The role of hypoxia inducible factor in nasal inflammations

K.-J. CHENG, Y.-Y. BAO, S.-H. ZHOU

Department of Otolaryngology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

Abstract. - OBJECTIVE: Hypoxia-inducible factor (HIF) is considered an important transcription factor due to its roles in glycolysis, angiogenesis, cell differentiation, apoptosis, and other cellular pathways. It takes the role in various physiological and pathological states, such as solid tumors, vascular injury, and atherosclerotic lesion progression. In recent studies, HIF is found as a master regulator of body inflammation and immunity, not only in hypoxia but also in normoxia. Nasal inflammation has a close relationship with anoxia. But the role of HIF in nasal inflammation is still unclear.

MATERIALS AND METHODS: We searched the Pubmed using the key words: “Hypoxia-inducible factor” and “nasal” or “Hypoxia-inducible factor”, and reviewed the related articles.

RESULTS: HIF is composed of HIF-α and HIF-β subunits. HIF-α is an adjusting relational subunit, which is divided into three subtypes: HIF-1α, HIF-2α, and HIF-3α. HIF-1α is the key component and best understood. HIF-1α can be activated under hypoxic conditions or by various cytokines and growth factors. HIF-1α accumulation is critical for sustaining human allergic effector cell survival and function. The level of HIF-1α is increased in the patients with allergic rhinitis and become a new therapeutic target. HIF-1α also plays an important role in the pathogenesis of CRS and polyp formation. Some research found that the expression of HIF-1α was increased in CRS with polyps.

CONCLUSIONS: HIF-1α takes an important role in allergic rhinitis and chronic sinusitis. It will be a key therapeutic target of these diseases in the future.

Key Words: Hypoxia inducible factor, Allergic rhinitis, Sinusitis, Chronic sinusitis with polyps, Inflammation, Cancer.

Introduction

Hypoxia-inducible factor (HIF) was first identified for its role in erythropoietin regulation, and today it is considered an important transcription factor due to its roles in glycolysis, angiogenesis, cell differentiation, apoptosis, and other cellular pathways. Recent studies have shown that HIF is a master regulator of body inflammation and immunity, not only in hypoxia but also in normoxia. It can affect antimicrobial and cytotoxic activities, and the recruitment and apoptosis of inflammatory cells.

Nasal inflammation has a close relationship with anoxia. Moreover, the nasal cavity is typically described as an “immune organ,” in which systemic or local allergic inflammation can occur. However, there has been little research on the functions of HIF in nasal inflammation. Indeed, any relationship between HIF and nasal inflammation has remained unclear. The aim of this review was to investigate how HIF acts as a regulator in inflammation in the nasal cavity and sinuses and to define new therapeutic targets.

The structure of HIF

HIF, also known as “aryl hydrocarbon receptor nuclear translocator” (ARNT), is a basic helix-loop-helix transcription factor, composed of HIF-α and HIF-β subunits. HIF-β is a constitutively expressed nuclear subunit. In contrast, HIF-α is an oxygen-regulated subunit, which is mostly degraded in normoxia and physiological conditions. For the HIF-1 transcriptional complex to be functional, HIF-1 levels must be induced. The human HIF-1α gene is located on chromosome 14 (14q21-q24), whereas the HIF-1β gene is located on chromosome 1 (1q21).

HIF-α is divided into three subtypes: HIF-1α, HIF-2α, and HIF-3α, of which HIF-1α is the best understood. In most cases, HIF-1α and HIF-2α are closely related and have similar properties. However, they differ in tissue distribution: HIF-1α is expressed in all kinds of tissue, whereas HIF-2α is expressed primarily in vascular endothelial cells. In contrast, little is yet known about the function of HIF-3α, and it may be...
antagonistic to HIF-1α and HIF-2α. Although all subunits are apparently involved in the response to hypoxia, the key components are HIF-1α and HIF-1β.

Physiological and pathological roles of HIF

HIF-α is the subunit that can be regulated by hypoxia and helps to restore oxygen homeostasis at a cellular, local, and systemic level\textsuperscript{11,12}. In normoxia, HIF-α is degraded rapidly by hydroxylation reactions, which are catalyzed by oxygen-sensitive prolyl hydroxylases (PHD) in the ubiquitin-proteasome pathway\textsuperscript{13}. HIF-α has an oxygen-dependent degradation domain (ODD), through which specific degradation of HIF-1 is triggered in normoxia. The level of HIF-α protein is low but present in the brain, liver, heart, and skeletal muscle tissues under normal oxygen conditions.

Hypoxia can arise in various physiological and pathological states, such as solid tumors, vascular injury, and atherosclerotic lesion progression. Under these hypoxic conditions, HIF is involved in the response to hypoxia and the regulation of human intra-plaque angiogenesis\textsuperscript{14,15}. In these cases, the degradation of HIF-α is inhibited because of substrate (O\(_2\)) deprivation, and HIF-α accumulates, combines with HIF-β, and mediates profound changes in gene expression\textsuperscript{16}. HIF-1 targets many factors involved in metabolism and angiogenesis, such as the inducible form of nitric oxide (NO) synthase (iNOS), vascular endothelial growth factor (VEGF), glucose transporter-1, and several glycolytic enzymes\textsuperscript{17}.

Apart from hypoxia, some non-hypoxic activators can also regulate the expression of HIF-1, such as growth factors, cytokines, vascular hormones, and viral proteins\textsuperscript{18,19}. In contrast to hypoxia, stabilization of HIF-1α does not seem to play a role in the non-hypoxic induction of HIF-1. The main mechanism implicated in this induction is an increase in HIF-1α protein translation. The degradation of HIF-1α does not seem to be inhibited in the non-hypoxic activation of HIF-1\textsuperscript{20}.

In recent research, HIF-1α has been found to be a central factor in inflammatory and immune reactions\textsuperscript{20,21}. It has been demonstrated that HIF-1α controls inflammatory responses via regulation of the metabolic switch to glycolysis and that it plays a critical role in the HIF-1α pathway in inflammatory cell recruitment\textsuperscript{22}.

HIF and cancer

Hypoxia is common in cancer tissue and can lead to necrotic areas, in which cancer cells have died due to inadequate oxygenation\textsuperscript{23}. The ability to adapt to reduced O\(_2\) availability is important for the survival of cancer cells. A major mechanism mediating this adaptive response is regulated by HIF-1 and HIF-2\textsuperscript{24}. As a result, the adaptation to hypoxia promotes many key aspects of cancer progression and patient mortality\textsuperscript{25,26}. The HIFs play important roles during tumor cell expansion by regulating energy metabolism and the induction of angiogenesis\textsuperscript{27}.

HIF-1α and HIF-2α levels are increased in many human cancers\textsuperscript{28-30}. Griffiths et al\textsuperscript{41} observed that HIF-1α was involved in gastric carcinogenesis and disease progression, but was only a weak prognostic factor for survival. Stoeltzing et al\textsuperscript{25} found that inhibition of HIF-1α activity impaired gastric tumor growth, angiogenesis, and vessel maturation. Using immunohistochemistry and \textit{in situ} hybridization, expression of HIF-1α was recognized in 55.1% and 69.6%, respectively, of transitional cell carcinomas of the upper urinary tract\textsuperscript{23}. Krishnamachary et al\textsuperscript{42} showed that hypoxia or HIF-1 overexpression stimulated Matrigel invasion by HCT116 human colon carcinoma cells, whereas the process was inhibited by a small interfering RNA directed against HIF-1\textsuperscript{34}. HIF-1α and HIF-2α are positive regulators of tumor and metastatic potential, and have become therapeutic targets for cancer.

HIF and inflammation

In recent years, many scientists have found that HIF expression in immune cells can be triggered not only by hypoxia and cancer, but also by other pathological conditions, such as inflammation and infection\textsuperscript{26}. It is usually regulated via the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) and nuclear factor-kappa B (NF-κB) pathways. In inflammatory and infectious conditions, HIF can be upregulated by viral and bacterial proteins, growth factors, proinflammatory cytokines, and “inflammatory hypoxia”\textsuperscript{37}. HIF transcription factors are key elements in the control of immune cell metabolism and function and play important roles in innate and adaptive immunity\textsuperscript{38}. HIF induces a number of immune roles in T-cells, dendritic cells (DCs), macrophages, neutrophils, and epithelial cells, from boosting
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HIF-1α can regulate NF-κB and adaptive immune responses, and together with DCs, they link innate and adaptive immune responses, including ROS and NO production, PI3K, and/or NF-κB activation. IL-1β upregulates HIF-1α levels at the level of translation. During inflammation, bacteria or bacterial cell wall components, such as lipopolysaccharides (LPS), can stimulate HIF-1α protein accumulation and HIF-1 activation through an increase in HIF-1α mRNA levels. This mechanism is induced primarily by NF-κB, which is a master transcriptional regulator during inflammation and becomes activated via Toll-like receptor stimulation. NF-κB is a family of transcription factors that play key roles in a wide variety of physiological (such as immunity) and pathophysiological cellular responses, such as chronic inflammation, diabetes, and cancer. However, the exact mechanisms involved in the activation of NF-κB and the upregulation of HIF-1α induced by NF-κB remain to be determined. Moreover, HIF-1α can regulate NF-κB.

The PI3K/AKT/mTOR pathway plays a role in many cellular processes, such as metabolism, inflammation, cell survival, motility, and cancer progression. PI3K, a classical upstream kinase in the mTOR pathway, has been implicated in various immune response and inflammatory processes. The kinase AKT is the main intermediate between PI3K and mTOR kinase. mTOR is an important factor because it stands at the intersection of multiple important signaling pathways. Activated mTOR phosphorylates at least two targets, p70S6K and 4E-BP1. These two components lead to active translation of mRNAs in which HIF-1α expression is involved. So, it could upregulate the expression of HIF-1α in inflammation through the PI3K/AKT/mTOR pathway. Thus, mTOR inhibition can reduce HIF-1α activity.

Role of HIF in inflammation

First, HIF can regulate macrophage and DC activity. Macrophages coordinate inflammation, and together with DCs, they link innate and adaptive immune responses. Macrophages usually accumulate in large numbers within O2-deprived areas, suggesting that hypoxic responses regulate the biological activities of macrophages. Moreover, HIF-1α appears to be required for macrophage maturation. HIF-1α can also mediate macrophage inflammatory responses and act as an important transcriptional effector, regulating hypoxic gene expression in macrophages. Hypoxia and HIF-1α can also modulate DC maturation, activation, and antigen-presenting functions.

Second, HIF can regulate the function of neutrophils, key mediators of the innate immune response. Inflammatory hypoxia and HIF can lead to the early accumulation of neutrophils. HIF-1α and HIF-2α are essential for neutrophil survival in hypoxia and inflammation. In an in vivo model of LPS-mediated lung injury, HIF-2α deficiency was associated with reduced neutrophilic inflammation during resolution, with fewer neutrophils in BAL samples, an increase in neutrophil apoptosis, and a reduction in lung damage and vascular leakage. Moreover, HIF-1α can delay the resolution of inflammation. This delay is a consequence of both reduced neutrophil apoptosis and increased retention of neutrophils at the site of tissue injury.

Finally, HIF can regulate T cell development, differentiation, and function. HIF-1α has important roles in negatively regulating T cell function in vivo and in vitro. Beyond that, it is involved in the regulation of the balance between Treg and Th17 cell differentiation. Indeed, it can promote Th17 differentiation and inhibit Treg differentiation.

HIF expression in body inflammation

HIF levels tend to be upregulated in the inflammation of many organs and tissues. Deng et al. showed that HIF-1α was highly expressed in both glomerular and tubulointerstitial tissues in lupus nephritis. HIF-1α may promote mesangial cell growth through the induction of proliferation and inhibition of apoptosis. Kim et al. indicated that HIF-1α mediated prostate enlargement under inflammatory conditions. Some research has implied that HIF-1α expression is strongest in the sub-lining layer of rheumatoid arthritis (RA) synovium and is related to both angiogenesis and inflammation in synovium from RA patients. HIF-1α also plays an important part in the fibrosis and inflammation of adipose tissue, skin inflammation, wound healing, gastroesophageal reflux disease, systemic lupus erythematosus, and middle ear cholesteatoma.

macrophages microbicidal capacity to driving T cell differentiation and cytotoxic activity.
HIF also plays an important role in lower airway inflammation, under hypoxic or normoxic conditions. It can induce the proliferation of smooth muscle cells of the pulmonary artery under hypoxic conditions\(^95\). HIF-2\(\alpha\) is involved in arsenite-induced inflammation of human bronchial epithelial cells\(^84\). HIF-1\(\alpha\) plays an important part in protection against pulmonary *Aspergillus fumigatus* infection\(^85\). HIF also acts at a key point in allergic or eosinophilic inflammation of the lower airway\(^86-90\).

Anoxia and HIF expression in nasal inflammation

**Allergic rhinitis**

As described above, HIF-1\(\alpha\) can be activated under hypoxic conditions or by various cytokines and growth factors. Much evidence suggests that HIF expression is elevated in asthma patients and plays an important role in allergic airway inflammatory responses\(^91-93\). HIF-1\(\alpha\) accumulation is critical for sustaining human allergic effector cell survival and function\(^94\). Allergic airway inflammation is regulated by the PI3K/AKT/mTOR/HIF-1\(\alpha\)/VEGF pathway.\(^95\) However, little is known about the exact role of HIF in allergic rhinitis (AR)\(^96\). Han et al reported that HIF-1\(\alpha\) and VEGF levels were locally upregulated in nasal mucosa during AR and could be attenuated by the HIF-1\(\alpha\) inhibitor 2-methoxyestradiol (2ME2)\(^96\). Mo et al\(^97\) detected an increase in HIF-1\(\alpha\) and VEGF expression in the nasal mucosa of patients with AR. Moreover, they reported that the HIF-1\(\alpha\) inhibitor 2ME2 induced anti-allergic effects by decreasing both local and systemic Th2 cytokine (IL-4 and IL-5) production, IgE production, and eosinophil infiltration into the nasal mucosa in an AR mouse model. The levels of HIF-1\(\alpha\) and VEGF increased in the nasal fluid of AR patients after challenge\(^98\). Benzaldehyde can have anti-allergic effects in murine AR, possibly through inhibition of HIF-1\(\alpha\) and VEGF\(^98\). Thus, HIF may become a new therapeutic target in AR.

**Sinusitis and nasal polyps**

Sinusitis can be divided into two major types: acute and chronic sinusitis (CRS). CRS is persistent inflammation of the nasal cavity and sinus membranes, with a duration of longer than 12 weeks. It has become a common health problem with significant morbidity, which impacts the general health of affected individuals and increases medical costs\(^99\). According to whether nasal polyps (NPs) are present, CRS has been divided into two subtypes: CRS with polyps (CRS\(wNP\)) and CRS without them (CRS\(sNP\)). CRS has an extremely complex pathogenesis, especially CRS\(wNP\), however, the exact origin of CRS\(wNP\) is still unclear. According to the type of inflammatory cell infiltration, CRS\(wNP\) can be divided into two subgroups: eosinophilic and non-eosinophilic or neutrophilic\(^100\). The subgroups have varying pathogeneses and may require different therapeutic options.

Hypoxia may play an important role in the pathogenesis of CRS and polyp formation\(^101-104\). First, hypoxia can impair sinonasal transepithelial ion transport and cause mucociliary dysfunction, which may lead to CRS\(^105,106\). However, other studies have suggested the opposite\(^95\). Second, hypoxia may reduce nitric oxide output in the nasal airways, which may induce CRS\(^108\). Third, hypoxia may lead to the formation of NPs\(^109\). Chronic inflammation of the nasal mucous membrane, as a major cause of NPs, is common. Local hypoxia usually takes place in CRS, especially in the microenvironment of the middle meatus, from where NPs commonly arise. Blocking of the ostium by swelling of the nasal mucosa may induce hypoxia and secondary mucosal swelling in the sinuses\(^110\). Under a hypoxic microenvironment, HIF-1\(\alpha\) and VEGF expression are upregulated\(^109\). These could then increase vascular permeability and lead to tissue edema, which might be a pathological change in the early stages of NP formation.

Some research has been reported on the role of the PI3K/AKT/mTOR/HIF/VEGF pathway in CRS\(^111\). Shin et al\(^112\) showed that the expression of the HIF-1\(\alpha\) and HIF-2\(\alpha\) proteins was upregulated in NPs. They may induce the formation of NPs by causing an epithelial-to-mesenchymal transition. Chien et al\(^113\) used real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) and immunohistochemistry methods to detect levels of HIF-1\(\alpha\) protein and mRNA. They found that levels of HIF-1\(\alpha\) protein, but not mRNA, were significantly increased in NPs. Expression of VEGF was also upregulated in NP tissue\(^114-116\). Liu et al\(^117\) found essentially the same results as Chien et al. Yang et al\(^118\) observed that expression of HIF-1\(\alpha\) protein was increased in the epithelial cells of NPs. The upregulation of HIF-1\(\alpha\) and VEGF could be suppressed by dexamethasone\(^119\).

Fibroblasts are found in the stroma and are actively involved in the accumulation of the extracellular matrix and can be further activated by pro-inflammatory cytokines. They show strong correlations with CRS, especially CRS\(wNP\)\(^20\).
Some researchers\textsuperscript{121,122} have investigated the upregulation of HIF-1α protein and mRNA in NP fibroblasts. VEGF levels are also increased in NP fibroblasts\textsuperscript{123}. This upregulation of VEGF can be inhibited by macrodilides\textsuperscript{124}.

CRSwNP subgroups have different pathogenicities. In Asians, patients with CRSwNP usually manifest a non-eosinophilic or neutrophilic subtype and Th17-related inflammation. As described above, HIF can induce neutrophilic inflammation and promote Th17 differentiation and inhibit Treg differentiation. Hypoxia may induce this neutrophilic inflammation in NPs\textsuperscript{125}. Some investigations\textsuperscript{126-128} have implied that the HIF pathway plays an important role in neutrophilic CRSwNP. HIF-1α also can promote Th17 differentiation in NPs\textsuperscript{129}.

**HIF inhibitors**

Given the important roles of HIF in cancer and inflammation, HIF inhibitors could be useful for the development of novel therapeutics. HIF inhibitors can be tentatively divided into agents that modulate HIF-1α mRNA levels, protein translation, protein degradation, DNA binding, or transcriptional activity\textsuperscript{130}. HIF inhibitors have shown positive results in animal models. However, those described to date lack specificity and none specifically targets HIF-1\textsuperscript{131}. Further translation of basic scientific research into clinical applications will require new methods for establishing the proper context for the administration of HIF-1 inhibitors and improved specificity\textsuperscript{132}.

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