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ROLE OF HIF-1 SIGNALING PATHWAY IN CELLULAR ADAPTATION TO HYPOXIA

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ABSTRACT

Hypoxia accompanying chronic inflammatory diseases leads to dysregulation of cells' homeostasis, causes energy deficits and intensifies inflammatory processes. Hypoxia-inducible factors (HIFs) are the central regulators of the response to hypoxia, enabling metabolic and functional adaptation of immune cells by altering gene expression. HIF-1α and HIF-2α modulate the lifespan, differentiation, priming and activation of neutrophils, macrophages, lymphocytes, and dendritic cells-playing a key role in influencing the balance between proinflammatory and reparative responses. Interactions between HIF and NF-κB pathways regulate hypoxic and inflammatory signaling, and as a result determine course, severity and treatment efficacy of many chronic diseases. Those two pathways are capable of influencing each other in a manner of negative feedback-loop. Understanding the mechanisms of this regulation opens up new therapeutic perspectives in the treatment of pulmonary diseases associated with hypoxia and inflammation, and a hypothetical possibility to slow down the ratio at which chronic inflammatory response contributes to deterioration of patients' quality of life.

KEYWORDS

Hypoxia-inducible Factor; HIF Signaling Pathway; NF-κB Signaling Pathway, Cellular Adaptation to Hypoxia, Inflammatory Response

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Introduction

In numerous pathological conditions, including chronic inflammatory lung diseases, pulmonary fibrosis, and chronic respiratory failure, there is an imbalance between the oxygen demand of cells and its supply [1-3]. A deficit of oxygen, which is the final electron acceptor in the mitochondrial respiratory chain, leads to collapse of mitochondrial bioenergetic function, reducing yield of adenosine triphosphate (AT) production, and in consequence insufficient energy for cell's physiological processes [2]. In areas of ongoing inflammation, a specific hypoxic microenvironment develops, referred to as "inflammatory hypoxia" [3]. Acccelerated metabolism of activated immune cells (neutrophils, monocytes) promotes cell proliferation and the expression of oxygenase enzymes, which further deepens deficit of oxygen [4]. By exacerbating tissue dysfunction pathological hypoxia contributes to disease's progress through the disregulation of the immune response [5]. Furthermore, state of hypoxia by itself influences the course of inflammatory processes by regulating the activity of oxygen-dependent signaling pathways in many types of immune cells [6,7].

HIF Pathway Modulates Cellular Adaptation in Response to Hypoxia

HIF transcriptional complex acts as the key regulator of the cellular response to oxygen deficiency [8]. The discovery of the molecular mechanism of HIF-dependent cellular adaptation as a response to hypoxia was awarded the Nobel Prize in Physiology or Medicine in 2019 (W.G. Kaelin, G.L. Semenza, PJ.Ratcliffe) [9).

HIF is a heterodimeric transcription factor consisting of an oxygen-regulated HIF- α subunit and a constitutively present HIF-1β subunit, also known as aryl hydrocarbon receptor nuclear translocator (ARNT). So far, three isoforms of the HIF-α have been identified: HIF-1α; HIF-2α; and HIF-3α, each differing in the range of regulated genes and their function [10-12]. **Table 1**. includes key differences between HIF- α isoforms.

Table 1. Isoforms of HIF- α

Isoform	Primary Functions	Clinical significance
HIF-1α	Regulation of glycolysis, cell survival in hypoxia	Inflammation Targeting Cancers
HIF-2α	Angiogenesis, endothelial cell proliferation	Anemia Targeting Cancers
HIF-3α	Regulation of HIF-1/2 activity, less known	Potential biomarker

In conditions of normoxia, HIF-a is hydroxylated by the dioxygenase families (PHD1-3 and FIH), then degraded by the von Hippel-Lindau protein (pVHL) via 26S proteasome(13]. Hypoxia inhibits the activity of hydroxylases, leading to the stabilization of HIF- α, its dimerization with HIF-1β, and activation of target genes through binding to HRE (hypoxia response element) sequences in DNA [14].

HIF, NF-κB and Intertwinement of Two Signaling Pathways

HIF-signal pathway interacts strongly with another central pathway regulating the inflammatory response, the nuclear transcription factor NF-κB [15,16]. Both pathways share regulators, target genes and activate in response to cytokines and pathogenes. PHD hydraxylases, which control HIF stability, also participate in regulation of NF-κB pathway[17]-

In conditions of chronic inflammation, typical for example in COPD, increased NF-κB activity enhances HIF-1a transcription, which promotes hypoxia [18].

Studies in animal models of COPD have shown that pharmacological inhibition of NF-kB activity reduces HIF-1α expression, leading to a reduction in inflammation and improvements in epithelium [19].

HIF Signaling Pathway Regulates Immune Cells' Metabolism

HIF controls the effector function of immune cells primarily by regulating their metabolism [14,25–27], as per **Table 2.**

Table 2. Effect of HIF on various immune cells.

Cell Type	Effect of HIF	Results
Neutrophils	Extended Lifespan; Production of antimicrobial peptides	Innate immunity Increase
Macrophages	M1/M2 polarization; migration to inflammatory foci	Increase of Inflammatory Response
T cells	Th17/Treg equilibrum control; CD8+ cytotoxic activity	Autoimmunity, Anti-Cancer Cells
B Lymphocytes	Proliferation, Promotion of humoral response	Increase in Antybody Production
Mast cells/eosinophils	Production of Cytokines, VEGF	Asthma, allergic reactions

In inflammatory niches, cells migrate from the blood to an environment with low pO_2 and must undergo metabolic adaptation. In granulocytes, glycolysis—regulated by HIF—is the main source of ATP [26]. Both isoforms (HIF-1α and HIF-2α) reduce dependence on OXPHOS, inhibit the TCA cycle, and shift metabolism toward anaerobic ATP production [28–30].

HIF-1α prolongs neutrophils' lifespan, increases the expression of β2-integrins, the production of antibacterial peptides and key glycolysis enzymes; the absence of HIF-1α impairs ATP generation, aggregation, chemotaxis and bacterial killing [26,31,32].

Macrophages- HIF-1α promotes macrophages' differentiation into M1 (pro-inflammatory) phenotype, while HIF-2α promotes the M2 (repair) phenotype. Deletion of HIF-1α reduces ATP, survival, invasion, and bactericidal activity [32]; HIF-1α increases migration to sites of infection via ↑CXCR4 and ↓CCR5 [14]. IL-8 is a target of HIF-1α; increased secretion of IL-8 by alveolar macrophages may accelerate ARDS.

Dendric Cells- HIF-dependent metabolic reprogramming participates in dendric cells' activation, differentiation, proliferation, migration, and apoptosis; HIF regulates the production of IFN-γ, IL-22, IL-10, and the expression of chemokine receptors that attract neutrophils [14,31,33].

T lymphocytes - HIF-1α is crucial for T-cell survival; it controls the Th17/Treg switch (important in autoimmunity) [14,31]. In $CD8^+$ T cells, HIF-1α promotes glycolysis necessary for effector function and the generation of populations with antitumor properties; conditional VHL knockout (permanently stable HIF) accelerates the differentiation of long-lived memory effectors against viral infections. HIF-1α deletion limits CTL infiltration and their killing of cancer cells [25]. Hypoxia and HIF enhance glycolysis in B cells, affecting the development, proliferation, apoptosis, and maturation of high-affinity antibody responses [14].

Mast cells, eosinophils, basophils. HIF-1α stabilization supports survival and function; after TLR stimulation, HIF-1α enhances IL-8 and TNF-α and the expression of histidine decarboxylase (→ histamine) [14]. In the bronchial epithelium, HIF-1 induces VEGF, increasing vascular permeability and airway edema [14]. HIF-1α and HIF-2α modulate eosinophil chemotaxis and asthma pathogenesis; HIF-1α supports basophil activity in chronic inflammation. HIF is also associated with the formation of extracellular traps (METs, NETs) with antimicrobial significance.

Mitochondrial regulation and the role of ROS

Mitochondria participate in the modulation of HIF stability through reactive oxygen species (ROS) generated in the respiratory chain [28]. ROS inhibit the degradation of HIF-1α and enhance its transcriptional activity. The use of antioxidants such as ebselen reduces HIF-1α stabilization, confirming the role of oxidative stress in the regulation of this pathway [29].

Clinical Significance and Application

The HIF pathway is an attractive therapeutic target in diseases involving hypoxia and chronic inflammation. The best-known group of substances are HIF hydroxylase inhibitors, which stabilize HIF-α and enhance the adaptive response [30]. Preclinical studies have shown that modulation of HIF activity can both reduce tissue damage and increase antimicrobial resistance [31,32].

At the same time, due to the strong connection between the HIF pathway and other regulatory systems (NF-κB, p53, Notch), therapeutic targeting requires particular caution and further research [33].

Conclusions

Hypoxia-inducible factors (HIFs) play a central role in regulating gene expression under hypoxic conditions. Stabilization of HIF-1α enables cells to adapt metabolically and functionally, but may also contribute to immune dysfunction and the progression of chronic diseases. The interaction between HIF and NF-κB pathways forms the basis for the integration of inflammatory and hypoxic responses, opening up new therapeutic perspectives in the treatment of lung diseases and other conditions associated with chronic inflammation and hypoxia.

Authors' Contributions:

Illia Koval-methodology; formal analysis
Kamil Borysewicz (corresponding author)— conceptualization; investigation; writing - original draft
Bartłomiej Czarnecki — methodology; formal analysis; project administration
Jan Nowak - methodology; formal analysis
Bartosz Zwoliński — software; validation/check; data curation
Kacper Sukiennicki — resources; writing - original draft
Wirginia Bertman -investigation; writing - review & editing
Natalia Kołdej — investigation; writing - review & editing
Klaudia Romejko — investigation; writing - original draft
Wiktor Kubik— data curation; writing - original draft
Zuzanna Kępczyńska — data curation; supervision
Katarzyna Szewczyk - validation/check; supervision; project administration
Barbara Kujawa- investigation; writing—review, language check

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