This was mediated via trained immunity in myeloid cells, with enhanced cytokine production on encountering viral pathogens, following BCG vaccination [32••].

HIF activation has now been established to play an indispensable role in trained immunity. Induction of trained immunity in macrophages requires a metabolic switch from oxidative phosphorylation to aerobic glycolysis. This is in keeping with previous studies examining the neuroprotective effect of hypoxia on brain injury outcomes by inducing an altered metabolic state [33]. Exposure of monocytes to β-Glucan (the main cell wall component of *Candida albicans*) strongly potentiated cytokine production upon restimulation with LPS. In this model, the crucial switch in macrophage metabolism, responsible for the enhanced cytokine response, was mediated via activation of the Akt/mTOR/HIF1α pathway [34••]. Moreover, trained immunity was abrogated in HIF1α myeloid-specific knock out mice (mHIF1α KO) and by chemical inhibition of HIF. Pre-exposure to β-Glucan increased survival in wild type mice inoculated with *Staphylococcal aureus*, however, this phenomenon was lost in mHIF1α KO mice [34••].

Preconditioning of the innate immune system

In parallel to the trained immune response within the macrophage population, more recent evidence exists demonstrating that short lived cells can also be reprogrammed by hypoxia. In a study by Thompson *et al.*, mice which were preconditioned with chronic hypoxia before

exposure to *S. pneumoniae* had significantly improved morbidity and mortality in comparison to controls, despite equal bacterial burdens existing in both groups [35••]. This was mediated by a recalibration of leucocyte metabolism, via suppression of HIF during prolonged hypoxia. Moreover, this effect was long lasting as shown by improved outcomes up to 28 days after pre conditioning, suggesting that chronic hypoxia has the ability to induce metabolic reprogramming of leucocyte populations, with improved host pathogen outcomes.

Immune tolerance

Whilst trained immunity can lead to greater cytokine production and improved host pathogen outcomes, functional reprogramming of myeloid cells can also lead to the immune phenomenon of 'tolerance'. Essentially the converse outcome of innate immune memory, tolerance describes diminished immune responses on re-exposure. LPS stimulation of macrophages has long been recognised to exhibit this phenomenon [36]. LPS tolerance is thought to underpin the concept of immune paralysis, a major source of morbidity in intensive care units. Crucially, here too, HIF activation and hypoxia play a critical role. Shalova *et al.* have shown that during sepsis, human monocytes undergo significant reprogramming to an immunosuppressive state [37]. This reprogramming is regulated by HIF activity. During sepsis, monocytes upregulate HIF1-α. HIF1-α in turn upregulates IRAKM, which suppresses Toll Like Receptor signalling, thus inducing a programme of immune tolerance. This can be beneficial in limiting the cytokine storm and systemic inflammation induced by LPS stimulation but leaves patients exposed to secondary infections.

Hypoxia mediated immune reprogramming in T cells

It is worth noting that a similar concept exists in cells of the adaptive immune system. The host's success in surviving chronic infections can depend on its ability to dampen the response to prolonged pathogen exposure and there is evidence of 'immune exhaustion' in T cells following chronic viral infections such as Hepatitis B and C [38]. Once more, this adaptation is regulated by HIF. T Cells deficient in VHL (which targets HIF for degradation) are refractory to T cell immune exhaustion. HIF accumulation leads to enhanced glycolytic metabolism with augmented effector function, such as granzyme and TNF release. In this model, HIF stabilisation, in contrast to its role in LPS tolerance in monocytes, abrogates immune tolerance and re programmes T cells towards a more inflammatory state. Though viral loads were reduced in mice with VHL deficient T cells, a more aggressive immune response ultimately increased mortality due to ensuing tissue damage [39].

Pathogens

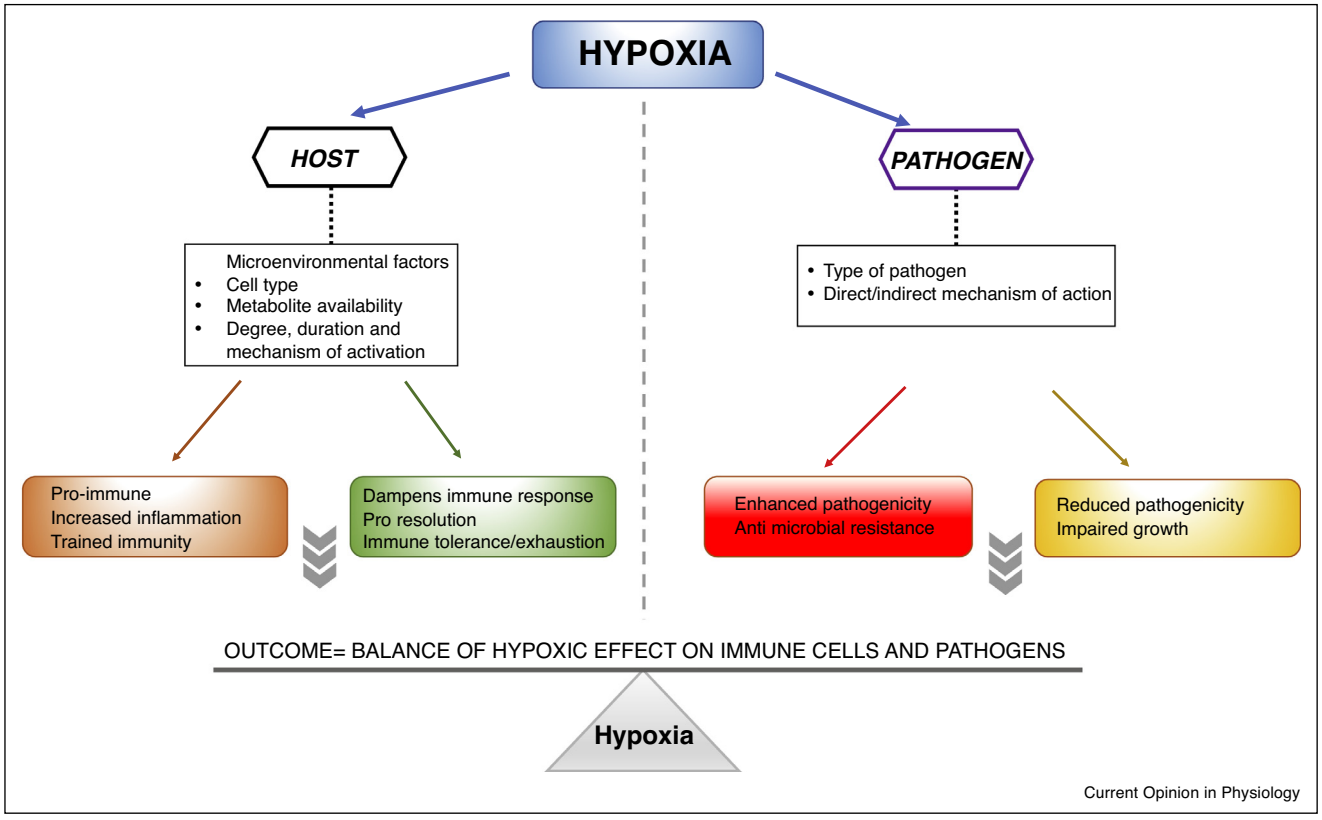
As discussed, simultaneous to adaptions in the host, pathogens are also constantly adapting to hypoxic environments. Though less characterised than the changes evoked in the immune system, hypoxia may impact on key functions of invading pathogens such as virulence and growth. For example, *S. aureus*, the causative pathogen in hypoxic disease processes such as osteomyelitis and abscess formation, exhibits increased virulence in hypoxic conditions [40,41]. Conversely low oxygen availability reduces both virulence and invasiveness in Group B Streptococcus [42]. Hypoxia may assist latency in *Mycobacteria tuberculosis* by slowing down replication and inducing an altered metabolic programme [43]. Recent evidence has emerged suggesting that hypoxic growth conditions confer antimicrobial resistance in approximately a third of MTB clinical isolates [44].

Major advances have recently taken place, characterising the hypoxic response in the bacterial species *Pseudomonas*. *Pseudomonas* contains a 2-oxoglutarate (2OG)-dependent *Pseudomonas* prolyl hydroxylase (PPHD), which is homologous to the PHDs in eukaryotes, and provides a mechanism for *Pseudomonas* to directly sense and respond to oxygen availability [11]. Hypoxia reduces the pathogenicity of *Pseudomonas* by decreasing a number of virulence factors [45•]. One of these factors, pyocyanin, is a toxic phenazine metabolite which directly affects neutrophil function and induces apoptosis. Pyocyanin production is reduced in hypoxia, with a consequent reduction in pyocyanin induced neutrophil apoptosis [46•]. Critically, expression of the oxygen sensing domain of *Pseudomonas* was found to regulate pathogenicity, even in normoxic conditions. A PPHD deficient strain of *Pseudomonas* had increased pyocyanin production and resulted in higher mortality and acute lung injury using an *in vivo* model [46•].

Conclusions

In summary, many host pathogen interactions take place in areas characterised by hypoxia. The ability of both the host and pathogen to respond and adapt to hypoxia leads to profound alterations in immune defences and pathogen virulence and growth. Recent advances have highlighted the pivotal role of hypoxia and HIF activation in immune reprogramming, regulating key elements of trained immunity, tolerance and hypoxic preconditioning of the immune response. HIF activation can occupy divergent roles in regulation of the inflammatory response in the host and the net outcome is highly dynamic and context and cell type specific (Figure 1). This is an increasingly important phenomenon to recognise in the therapeutic setting. Whilst manipulation of the HIF/hydroxylase pathway may offer enticing therapeutic opportunities in the future, considerations will have to be given to the effect this will have on pathogens and understanding the net balance of these outcomes will be of critical importance.

Figure 1



The dynamic balance between pro and anti-host hypoxic activation determines the outcome of hypoxic host pathogen interactions.

Funding

This research was supported by a Wellcome Trust Research Training Fellowship (Ref 203644 - EMR) and a Wellcome Trust Senior Clinical Fellowship award (Ref 098516 and 209220 - SRW)

Conflict of interest statement

Nothing declared.

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- • of special interest
- •• of outstanding interest

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