HIF1α is a common component of pathways involved in the control of cellular metabolism and has a role in regulating immune cell effector functions. Additionally, HIF1α is critical for the maturation of dendritic cells and for the activation of T cells. HIF1α is induced in LPS-activated macrophages, where it is critically involved in glycolysis and the induction of proinflammatory genes, notably Il1b. The mechanism of LPS-stimulated HIF1α induction involves succinate, which inhibits prolyl hydroxylases (PHDs). Pyruvate kinase M2 (PKM2) is also induced and interacts with and promotes the function of HIF1α. In another critical inflammatory cell type, Th17 cells, HIF1α acts via the retinoic acid–related orphan receptor-γt (RORγt) to drive Th17 differentiation. HIF1α is therefore a key reprogrammer of metabolism in inflammatory cells that promotes inflammatory gene expression.
**HIF1α and metabolic reprogramming in inflammation**


School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College, Dublin, Ireland.

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**Introduction**

ATP production is required to support physiological function in all cells. Methods of ATP production vary between cell types and cellular activation states. Glucose can be used to fuel ATP production through two linked metabolic pathways: glycolysis and the TCA cycle. In glycolysis, glucose is converted into pyruvate in the cytoplasm and phosphates are transferred to ADP to generate two molecules of ATP. Pyruvate can also be converted into acetyl-CoA, which enters the TCA cycle, linking the two processes. The TCA cycle produces NADH and flavin adenine dinucleotide (FADH2), which are used to fuel oxidative phosphorylation (OXPHOS) in the mitochondria to produce an additional 36 molecules of ATP. Cells can utilize other substrates aside from glucose depending on the context. Fatty acids and glutamine can both be used to fuel OXPHOS in some cells (1, 2).

A key feature of metabolic pathways is their plasticity. Changes in nutrient availability or oxygen levels are the best-characterized drivers of metabolic reprogramming. For example, hypoxia is a well-known driver of glycolysis, as an oxygen deficit results in limited OXPHOS. Under these circumstances cells must rely on glycolysis to generate ATP. HIF1α is critical for this process, as it induces the expression of glycolytic enzymes such as hexokinase and phosphofructokinase, thereby allowing for sustained ATP production (3, 4). Hypoxia and inflammation are inherently linked. Decreasing oxygen levels induce metabolic changes to sustain ATP production. Similarly, quiescent immune cells can be viewed as metabolically inert and require significant metabolic reprogramming upon activation to provide sufficient ATP for effector functions. The HIF pathway provides a switch through which metabolic phenotypes can be amended in both of these scenarios and therefore is a critical transcriptional regulator of immunity and inflammation (2).

HIF is a highly conserved member of the PER-ARNT-SIM (PAS) subfamily of the basic helix-loop-helix (bHLH) family of transcription factors (5). During active HIF signaling, HIF forms a heterodimeric complex that consists of an α and a β subunit. The α subunit can be of two primary forms, HIF1α or HIF2α. The β subunit is the constitutively expressed aryl hydrocarbon receptor nuclear translocator (ARNT). Upon dimerization, the HIF1α/ARNT complex translocates to the nucleus where it binds to the promoters of target genes containing hypoxia response elements (HREs). This binding initiates transcription of a battery of genes involved in cellular adaptation to hypoxia, metabolism, and cell function. HIF signaling is primarily regulated by the stability of its α subunit. In a resting cell, HIF1α is hydroxylated at conserved proline residues by the prolyl hydroxylases (PHDs). This hydroxylation allows for HIF1α ubiquitination by the von Hippel-Lindau (VHL) E3 ubiquitin ligase, marking it for rapid proteasomal degradation. The PHDs are oxygen dependent; thus, under normoxic conditions, HIF1α is continuously turned over by means of degradation, resulting in low basal HIF1α levels. In normoxia HIF1α has a remarkably short half-life of less than 5 minutes (6). Hypoxic conditions result in PHD inhibition and an attenuation of HIF1α hydroxylation. In the absence of proteasomal degradation, HIF1α accumulates, translocates to the nucleus, and increases transcription of HRE-containing genes.

In addition to changing levels of oxygen, another well-characterized example of a HIF-mediated switch to glycolysis has been described in tumors, whereby under normoxia, glycolysis still predominates. This metabolic switch has been termed the Warburg effect (7) and can be driven by mutations in proto-oncogenes such as Myc or Ras, which ultimately result in HIF1α-mediated metabolic reprogramming towards a glycolytic phenotype. Hypoxia is a prominent component of solid tumors, primarily as a pathophysiological consequence of disturbed microcirculation due to insufficient vascularization following rapid tumor growth. HIF1α plays an important role in modifying tumor metabolism in response to an increasingly inhospitable hypoxic microenvironment. The changes in gene expression induced by HIF signaling contribute to many of the hallmarks of cancer that enable tumor growth, survival, and invasion. Hypoxia is seen as a poor prognostic marker in many cancer types. Importantly, HIF-inducible...
The role of HIF in environmental adaptation marks it as a crucial pathway in local and infiltrating innate immune cells under these suboptimal conditions.

While historically the HIF pathway has been implicated solely in this adaptation to the environmental milieu, multiple studies have detailed a clear role for HIF signaling that is independent of environmental changes in some cell subsets. The HIF pathway has been linked to the key metabolic changes that occur following innate immune cell activation downstream of pattern recognition receptor (PRR) ligation and other signaling events, which mirror some of the hallmark metabolic changes seen in cancer cells (23).

There is an important association between hypoxia and inflammation. A classic example of a hypoxic inflammatory setting is in joints affected by rheumatoid arthritis (RA), where areas of hypoxia and inflammation coincide. RA is characterized by chronic inflammation of the synovium of joint tissues, leading to localized erosion of these tissues and debilitating pain and deformity. The hypoxic RA joint is highly infiltrated with synoviocytes, lymphocytes, and macrophages (24). Similarly, colitis deformity. The hypoxic RA joint is highly infiltrated with synovial cells, lymphocytes, and macrophages (24). Similarly, colitis

HIF1α and immune-related genes

HIF1α is expressed in several types of innate immune cells, including macrophages, DCs, neutrophils, and Th17 cells (19–22). In these cells, HIF1α plays a fundamental role in the response to pathological stress as well as environmental adaptation. Immune cells have varied energy requirements depending on their activation state and must be able to alter their metabolic profile accordingly. The HIF pathway provides these cells with a metabolic switch, allowing them to respond appropriately to the significant changes in energy requirements that occur upon activation, as well as adapt to the hypoxic conditions that might prevail in inflamed tissue. Foci of inflammation, generated by a plethora of conditions such as tissue insult, infection, or autoimmune responses, can represent a difficult microenvironment for a cell. Hypoxia, acidosis, redox stress, and hypoglycemia are common features that cells must adapt to in order to survive. The role of HIF in environmental adaptation marks it as a crucial pathway in local and infiltrating innate immune cells under these suboptimal conditions.

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to increase erythrocyte numbers to promote oxygen transport, and genes involved in angiogenesis such as VEGF, which acts to rescue ambient oxygen levels (37, 38). Additionally, there is a whole range of immune-related genes that have HREs in their promoters. In macrophages, pathogen-associated molecular pattern (PAMP) receptors such as certain members of the Toll-like receptor (TLR) family contain an HRE site that results in pattern (PAMP) receptors such as certain members of the Toll-like receptor (TLR) family contain an HRE site that results in

![Table 1. Genes controlled by HIF1α](https://www.jci.org/content/126/10/3701/ggs3701/6)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Target gene</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolytic machinery</td>
<td>Hexokinase II</td>
<td>Catalyzes the first step in glycolysis</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Phosphofructokinase-1</td>
<td>Rate-limiting enzyme of glycolysis</td>
<td>3, 35</td>
</tr>
<tr>
<td></td>
<td>Glucose-6-phosphate dehydrogenase</td>
<td>Catalyzes first step in the pentose phosphate pathway</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>Lactate dehydrogenase</td>
<td>Catalyzes lactate production</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Pyruvate dehydrogenase kinase</td>
<td>Inhibits PDH-catalyzed production of acetyl-CoA</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>Glutamate transporter-1</td>
<td>Glucose uptake</td>
<td>94</td>
</tr>
<tr>
<td>Inflammatory responses</td>
<td>TLR 2/4</td>
<td>Recognition of PAMPs and DAMPs</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>IL-1β</td>
<td>Proinflammatory cytokine</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>CXC receptor 4</td>
<td>Chemokine receptor</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>β2 integrin</td>
<td>Adhesion molecule</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>RORγt</td>
<td>Th17 differentiation</td>
<td>22</td>
</tr>
</tbody>
</table>

HRE-containing genes encode for proteins that allow for cell adaptation to low-oxygen environments and inflammatory effector processes.

Metabolic reprogramming is crucial to both macrophage and DC activation. DC activation by LPS under normoxia promotes production of HIF1α mRNA and protein to greater levels than the levels induced by hypoxia alone (20). Inhibition of glycolysis using the glucose analogue 2-deoxyglucose (2-DG) blocks DC maturation in response to LPS, as measured by the reduced expression of the costimulatory molecules CD80 and CD86. HIF1α is implicated in this process, as the transcription of classic hypoxic response genes such as GLUT1 is increased and HIF1α deficiency similarly reduces expression of costimulatory molecules (20).

Macrophage activation following LPS stimulation is also dependent on this metabolic shift towards glycolysis. Inhibition of glycolysis with 2-DG blunts the inflammatory response in LPS-treated macrophages. Inhibitors of oxidative phosphorylation have no effect following LPS treatment, indicating that this process is already downregulated by LPS (46). IL-1β production in response to LPS treatment has been shown to be inhibited by 2-DG, and HIF1α has been implicated in this process (17, 47).

Stimuli such as LPS cause macrophage polarization towards a classically activated phenotype (termed M1), which exhibits inflammatory activities, or an alternatively activated phenotype (termed M2), which exhibits antiinflammatory activities (48). These polarization events are accompanied by HIF-dependent metabolic changes that provide macrophages with the functional ability to respond adequately to their respective stimuli (Figure 1). LPS in combination with IFN-γ induces metabolic reprogramming in M1 macrophages via HIF1α. Metabolism in M1 macrophages is characterized by increased glycolysis and pentose phosphate pathway (PPP) activity. LPS boosts HIF1α mRNA transcription in phagocytes via induction of NF-κB activity, further increasing signaling through the HIF pathway (49–51). M2 macrophages display a more oxidative metabolic profile compared with M1 macrophages, using oxidative phosphorylation and exhibiting high levels of fatty acid oxidation (FAO) (52, 53). While recent studies have questioned whether FAO has a correlative role or causal role in macrophage polarization (54), it is clear that FAO is essential to energetically support effector functions over a prolonged period of time, as required by M2 macrophages in the defense against parasites and in the resolution phase of infection and injury (55, 56).

Interestingly, HIF1α and its closely related isoform HIF2α may exert opposing effects in macrophage polarization. While
depletion of both HIF1α and HIF2α is broadly antiinflammatory, HIF2α does not appear to have a role in the regulation of NO production or the expression of costimulatory molecules. HIF2α is suggested to be critical for the production of proinflammatory cytokines under hypoxic conditions (19, 57). It has been shown that HIF1α and HIF2α are differentially expressed in M1 and M2 macrophages, with HIF1α induced in M1 macrophages, and HIF2α increased in M2 macrophages (58). However, in models of sterile inflammation during muscle regeneration, HIF1α and HIF2α have been identified as redundant, as macrophage polarization and effector functions were largely unaltered in mice depleted of myeloid HIFs (59).

The importance of HIF1α in acute innate cell function was dramatically demonstrated by murine HIF1α deletion studies. Conditional deletion of HIF1α in the myeloid lineage is not embryonically lethal in a murine model, nor do the mice exhibit any deficiencies in monocyte or neutrophil development and differentiation. However, these mice exhibit impaired inflammatory responses, specifically a defect in cell metabolism that renders the myeloid cells unable to adequately upregulate glycolytic metabolism upon inflammatory stimulation. In the absence of HIF1α, macrophages exhibit decreased glycolytic rates and energy generation, as well as reduced motility and migration (19). HIF1α deletion in macrophages causes defects in phagocytic uptake and killing in various bacterial infection models (19, 60). Importantly, mice with myeloid cell–specific deletion of HIF1α are resistant to LPS-induced lethality, confirming the importance of HIF1α in a classic in vivo model of innate immune activation (61).

An interesting consequence of the recognition of metabolic involvement in innate immune responses has been the identification of certain individual metabolites as signals in inflammation. The nonhypoxic stabilization of HIF1α in LPS-activated macrophages is mediated by metabolic intermediates with hitherto unknown roles in cell signaling. The TCA cycle intermediates succinate and citrate accumulate following LPS treatment in macrophages (17, 44, 62). Succinate accumulation leads to HIF1α stabilization and increased transcription of target genes such as Il1b (17). The mechanism of succinate accumulation may also involve the metabolite itaconic acid, which is synthesized by immune response gene 1 (IRG1) following citrate accumulation. IRG1 is induced by LPS and converts a citrate derivative, cis-aconitate, to itaconic acid. Itaconic acid inhibits an essential metabolic pathway, the glycoxylate shunt, which is necessary for the survival of some pathogenic bacteria (63). Itaconate is also a weak competitive inhibitor of SDH and may contribute to the accumulation of succinate in LPS-treated macrophages (64).

Citrates accumulation is a key event during the metabolic reprogramming process in M1 macrophages, and this reprogramming ultimately impacts HIF1α stability. Citrate accumulation leads to the production of three important proinflammatory mediators: NO, ROS, and prostaglandins (PGs) (65). Citrate also generates NADPH via pyruvate and malic enzyme. NADPH is required for expression of inducible NOS (iNOS), thereby playing a role in NO production. NO is an important inflammatory mediator that nitrosylates and inhibits components of the electron transfer chain.
The HIF1α signaling pathway modulates a significant number of crucial cellular processes and must be carefully controlled; thus, it follows that there exist multiple levels of regulation, including positive and negative feedback loops as well as extensive crosstalk with other signaling pathways. Responses may be dependent on time and context. For example, there are important differences in the regulation of HIF by hypoxia versus regulation by inflammatory stimuli such as LPS. HIF is required for the later shift to glycolysis that occurs in DCs, but the immediate metabolic switch is HIF independent and is mediated by the PI3K/Akt pathway (20). Many aspects have yet to be elucidated, but the primary model of HIF-mediated regulation is a multilevel regulatory network of great complexity that modulates responses such as proliferation, apoptosis, and differentiation (71).

HIF1α and the Th17/Treg axis

HIF1α plays a role in T cell differentiation. HIF1α directly activates RORγt transcription and is also involved in the regulation of IL-17 production through association with RORγt and recruitment of p300 at the IL17A promoter. HIF1α also impedes Treg differentiation by directly binding FOXP3, promoting its proteasomal degradation. Inhibition of glycolysis by 2-DG leads to an oxidative Treg phenotype (22, 72).

Pyruvate kinase M2 (PKM2) has been shown to be a critical determinant of metabolic reprogramming in macrophages via HIF in response to LPS stimulation. PKM2 is the rate-limiting enzyme of glycolysis that converts phosphoenolpyruvic acid (PEP) to pyruvate. Enzymatically inactive PKM2 monomers or dimers exist in equilibrium with enzymatically active PKM2 tetramers. PKM2 dimers can translocate to the nucleus, where they directly interact with HIF1α to regulate expression of proglycolytic enzymes (67). The highly active PKM2 tetramers are retained in the cytosol, supporting the final step of glycolysis (68). PKM2 is upregulated in tumors and LPS-activated macrophages (69, 70). Following LPS activation of macrophages, PKM2 dimers stabilize HIF1α, thereby regulating HIF1α target genes such as Il1b and genes encoding the glycolytic machinery. Forcing PKM2 into its tetrameric form using the small-molecule activator DASA-58 or TEPP-46 prevents nuclear translocation. This impairs interaction with HIF1α and reverses the LPS-induced, HIF1α-mediated shift towards glycolysis and IL-1β production, reprogramming macrophages to an M2-like phenotype (69). These findings support the importance of the PKM2/HIF1α axis for M1 macrophage differentiation and function, with PKM2/HIF1α acting as a pivot in the process of M1/M2 differentiation.

It is important to note that the role of HIF in macrophages and other immune cells is neither definitive nor without controversies. The HIF signaling pathway modulates a significant number of crucial cellular processes and must be carefully controlled; thus, it follows that there exist multiple levels of regulation, including positive and negative feedback loops as well as extensive crosstalk with other signaling pathways. Responses may be dependent on time and context. For example, there are important differences in the regulation of HIF by hypoxia versus regulation by inflammatory stimuli such as LPS. HIF is required for the later shift to glycolysis that occurs in DCs, but the immediate metabolic switch is HIF independent and is mediated by the PI3K/Akt pathway (20). Many aspects have yet to be elucidated, but the primary model of HIF-mediated regulation is a multilevel regulatory network of great complexity that modulates responses such as proliferation, apoptosis, and differentiation (71).
order to sustain ATP levels and support the biosynthetic needs of the rapidly dividing cells. This metabolic reprogramming occurs in a Warburg-like fashion, independently of oxygen levels (22, 72). The shift is primarily orchestrated by an mTOR-dependent nutrient-sensing pathway (73).

The inhibition of glycolysis by 2-DG abrogates Th17 development (72). Inhibition or knockdown of pyruvate dehydrogenase kinase (PDHK) indirectly fosters glycolysis by blocking pyruvate dehydrogenase (PDH) to suppress pyruvate oxidation and promote its conversion to lactate, which also inhibits Th17 differentiation (18). The blockade of acetyl-CoA carboxylase 1 (ACCL), a crucial enzyme in fatty acid synthesis, also limits Th17 proliferation and attenuates Th17-mediated pathologies (74). Pharmacological inhibition of glycolysis and glutaminolysis and promotion of FAO reduced the proliferation of lymphocytes, particularly effector T cells, in a transplantation model (75).

HIF1α is implicated in the Th17 cell differentiation process through its direct activation of RORγt and regulation of IL-17 production through association with RORγt at the Il17a promoter to recruit the transcriptional coactivator p300 (22). Under conditions favoring Th17 differentiation, HIF1α is upregulated in a STAT3-dependent manner. Murine studies have shown that HIF1α deficiency specifically impedes Th17 development and protects mice from experimental autoimmune encephalitis, further implicating HIF1α in Th17 differentiation and effector functions in a classic model of Th17-dependent pathology (22).

Tregs are classified as professional suppressors of varied immune responses and inflammatory processes, and central keepers of self tolerance (76). Tregs functionally oppose Th17 cells by producing the antiinflammatory cytokine IL-10. Deficiency in Tregs leads to systemic autoimmunity in mouse models and in patients (termed immunodysregulation polyendocrinopathy enteropathy X-linked) (77). Treg function is intrinsically linked to their metabolic profile, where FAO predominates (40).

HIF1α impedes the development of Tregs by directly binding FOXP3, a crucial transcription factor in Treg development, and targets it for ubiquitination and subsequent proteasomal degradation (Figure 2) (22). Loss of VHL results in excessive production of IFN-γ by Tregs, leading to induction of a Th1-like phenotype and an inability to prevent the induction of colitis. Silencing of HIF1α in Tregs reverses these proinflammatory effects and restores their regulatory function (78). This direct modulation of the TH17/Treg balance marks HIF1α as an important director of T cell fate and immune effector functions (22, 79).

HIF1α in neutrophils

Neutrophils are short-lived granulocytes that are crucial for the defense against microbes. They induce pathogen killing via ROS, NO, and phagocytosis (80), and on occasion the generation of extracellular traps (81).

Metabolic reprogramming in response to immune stimuli has long been described in neutrophils. The Warburg-like shift toward a more glycolytic phenotype was first observed in neutrophils in 1959 (43). Stimulation with LPS induces an increase in glucose uptake and oxygen consumption by neutrophils. Increased oxygen consumption is required for the production of H2O2 for pathogen clearance (82). HIF signaling and expression of the PHD enzymes, specifically PHD3, have been implicated in the prolonged survival of neutrophils in hypoxic conditions (83).

Interestingly, neutrophil-driven hypoxia in the microenvironment has been shown to be antiinflammatory in a model of severe colitis. Neutrophil activation and migration rapidly depletes local oxygen and leads to localized induction of HIF signaling in epithelial cells, increasing barrier function and preventing further infiltration of proinflammatory immune cells. Further, mice lacking a neutrophil respiratory burst developed severe colitis, which was attenuated by stabilizing HIF in the mucosa (84). The intestinal epithelium is characterized by a steep gradient in cellular oxygen tension, in which the tips of the villi are hypoxic and oxygenation increases with distance from the intestinal lumen. Dysregulated oxygen tension is a feature of inflammatory bowel disease (IBD) (85, 86). Expression of HIF1α and HIF2α is augmented in epithelial cells in ulcerative colitis and Crohn’s disease patients (25). Increased HIF1α expression enhances epithelial barrier function and antimicrobial defense, whereas increased HIF2α expression activates inflammatory cytokines to stimulate epithelial proliferation for inflammatory resolution and tissue regeneration (25, 87).

Hypoxic signaling and additional metabolic pathways

Recent work in the field has illustrated an additional role for hypoxic signaling in regulation of additional metabolic pathways that may be important in immune regulation. Amino acid metabolism such as the catabolism of tryptophan has been shown to be affected by the inhibition of PHD enzymes. Inhibition of PHD2 results in the accumulation of α-ketoglutarate which in turn boosts hepatic kynurenic acid production (88). Kynurenic acid has been shown to be protective in certain models of tissue injury such as cardiac ischemic protection (88–90).

Conclusions and future perspectives

The observation that succinate can modulate HIF1α activation in macrophages and that HIF1α is critical for macrophage function has resulted in the recognition of the roles played by metabolites outside their classical function as metabolic pathway intermediates. This presents an exciting frontier in immunology, as the roles of metabolites expand to include mediation of immune responses. The metabolic changes that underlie innate immune cell function and, more importantly, the pathways that induce metabolic reprogramming leading to altered immune cell phenotypes represent tangible new therapeutic targets for immune modulation.

The delineation of cellular subsets by their primary metabolic pathways will be critical in therapeutic targeting for the treatment of certain pathologies. For example, Th17 cells play a pathogenic role in many autoimmune pathologies and represent an attractive target for therapy. Distinct, targetable metabolic differences are exhibited by proinflammatory Th17 cells and Tregs. Pharmacological promotion of Treg differentiation in certain Th17-driven models such as experimental autoimmune encephalitis, for example via impairment of glycolysis by administration of 2-DG, has proven promising (72). Skin and heart allograft rejection can be prevented by inhibiting glycolysis with...
2-DG, glutamine metabolism with the glutamine analog DON, and augmenting FAO with metformin (75). Thus, there are multiple pharmacological modalities that could potentially be used to alter immune metabolic programs.

The HIF pathway is critically involved in both the adaption to environmental changes such as alterations in oxygen level and in governing immune responses. The pathogenesis of several conditions, including RA and IBD, result from the simultaneous deregulation of both inflammatory and hypoxia response pathways. A further consideration is that hypoxic signaling has pleiotropic effects on additional metabolic pathways that may be important in immune regulation. Dissection of the metabolic regulation of and crosstalk between these pathways is an important research goal that may lead to the development of novel therapeutic strategies.

Acknowledgments

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