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Role of oxygen sensing and hypoxia-inducible factors in orchestrating innate immune responses

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Oxygen availability and fluctuation are common changes in tissues and organs undergoing infection and damage. While acute hypoxia can rapidly alter immune cell metabolism and activity, chronic hypoxia can induce long-lasting changes in immune responses via oxygen-guided adaptation in signaling cascades and epitranscriptomic programs. These adaptations are orchestrated mainly by oxygen-sensing hydroxylases and oxygen-sensing epigenetic modifiers that regulate downstream hypoxia-inducible factor pathways and epigenetic reprogramming. In this Review, we summarize how acute and chronic hypoxia influence innate immune cell function and metabolism, thereby tailoring immune cell behavior within the tissue microenvironment. We further highlight the dual roles of hypoxia in regulating innate immune cell function in different (patho)physiological contexts and evaluate therapeutic strategies that target oxygen-sensing pathways to restore immune competence and tissue homeostasis.

Oxygen is essential for aerobic organisms, particularly for sustaining cellular energy production through oxidative metabolism. To maintain bioenergetic homeostasis, cells require a continuous supply of molecular oxygen. While the partial pressure of atmospheric oxygen (pO_2) levels is around 160 mm Hg, pO_2 decreases notably under normal physiological conditions as blood circulates through peripheral tissues due to local oxygen consumption. Consequently, most tissues operate at much lower pO_2 levels (30–76 mm Hg), a range known as physioxia[1]. By contrast, the gastrointestinal tract and bone marrow naturally function at even lower pO_2 levels under homeostatic conditions[2,3]. It is generally believed that these hypoxic niches critically influence immune cell localization and function, particularly in regions of active cell proliferation and elevated metabolic demand. Conversely, pathological hypoxia, arising in inflamed, fibrotic or neoplastic tissues, can profoundly alter immune cell metabolism, gene expression profiles and effector function. To maintain tissue homeostasis in response to physiological and pathological scenarios, immune cells should rapidly adapt to fluctuating oxygen levels. Among immune cells, myeloid cells are uniquely positioned as frontline sentinels due to their broad tissue distribution and prompt responsiveness to changes in the microenvironment, especially oxygen availability.

In this Review, we focus on how myeloid cells detect and respond to oxygen availability in the local tissue microenvironment and discuss how acute and chronic hypoxia modulates myeloid cell functions and influences their overall outcomes. We summarize the molecular mechanisms underlying these responses and highlight their relevance in inflammation, fibrosis and cancer. This understanding could serve as a springboard for us to delineate adaptation engaged by other immune cells, which can be applied for developing treatments and synthetic circuits for cellular therapies.

Oxygen sensing and downstream signaling axes

The 2-oxoglutarate (2-OG)-dependent dioxygenases (2-OGDDs) are an oxygen-sensitive protein family. Their catalytic activity begins with binding 2-OG and ferrous iron at the active sites, followed by molecular oxygen that drives the decarboxylation of 2-OG to succinate[4]. While oxygen availability is the main regulator, 2-OGDDs are also highly sensitive to metabolic and redox cues. Metabolites such as succinate and

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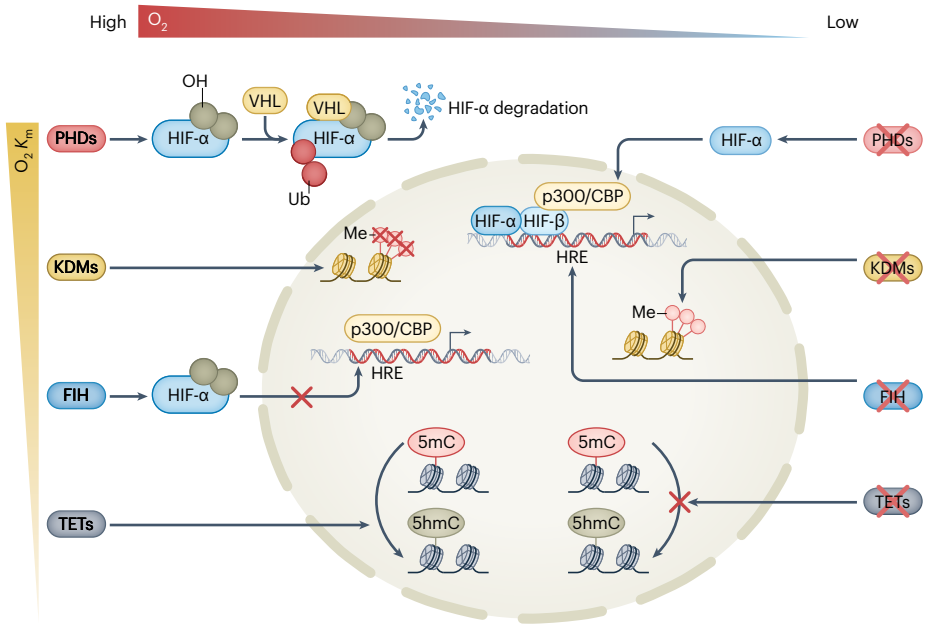

Fig. 1 | Mechanisms of oxygen sensing. The family of 2-OGDDs has distinct affinities to oxygen measured by the Michaelis constant (K_m value). PHDs and FIH regulate HIF-α and bind to von Hippel–Lindau (VHL) protein, which results in polyubiquitylation for proteasomal degradation in normoxia. When oxygen levels drop, PHDs and FIH are inactivated and HIF-α translocates to the nucleus to create a heterodimeric complex with HIF-1β that binds to hypoxia-responsive elements (HREs) on HIF target genes. Demethylation of histones and DNA by KDMs and TET enzymes, respectively, are carried out by HIF-independent epigenetic regulators that modify chromatin accessibility and transcription. Me, methyl; Ub, ubiquitin; 5mC, 5-methylcytosine; 5hmC, 5-hydroxymethylcytosine.

fumarate act as competitive inhibitors[5,6], and oxidative stress can inactivate their iron center and impair enzymatic activity[7–9]. These features integrate metabolic and redox stress into oxygen-sensing pathways.

Among 2-OGDDs, prolyl hydroxylase domain proteins 1–3 (PHD1–PHD3) and factor inhibiting hypoxia-inducible factor (HIF) (FIH) are well-characterized oxygen sensors[10,11] (Fig. 1). These enzymes regulate the stability and transcriptional activity of HIFs, which are key transcriptional regulators of hypoxic responses. HIF-1α is ubiquitously expressed in immune cells, whereas HIF-2α is more restricted and is particularly expressed among myeloid cells in tumor-associated macrophages (TAMs) and neutrophils[12,13]. The functions of HIF-3α remain largely unknown, although it may antagonize HIF-1α and HIF-2α[14]. Under normoxia, PHDs hydroxylate proline residues on HIF-α subunits (HIF-1α, HIF-2α and HIF-3α), which marks their ubiquitination by the von Hippel–Lindau E3 ubiquitin ligase complex and leads to subsequent proteasomal degradation[15]. Meanwhile, FIH hydroxylates asparagine residues within the HIF-α C-terminal transactivation domain, which blocks its interaction with their transcriptional coactivators[15,16]. By contrast, hypoxia inactivates these enzymes, allowing HIF-α to stabilize, dimerize with HIF-1β (also called aryl hydrocarbon nuclear translocator), translocate to the nucleus and recruit cofactors, including p300 and CBP, to bind hypoxia-responsive elements located in the promoter regions of HIF target genes[16]. The coordination of these actions promotes hypoxia-induced signaling cascades and metabolic reprogramming. Of note, PHDs and FIH preferentially hydroxylate HIF-1α more efficiently than HIF-2α[17], which may contribute to context-specific function in tissues such as the liver. For instance, HIF-2α activation in hepatic macrophages can limit inflammation in acetaminophen-driven liver injury[18], highlighting the context-dependent roles of HIF isoforms in tissue immunity.

In addition to modulating signaling cascades and metabolic reprogramming via HIFs, other 2-OGDDs, including Jumonji C domain-containing lysine demethylases (KDMs) and ten–eleven translocation (TET) enzymes, can orchestrate dynamic alterations in histone and DNA methylation patterns in an oxygen-dependent manner, independently of HIFs[19–21]. For instance, hypoxia-induced inactivation of KDM5A and KDM6A alters chromatin accessibility and can mimic an acute hypoxic transcriptional landscape[20,22]. Similarly, TET enzymes mediate DNA demethylation through 5-methylcytosine oxidation to 5-hydroxymethylcytosine and alter their epigenetic profile in oxygen- and metabolic-dependent responses[21,23].

Because multiple 2-OGDD enzymes can modulate cellular behaviors by sensing oxygen availability, it is critical to have a tight control on governing the participation of those enzymes. Intriguingly, 2-OGDD enzymes exhibit distinct oxygen affinities that result in a graded sensitivity to varying hypoxia. PHDs with low oxygen affinity (Michaelis constant (K_m) = 230–250 μM) are rapidly inactivated in response to hypoxia[24]. By contrast, FIH with substantially higher affinity (K_m = 90 ± 20 μM) remains active at moderate hypoxia[17], suggesting that FIH may continue to repress HIF transcriptional activity after PHDs are inactivated and FIH may provide a particular significance in fine-tuned responses across oxygen gradients. On the other hand, TETs and KDMs have even higher oxygen affinities (TETs, K_m = 30 μM; KDMs, K_m = 20–180 μM)[22,25,26], which implies that they are inhibited only during severe or sustained hypoxia. As TETs and KDMs have higher oxygen affinities, they may function as oxygen-dependent effectors that shape transcriptional and epigenetic networks under chronic hypoxia, rather than as precise sensors of oxygen availability[19]. Their sustained activity over longer hypoxic exposures may contribute to epigenetic changes that alter immune cell function in a context-dependent manner.

Modulation of inflammatory responses during acute hypoxia

Inflammation is often accompanied by acute hypoxia that is driven by several converging mechanisms. First, tissue and vascular damages impair oxygen delivery[27]. Second, the increased metabolic demand from infiltrating immune cells for ATP production, cytokine synthesis and other biosynthetic processes heightens oxygen consumption in the inflamed microenvironment[28]. Lastly, the oxidative burst from immune cells, such as neutrophils, consumes large amounts of oxygen[29]. Of note, the resulting hypoxic environment could further orchestrate both pro- and anti-inflammatory effects in innate immune cells by modulating

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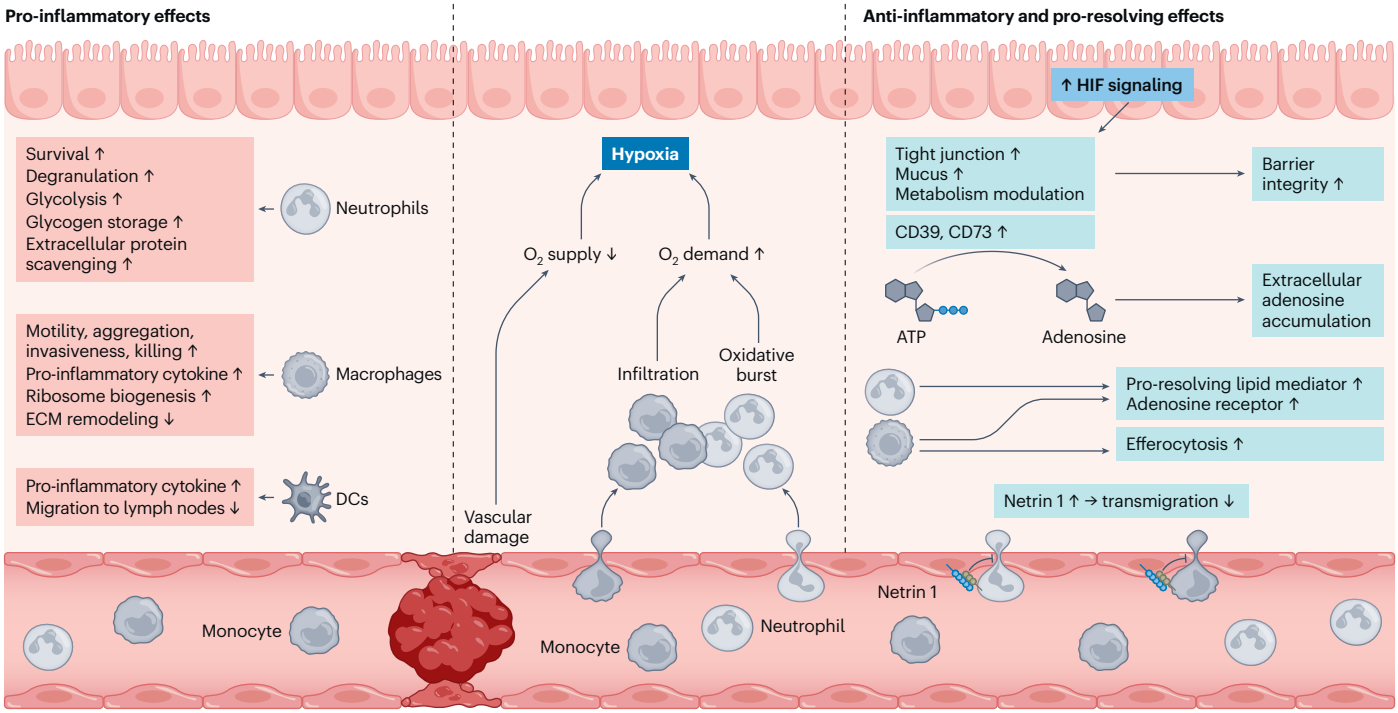

Fig. 2 | Influence of acute hypoxia on immune cells during inflammation. Acute hypoxia develops during inflammation due to decreased oxygen supply from vascular damage and increased oxygen demand from recruited leukocytes, which consume oxygen through oxidative bursts to produce reactive oxygen species. Hypoxia plays a dual role in inflammation, exerting both pro-inflammatory and anti-inflammatory effects. On the pro-inflammatory side, hypoxia enhances neutrophil survival and degranulation while modulating their metabolism to adapt to low-oxygen conditions. Additionally, HIF signaling is crucial for regulating macrophage and DC functions. Conversely, hypoxia suppresses inflammation, mainly through HIF-mediated mechanisms. HIF signaling preserves epithelial barrier integrity, thereby limiting tissue damage. Hypoxia also induces the upregulation of CD39 and CD73, leading to the accumulation of extracellular adenosine, a prominent anti-inflammatory mediator. HIF enhances adenosine signaling by upregulating its receptors on immune cells and suppresses leukocyte transmigration through upregulation of netrin 1. Additionally, hypoxia facilitates resolution of inflammation by promoting secretion of lipid mediators and enhancing efferocytosis.

downstream signaling pathways, which increases the complexity of the regulation of inflammation (Fig. 2).

Hypoxia-driven pro-inflammatory responses

Neutrophils, the first responders during inflammation, are strongly influenced by hypoxia. Neutrophils depend mainly on glycolysis and have minimal reliance on mitochondrial respiration for their bioenergetic demands[30]. Under hypoxia, glycolytic gene expression is upregulated in a HIF-1-dependent manner[31]. Low oxygen tension enhances neutrophil survival by suppressing apoptosis and promotes their bioenergetic activity through increased degranulation, collectively contributing to heightened neutrophilic inflammation and tissue damage[32,33]. Loss of PHD2 leads to excessive neutrophilic inflammation due to increased glycolysis and glycogen storage[34]. Hypoxia promotes glycogen accumulation through upregulation of glycogen synthase 1 (ref. 35). Glucose derived from glycogen also fuels the pentose phosphate pathway to support NADPH regeneration, which is required for oxidative bursts[36]. Additionally, hypoxia further facilitates nutrient uptake and recycles extracellular proteins by modulating mTOR activity, which can be used for de novo protein synthesis to meet biosynthetic demands of activated neutrophils[37].

Macrophages are also influenced by hypoxia during inflammation. Hypoxia potentiates production of the pro-inflammatory cytokine IL-1β in bone marrow-derived macrophages after lipopolysaccharide stimulation via HIF-1α-driven metabolic reprogramming[6]. HIF-1α also controls macrophage motility, aggregation, invasiveness and microbicidal capacity. Thus, the genetic ablation of HIF-1α in myeloid cells alleviates pathology in several inflammatory models[38]. Similarly, HIF-2α can also regulate the expression of pro-inflammatory cytokines under hypoxic conditions[12]. In contrast to macrophages, the influence of hypoxia on dendritic cell (DC) functions is largely underexplored. Monocyte-derived DCs exposed to hypoxia exhibit increased production of pro-inflammatory cytokines while simultaneously downregulating costimulatory molecules and having impaired migration to lymph nodes[39]. Furthermore, hypoxia can induce the expression of triggering receptor expressed on myeloid cells 1 in DCs, at least in part through HIF-1α activity. Subsequent interaction of triggering receptor expressed on myeloid cells 1 with its adaptor protein DAP12 activates downstream signaling pathways that promote pro-inflammatory cytokine production[40]. Altogether, the impact of acute hypoxia on myeloid cells, however, is highly context dependent. In certain settings, acute hypoxia can enhance inflammatory responses by influencing survival, metabolism and effector functions in neutrophils, macrophages and DCs. Yet other studies demonstrate that HIF signaling can also restrict inflammatory activity in these cells during acute hypoxia. This duality highlights the complexity of HIF biology, and, in the following section, we further discuss its anti-inflammatory functions.

Anti-inflammatory roles of HIF signaling

Although acute hypoxia promotes inflammation responses in myeloid cells, pharmacological stabilization of HIFs via hydroxylase inhibition can paradoxically elicit anti-inflammatory effects that are essential for tissue-protective adaptive responses[41–43]. These contradictory outcomes in immune cells and animals treated with stabilizers of HIFs raise a possibility that HIF signaling can elicit cell type-specific and/or duration-dependent regulation of inflammation and tissue repairing. Supporting this, a recent clinical trial of HIF stabilizers in patients with acute respiratory distress syndrome showed significant

improvement in disease outcomes and greater overall benefit after treatment[44]. Similarly, HIF stabilization driven by local hypoxia during intestinal inflammation results in transcriptional changes in the local tissue that enhance barrier function[27]. HIF-1α upregulates genes encoding tight junction proteins and mucus production in intestinal epithelial cells, strengthening gut barrier integrity[45]. HIF-2α can also promote myocardial protection during ischemia–reperfusion injury by inducing amphiregulin expression in cardiac myocytes, thereby enhancing ischemia tolerance[46]. Interestingly, myocardial infarction is influenced by diurnal amphiregulin expression, which is regulated by BMAL1–HIF-2α under acute hypoxia. In line with this disease kinetic, pharmacological stabilization of HIF-2α provides significant protection in patients with myocardial infarction[47]. In addition, HIFs also exert anti-inflammatory effects through modulation of the adenosine signaling pathway. Adenosine, a nucleoside integral to both nucleic acid structure and energy metabolism, also functions as a potent anti-inflammatory mediator[48]. During inflammation, activated immune cells, especially neutrophils, and dying cells release large amounts of ATP, which acts as a pro-inflammatory danger signal[49,50]. Under hypoxic conditions, HIF-1α and SP1 coordinately upregulate the expression of CD39 and CD73, ectoenzymes that convert extracellular ATP and ADP into adenosine[51,52]. This shift results in the accumulation of anti-inflammatory extracellular adenosine and the depletion of pro-inflammatory ATP. The relevance of this pathway is supported by findings that deficiency in CD39 or CD73 exacerbates disease severity in mouse acute lung injury through excessive inflammation, whereas treatment with adenosine A2B receptor agonist ameliorates the disease[53]. In addition to promoting adenosine production, HIFs enhance this pathway by upregulating adenosine receptors on various immune cells, further amplifying the anti-inflammatory effects of adenosine[54,55]. In addition to the adenosine signaling axis, HIF-1α can stimulate anti-inflammatory responses by upregulating netrin 1 expression, a neuronal guidance molecule. Under hypoxic conditions, epithelial cells upregulate netrin 1, which interacts with the adenosine A2B receptor on neutrophils to inhibit their transmigration and reduce inflammation[56]. Furthermore, netrin 1 expressed by endothelial cells also inhibits leukocyte migration by binding to its receptor UNC5B[57]. Myeloid cells can also substantially upregulate netrin 1 expression in response to hypoxia[58]. In lipopolysaccharide-induced lung injury models, myeloid-derived netrin 1 suppresses inflammation by limiting natural killer cell infiltration[59]. During myocardial ischemia and reperfusion injury, netrin 1 expression is upregulated in neutrophils in a HIF-1α-dependent manner, contributing to cardioprotection by limiting tissue damage[60]. In sum, HIF stabilization elicits anti-inflammatory effects through adaptive responses in tissues, particularly by enhancing barrier functions. These effects are further mediated by the increase in anti-inflammatory molecules such as extracellular adenosine and netrin 1, reinforcing the role of HIF signaling as a crucial modulator of inflammation. Overall, the HIF-mediated transition from pro- to anti-inflammatory responses under acute hypoxia warrants further investigation.

Resolution of inflammation and hypoxia

In addition to anti-inflammatory responses, emerging evidence suggests that hypoxia may play a role in resolving inflammation. Resolution of inflammation is a highly coordinated and active process involving multiple immune cells[61]. Macrophages play a central role in resolving inflammation by clearing apoptotic cells through efferocytosis. Notably, hypoxia promotes macrophage-mediated efferocytosis[62,63]. Mechanistically, oxidative bursts during inflammation create local hypoxia, which activates erythropoietin (EPO) signaling in macrophages. EPO promotes efferocytosis of apoptotic neutrophils, and macrophages egress from inflamed tissue via peroxisome proliferator-activated receptor γ-dependent pathways[63]. In addition to EPO, several lipids are reported as critical components of 'resolution metabolomes' for limiting acute inflammatory responses and modulating the clearance of pathogens, debris and apoptotic cells[64]. Among these lipid mediators participating in resolving inflammation, hypoxia can promote the biosynthesis of lipoxins and resolvins in both macrophages and neutrophils. These emerging findings further support the involvement of hypoxia in the resolution of inflammation and restoring tissue homeostasis[65]. However, it remains unclear how coordination among the responsible oxygen sensors, the severity and duration of hypoxia and the cell type determine which outcome (pro-inflammation, anti-inflammation or resolution of inflammation) occurs.

Modulation of immune responses during chronic hypoxia

Oxygen tension is dynamically regulated during the progression of tissue repair[1]. However, nonresolving inflammation profoundly depletes oxygen levels within dysregulated tissue architectures, which drives context-dependent effects on innate immune cells. Compared to structurally intact tissues, fibrotic and tumor tissues often exhibit oxygen levels below 2% (ref. 1). Fibrotic tissues and tumors are classified as a 'condensed' microenvironment and likely experience reduced oxygen supply due to decreased capillary density and abnormal vasculature[66]. In response to this hypoxic stress, innate immune cells must promptly adapt metabolic processes and alter their functional features on the basis of the nature of the deregulated microenvironment. Here, we summarize the key changes elicited by chronic hypoxia in fibrotic tissues and tumors (Fig. 3).

Hypoxia and immune dynamics in fibrosis

Fibrosis is a hallmark of many chronic diseases, including pulmonary fibrosis and liver cirrhosis, that are driven by chronic injury and nonresolving inflammation. Fibroblasts maintain extracellular matrix (ECM) homeostasis by depositing fibrous collagen, fibronectin and proteoglycans, which are essential components of the wound-healing process[67]. While sufficient oxygen supply is critical for the later stages of wound repair, acute hypoxia occurring during the early phase of repair promotes transforming growth factor β (TGF-β) secretion and fibroblast proliferation[68]. Persistent tissue hypoxia, however, leads to the activation of HIF-mediated signaling pathways, sustaining an environment conducive to fibrogenesis[66]. Prolonged differentiation of fibroblasts to myofibroblasts under hypoxic conditions further drives excessive ECM deposition, disrupting normal tissue architecture and resulting in pathological fibrosis[67]. The development of fibrosis involves a complex interplay between immune cells, fibroblasts and ECM components, highlighting the critical role of the immune system in orchestrating and exacerbating fibrotic processes.

Under hypoxic conditions, neutrophils exhibit heightened activities to secrete excessive neutrophil elastases and promote neutrophil extracellular trap (NET) formation, which is a glycolysis-dependent process. NET-driven inflammation significantly contributes to excessive myofibroblast proliferation, linking neutrophil activity to pulmonary fibrotic amplification[69,70]. Enhanced NET formation further intensifies inflammatory signaling cascades by activating fibroblasts through TGF-β signaling, which establishes a critical link between neutrophil-driven inflammation and fibrotic progression[71,72]. Moreover, HIF-2α supports neutrophil survival via cIAP-1 signaling and delays engulfment by macrophages, thereby promoting cardiac fibrosis after myocardial infarction[13]. Together, these HIF-mediated processes underscore the pivotal role of neutrophils in driving pathological fibrosis progression. However, it remains largely unclear whether spatial oxygen gradients within fibrotic tissues can dynamically shape neutrophil survival, effector functions and their interactions with stromal and immune cells, potentially opening new avenues for targeting fibrotic diseases. By leveraging new tools in spatial analyses, the information on this topic may further reveal how hypoxia can orchestrate neutrophil-mediated immune responses in vivo.

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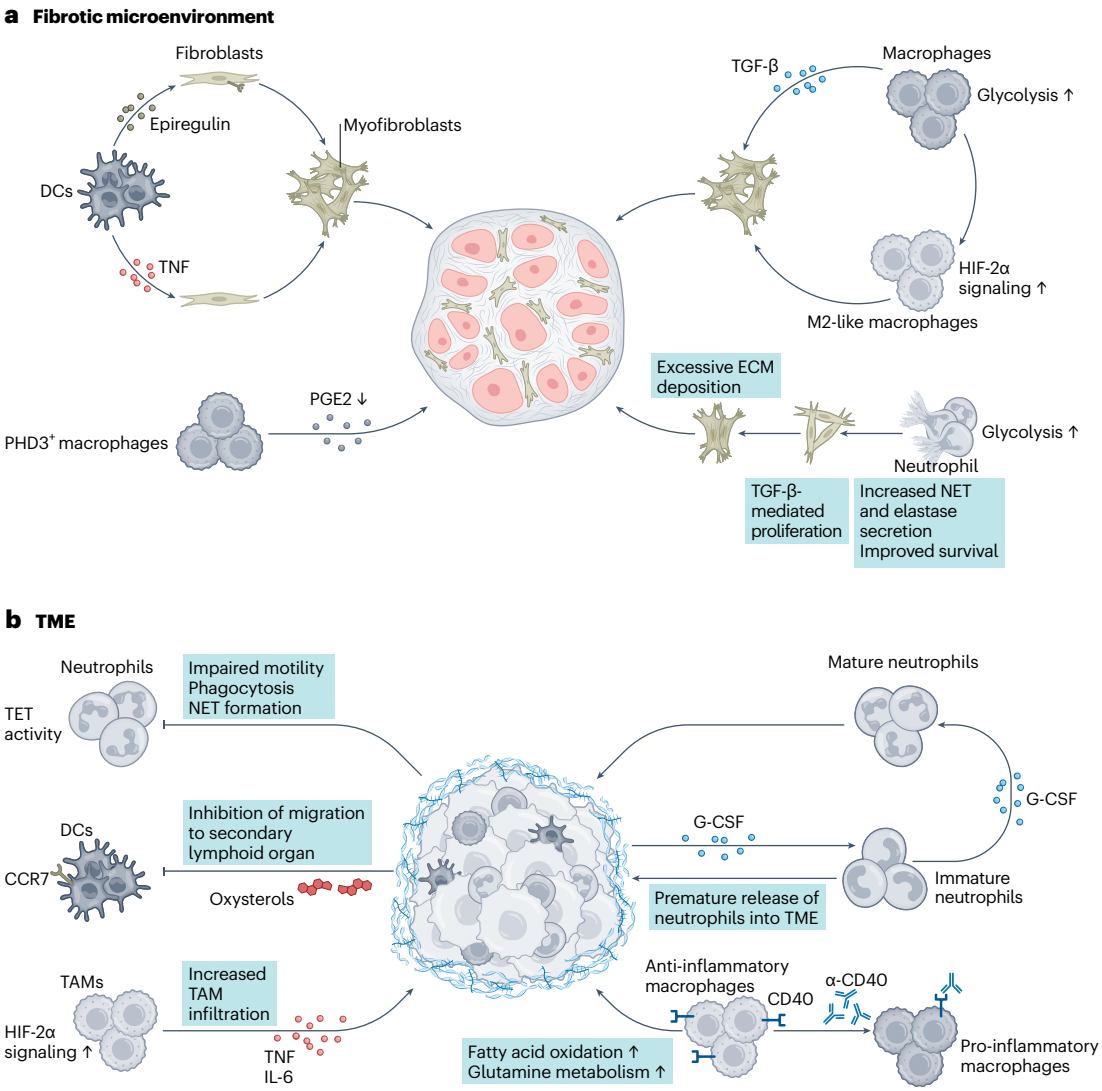

Fig. 3 | Myeloid cell adaptation to hypoxia in the fibrotic microenvironment and the TME. a, In the fibrotic microenvironment, persistent hypoxia drives neutrophil infiltration and the release of NETs and elastase, promoting TGF-β-mediated fibroblast activation and excessive ECM deposition. DCs secrete TNFand epiregulin, facilitating fibroblast-to-myofibroblast differentiation. Macrophages with increased glycolytic activity upregulate HIF-2α signaling and produce TGF-β, further contributing to myofibroblast activation and fibrosis. **b**, In the TME, granulocyte colony-stimulating factor (G-CSF) induces the premature release of immature neutrophils, which differentiate into mature neutrophils with impaired effector function due to TET enzyme activity. TAMs undergo metabolic reprogramming, marked by enhanced fatty acid oxidation and glutamine metabolism, supporting tumor growth and immune suppression. Agonistic anti-CD40 signaling reprograms macrophages toward a pro-inflammatory phenotype. Tumor-derived oxysterols inhibit DC migration by downregulating CCR7 expression.

Monocyte-derived macrophages infiltrate into injured tissues and modulate fibrotic processes[73,74]. For instance, monocyte-derived macrophages secrete growth factors such as TGF-β to activate myofibroblasts[75]. Hypoxia further supports survival of monocyte-derived macrophages by inducing HIF-1α-dependent metabolic reprogramming[76]. In addition, low oxygen tension activates HIF-2α-dependent signaling in macrophages, skewing their polarization toward an M2-like phenotype that exacerbates cardiac fibrosis after infarction[77]. In line with this, macrophage-specific deletion of the oxygen-sensing enzyme PHD3 can reduce fibrosis by promoting an anti-inflammatory phenotype, characterized by altered *Cyp2s1* expression and increased PGE2 secretion, without impairing blood flow recovery after ischemic injury[78]. These observations point to hypoxia as a key modulator of macrophage-driven fibrotic progression via HIF- and PHD3-dependent signaling cascades that shape the profibrotic activation states of macrophages and potentially coordinate their interactions with stromal and immune cells to sustain fibrosis. Notably, monocyte-derived alveolar macrophages express profibrotic gene signatures and drive the progression of bleomycin-induced lung fibrosis, whereas resident alveolar macrophages do not contribute to this pathology[79]. This suggests that the origin of macrophages may 'imprint' their ability to sense oxygen and elicit hypoxia-driven functional specialization.

In stiffer environments, such as fibrotic tissues, DCs are subjected to mechanical stress, which induces metabolic reprogramming of DCs toward a pro-inflammatory phenotype[80]. This involves increased tumor necrosis factor (TNF) secretion, which amplifies tissue fibrosis by stimulating fibroblast-mediated fibronectin release[81]. Moreover, DC-derived epiregulin is implicated in the pathogenesis of skin and lung fibrosis, reinforcing its profibrotic function. The secretion of epiregulin is also induced by type I interferon, which activates epidermal growth factor receptor on fibroblasts, creating a positive feedback loop through NOTCH signaling[82]. However, the exact role of hypoxia and HIF stabilization in DCs residing in fibrotic tissues remains elusive. In conclusion, fibrosis is driven by the interplay between immune cells,

stromal components and the hypoxic microenvironment. Hypoxia reprograms myeloid cells through HIF signaling and oxygen-sensing enzymes such as PHDs, promoting profibrotic phenotypes. These insights highlight the critical role of immune cells and hypoxia-induced feedback loops in sustaining fibrosis and suggest new therapeutic opportunities to restore tissue homeostasis.

Hypoxia-driven tumor immune dysregulation

Tumors have been proposed as wounds that do not heal since the 1980s, and this intertwined relationship between unhealed wounds and hypoxia can be commonly observed in the tumor microenvironment (TME)[83,84]. The combined effects of rapid cancer cell proliferation and immune cell infiltration generate and exacerbate these hypoxic niches in tumors. In response to low-oxygen availability, tumor cells can more efficiently shift their metabolic preference toward glycolysis and other adaptive pathways to support their growth[85]. Concurrently, hypoxia reshapes the immune landscape, favoring the infiltration of immunosuppressive myeloid cells, including regulatory T cells and neutrophils, which can adapt to hypoxic conditions and drive immune evasion[85,86]. In addition, the activation of HIF-1α and HIF-2α can empower cancer cells to restrain T cell-mediated antitumor responses by promoting PD-L1 expression in cancer cells[87]. Deregulated tumor metabolic programs can simultaneously hinder immunotherapy efficacy by perturbing immunometabolic regulation in tumor-infiltrating immune cells[88–92].

Neutrophils are among the first responders in cancer-associated 'emergency' granulopoiesis, a process driven by elevated tumor-derived granulocyte colony-stimulating factor, which prompts their premature release into circulation[93,94]. However, the extent of functional differences between mature and immature neutrophils remains elusive. Recent studies demonstrated that tumor-infiltrating neutrophils exhibit context-dependent functions, classified into three tumor-associated neutrophil (TAN) subsets: immature T1, mature T2 and long-lived T3 subsets. T3 neutrophils, preferentially localized in regions enriched with the hypoxia signature, highly express genes related to glycolytic flux and exhibit a protumorigenic phenotype. Moreover, the abundance of T3 neutrophils in tumors correlates with poor prognosis in pancreatic and other solid tumors[95]. Although a direct mechanistic link between HIFs and functional polarization in the T3 subset remains unestablished, hypoxia-related signaling pathways have been speculated to influence neutrophil function and TAN heterogeneity. In support of this, neutrophils lacking HIF-2α produce less inflammatory mediators and delayed colon tumorigenesis, highlighting a role for HIFs in shaping TAN activity and tumor-promoting ability in neutrophils[96]. Furthermore, hypoxia also leads to DNA hypermethylation by suppressing TET enzyme-mediated DNA methylation, which might impair neutrophil motility, phagocytosis and NET formation[25,97].

Although HIF-1 and HIF-2 mediate both short- and long-term hypoxic responses, emerging insights suggest that hypoxia may actively reprogram DC function in the TME, not only by impairing migration and survival, but potentially by altering their antigen-presenting capacity and crosstalk with other immune cells. Mechanistically, hypoxia in the TME impairs DC function by hindering their maturation and inducing HIF-mediated expression of proapoptotic genes, including *BAX* and *Bcl2*. These alterations limit DC migration to lymph nodes and tumor-specific T cell priming by reducing expression of the G protein-coupled receptor CCR7 (refs. 98–100). Together, these effects allow tumors to evade immune surveillance and promote disease progression[101]. TAMs preferentially accumulate in hypoxic tumor regions, where HIF-1α enhances glycolysis and suppresses tricarboxylic acid cycle activity[102]. Additionally, upregulation of CD36 enables lipid scavenging and fuels fatty acid oxidation despite low oxygen levels, reinforcing the protumorigenic phenotype[103]. Tumor-derived lipids further drive the metabolic reprogramming of TAMs, accumulating as lipid droplets and giving rise to lipid-laden TAMs. Lipid-laden TAMs secrete protumorigenic factors, thereby accelerating disease progression by dampening type I interferon signaling[91,103,104]. In addition to lipid overloading, lactic acids enriched in the hypoxic TME promote acquisition of protumorigenic features in TAMs[105]. Targeting these metabolic programs offers therapeutic potential, as agonistic anti-CD40 monoclonal antibodies have recently been shown to reprogram TAMs toward an antitumor state by rewiring engagement of fatty acid oxidation or glutamine metabolism[106,107]. Conversely, tumor-induced alterations in lipid composition can stimulate TAM-mediated immunosuppression[91], which indicates the importance of metabolic cues in defining macrophage functions. Recent studies also showed that genetic ablation of HIF-2α in macrophages reduces TAM abundance, lowers tumor cell proliferation and delays progression in both hepatocellular carcinoma and colitis-associated cancer models[12]. These findings underscore the critical role of HIF-2α in TAM recruitment, highlighting the potential of targeting hypoxia-driven metabolic pathways in TAMs to reprogram their function and inhibit tumor progression. In support of this, a recent study also revealed that hyperbaric oxygen therapy can switch the TAM phenotype into antitumorigenic ones in glioblastoma mouse models[108].

In summary, hypoxia plays a central role in shaping the immunosuppressive TME by reprogramming immune cells such as neutrophils, macrophages and DCs toward protumorigenic phenotypes. Through HIF-mediated metabolic and functional changes, these cells contribute to immune evasion and tumor progression. Collectively, these findings highlight the potential of targeting hypoxia-driven immune modulation as a strategy to restore antitumor immunity and improve therapeutic outcomes.

Oxygen gradient as a key regulator of immune responses

In addition to fibrosis and the TME, dynamic oxygen gradients can form in the normal physiological context due to local metabolic activity, vascular architecture and cellular composition, which create distinct microenvironmental cues in some organs. Immune cells are sensitive to such gradients, as their metabolic profiles, effector function and interaction with neighboring cells are influenced by these conditions. The liver represents an example for how oxygen availability in anatomic niches may influence resident immune cell functionality. Anatomically, it is organized into hexagonal lobules, each containing a central vein at its core and branches of the portal vein and hepatic artery at the corners. This arrangement results in a well-defined zonal oxygen gradient that ranges from lower pO_2 near pericentral regions to higher oxygenation at periportal regions[109]. Zonal variation in hepatic oxygenation affects metabolism and regeneration, partly by influencing the behavior of Kupffer cells (KCs), liver-resident macrophages. KCs that reside in the periportal region respond to systemic bacteria transported from the gut to the liver via the portal vein[110], whereas KCs in the hypoxic pericentral regions exhibit lower lysosomal enzymatic activity and phagocytic capacity than those near the periportal region[111]. This example illustrates how oxygen availability can alter immune homeostasis in a tissue-specific manner, implicating that disruption in oxygen gradients, especially in disease settings, can fundamentally alter the overall immune response.

Therapeutic approaches

Pharmacological inhibition of PHD activity offers potential therapeutic avenues for inflammatory resolution. By preventing the hydroxylation and proteasomal degradation of HIF-α, PHD inhibitors stabilize HIF-α and activate downstream transcriptional programs. Notably, FDA-approved daprodustat (GlaxoSmithKline) and vadadustat (Akebia Therapeutics) are oral PHD inhibitors used to treat anemia in chronic kidney disease by enhancing endogenous EPO production[112]. Interestingly, EPO expression in the kidney is regulated mainly by HIF-2, not HIF-1, supported by the broader role of HIF-2 in iron metabolism[113]. In addition to erythropoiesis, these compounds also influence immune responses, including macrophage polarization toward

profibrotic or wound-healing phenotypes[112,114]. However, current PHD inhibitors activate both HIF-α isoforms, which may lead to unwanted context-dependent side effects[115]. Generating isoform-specific inhibitors that selectively modulate HIF-α target gene expression in a tissue- or disease-specific manner remains an important future challenge.

By contrast, direct inhibition of HIF signaling represents an alternative therapeutic strategy particularly in cancer. Compounds, including EZN-2968 and PX-478, inhibit *HIF1A* translation and have shown promising outcomes in preclinical cancer models, characterized by limiting angiogenesis and tumor growth[112]. Acriflavine, which disrupts the HIF-1α–p300 transcriptional interaction, has demonstrated potential in models of retinal neovascularization[116]. In some tumors in which both HIF-α isoforms promote disease, dual inhibition of both HIF-1α and HIF-2α may provide synergistic therapeutic benefits, as targeting one isoform can lead to compensatory upregulation of the other[117]. Together these strategies highlight the therapeutic value of context-dependent modulation of HIF signaling in pathological diseases.

Overall, therapeutic interventions targeting oxygen-sensing pathways must be carefully tailored to the specific context. Intervention could inadvertently impair healing or weaken immune responses in cases of 'beneficial' transient hypoxia during inflammation or repair. Conversely, targeting oxygen-sensing mechanisms in 'pathological' hypoxia, such as within the TME or chronic inflammatory diseases, may offer therapeutic advantages by improving oxygenation, mitigating inflammation or suppressing tumor progression. Given that the activity of oxygen-sensing enzymes can be altered under normoxia through cytokines, metabolic intermediates and reactive oxygen species, further research is needed to encompass a wider oxygen-sensing regulatory network for safe and context-specific targeting[6,118].

Concluding remarks

Tissue oxygenation is not a static but a dynamic process that changes over time and is influenced by microenvironmental cues and anatomic structures. During inflammation, local oxygen tension fluctuates with vascular perfusion, metabolic demands and immune cell infiltration. In chronic pathological settings, hypoxia becomes sustained and may shape immune function differently than acute exposure. Yet how the duration and intensity of hypoxia exposure influence immune cell adaptation in vivo remains poorly understood, as we lack experimental models that accurately capture and record the temporal changes of hypoxia in immune cells. Current methodologies still rely on fixed oxygen in vitro systems or indirect pimonidazole staining, which lack sensitivity and spatial resolution to detect intermittent or cumulative oxygen exposure patterns in living tissues. Emerging technologies, such as intracellular oxygen nanoprobes, intravital imaging and three-dimensional organoids or organ-on-chip platforms, could offer innovative solutions to overcome the limitations by providing real-time, in situ oxygen mapping[119]. Developing more physiologically relevant models is essential for recording the kinetic and spatial complexity of oxygen exposure and to understand how oxygen-sensing pathways contribute to functional immune responses in vivo.

Oxygen-sensitive signaling pathways can drive both pro- and anti-inflammatory responses. Although HIFs contribute to both immune responses, the net outcomes of HIF activation tend to be anti-inflammatory, as evident from protective effects following pharmacological HIF stabilization. We speculate that this duality may depend on the severity and duration of hypoxia. During the early stages of inflammation, rapid infiltration of leukocytes induces severe acute hypoxia, which may amplify pro-inflammatory responses. As inflammation resolves and tissue injury subsides, oxygen demand decreases, leading to a milder hypoxic environment that may favor anti-inflammation. Another possible factor is the dynamic changes in immune cell composition within the tissue at different stages of inflammation. Different immune subsets likely interpret hypoxic signals distinctively, which further influences the balance between pro- and anti-inflammatory outcomes. In addition to HIFs, epigenetic enzymes regulated by oxygen levels could contribute to an additional layer of control as modulators of inflammation. However, most findings rely on global inhibition or genetic deletion without directly addressing the role of these enzymes in hypoxic environments. Thus, developing tools that allow temporal and spatial perturbation of these epigenetic regulators in immune cells could unveil the dynamic nature and contribution of these oxygen sensors in tailoring hypoxia-induced immune responses.

Finally, we still lack a unifying model that explains how varying oxygen levels elicit distinct cellular responses. A key factor may lie in the differential oxygen affinities of various oxygen sensors. PHDs are inhibited by mild hypoxia, while TETs and KDMs require more severe or sustained oxygen deprivation to lose activity. As epigenetic regulators typically induce slower changes than transcription factors, they may shape immune phenotypes mainly under chronic hypoxia. Mapping the sensitivity ranges of these sensors uncovers a hierarchy of oxygen thresholds that helps govern immune responses across fluctuating oxygen availability.

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Competing interests

P.-C.H. is a cofounder of Pilatus Biosciences.

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