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[1], and today it is considered an important transcription factor due to its roles in glycolysis, angiogenesis, cell differentiation, apoptosis, and other cellular pathways[2]. Recent studies have shown that HIF is a master regulator of body inflammation and immunity, not only in hypoxia but also in normoxia[3,4]. 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[5]. HIF-β is a constitutively expressed nuclear subunit[6]. 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[7]. The human HIF-1α gene is located on chromosome 14 (14q21-q24), whereas the HIF-1β gene is located on chromosome 1 (1q21)[7].

HIF-α is divided into three subtypes: HIF-1α, HIF-2α, and HIF-3α, of which HIF-1α is the best understood[8]. 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[9]. In contrast, little is yet known about the function of HIF-3α, and it may be

Corresponding Author: Shui-Hong Zhou, MD; e-mail: zhoushuihong127@163.com

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[10].

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[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[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[14-16]. 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[17]. 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[18].

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[19,20]. 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[7].

In recent research, HIF-1α has been found to be a central factor in inflammatory and immune reactions[21,22]. 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[4].

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[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[24]. As a result, the adaptation to hypoxia promotes many key aspects of cancer progression and patient mortality[25,26]. The HIFs play important roles during tumor cell expansion by regulating energy metabolism and the induction of angiogenesis[27].

HIF-1α and HIF-2α levels are increased in many human cancers[28-30]. Griffiths et al[31] observed that HIF-1α was involved in gastric carcinogenesis and disease progression, but was only a weak prognostic factor for survival. Stoeltzing et al[32] found that inhibition of HIF-1α activity impaired gastric tumor growth, angiogenesis, and vessel maturation. Using immunohistochemistry and *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[33]. Krishnamachary et al[35] 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[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[36]. 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"[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[38]. HIF induces a number of immune roles in T-cells, dendritic cells (DCs), macrophages, neutrophils, and epithelial cells, from boosting

macrophages microbicidal capacity to driving T cell differentiation and cytotoxic activity[39].

Activation of HIF during inflammation

Apart from hypoxia, cytokines released during inflammation, such as TNF-α and IL-1β, can activate HIF-1[40]. TNF-α activates HIF-1 by multiple pathways, including ROS and NO production, PI3K, and/or NF-κB activation[41,42]. 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[43,44]. This mechanism is induced primarily by NF-κB, which is a master transcriptional regulator during inflammation and becomes activated via Toll-like receptor stimulation[45]. NF-κB is a mandatory transcriptional activator of HIF-1α[46,47]. 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[48]. 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[40,49]. Moreover, HIF-1α can regulate NF-κB[50].

The PI3K/AKT/mTOR pathway plays a role in many cellular processes, such as metabolism, inflammation, cell survival, motility, and cancer progression[51]. 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[52]. mTOR is an important factor because it stands at the intersection of multiple important signaling pathways[53]. Activated mTOR phosphorylates at least two targets, p70S6K and 4E-BP1[53,54]. These two components lead to active translation of mRNAs in which HIF-1α expression is involved[55]. So, it could upregulate the expression of HIF-1α in inflammation through the PI3K/AKT/mTOR pathway[56-58]. Thus, mTOR inhibition can reduce HIF-1α activity[59].

Role of HIF in inflammation

First, HIF can regulate macrophage and DC activity[60]. Macrophages coordinate inflammation, and together with DCs, they link innate and adaptive immune responses[45]. Macrophages usually accumulate in large numbers within O_2-deprived areas, suggesting that hypoxic responses regulate the biological activities of macrophages. Moreover, HIF-1α appears to be required for macrophage maturation[61]. HIF-1α can also mediate macrophage inflammatory responses and act as an important transcriptional effector, regulating hypoxic gene expression in macrophages[4,61]. Hypoxia and HIF-1α can also modulate DC maturation, activation, and antigen-presenting functions[44].

Second, HIF can regulate the function of neutrophils, key mediators of the innate immune response[62]. Inflammatory hypoxia and HIF can lead to the early accumulation of neutrophils[63]. 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[64]. 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[65].

Finally, HIF can regulate T cell development, differentiation, and function[66,67]. HIF-1 has important roles in negatively regulating T cell function *in vivo*[68] and *in vitro*[69]. Beyond that, it is involved in the regulation of the balance between Treg and Th17 cell differentiation[70]. Indeed, it can promote Th17 differentiation and inhibit Treg differentiation[71-73].

HIF expression in body inflammation

HIF levels tend to be upregulated in the inflammation of many organs and tissues. Deng et al[74] 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[74]. Kim et al[75] 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[76]. HIF-1α also plays an important part in the fibrosis and inflammation of adipose tissue[77], skin inflammation[78], wound healing[79], gastroesophageal reflux disease[80], systemic lupus erythematosus[81], and middle ear cholesteatoma[82].

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[83]. HIF-2α is involved in arsenite-induced inflammation of human bronchial epithelial cells[84]. HIF-1α 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-1α 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-1α accumulation is critical for sustaining human allergic effector cell survival and function[94]. Allergic airway inflammation is regulated by the PI3K/AKT/mTOR/HIF-1α/VEGF pathway[95]. However, little is known about the exact role of HIF in allergic rhinitis (AR)[96]. Han et al reported that HIF-1α and VEGF levels were locally upregulated in nasal mucosa during AR and could be attenuated by the HIF-1α inhibitor 2-methoxyestradiol (2ME2)[96]. Mo et al[97] detected an increase in HIF-1α and VEGF expression in the nasal mucosa of patients with AR. Moreover, they reported that the HIF-1α inhibitor 2ME2 induced antiallergic 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-1α and VEGF increased in the nasal fluid of AR patients after challenge[98]. Benzaldehyde can have antiallergic effects in murine AR, possibly through inhibition of HIF-1α 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 pre-sent, CRS has been divided into two subtypes: CRS with polyps (CRSwNP) and CRS without them (CRSsNP). CRS has an extremely complex pathogenesis, especially CRSwNP, however, the exact origin of CRSwNP is still unclear. According to the type of inflammatory cell infiltration, CRSwNP 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[107]. 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-1α 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-1α and HIF-2α 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-1α protein and mRNA. They found that levels of HIF-1α 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-1α protein was increased in the epithelial cells of NPs. The upregulation of HIF-1α 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 CRSwNP[120].

Some researchers[121,122] have investigated the upregulation of HIF-1α protein and mRNA in NP fibroblasts. VEGF levels are also increased in NP fibroblasts[123]. This upregulation of VEGF can be inhibited by macrolides[124].

CRSwNP subgroups have different pathogeneses. 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[125]. Some investigations[126-128] have implied that the HIF pathway plays an important role in neutrophilic CRSwNP. HIF-1α also can promote Th17 differentiation in NPs[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[130]. HIF inhibitors have shown positive results in animal models. However, those described to date lack specificity and none specifically targets HIF-1[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[132].

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1. Bhandari T, Nizet V. Hypoxia-Inducible Factor (HIF) as a pharmacological target for prevention and treatment of infectious diseases. Infect Dis Ther 2014; 3: 159-174.
2. Melillo G. HIF-1: a target for cancer, ischemia and inflammation--too good to be true? Cell Cycle 2004; 3: 154-155.
3. Sumbayev VV, Nicholas SA. Hypoxia-inducible factor 1 as one of the "signaling drivers" of Toll-like receptor-dependent and allergic inflammation. Arch Immunol Ther Exp (Warsz) 2010; 58: 287-294.
4. Cramer T, Yamanishi Y, Clausen BE, Förster I, Pawlinski R, Mackman N, Haase VH, Jaenisch R, Corr M, Nizet V, Firestein GS, Gerber HP, Ferrara N, Johnson RS. HIF-1alpha is essential for myeloid cell-mediated inflammation. Cell 2003; 112: 645-657.
5. Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci U S A 1995; 92: 5510-5514.
6. Kaelin WG. Proline hydroxylation and gene expression. Annu Rev Biochem 2005; 74: 115–128.
7. Déry MA, Michaud MD, Richard DE. Hypoxia-inducible factor 1: regulation by hypoxic and non-hypoxic activators. Int J Biochem Cell Biol 2005; 37: 535-540.
8. Bhandari T, Olson J, Johnson RS, Nizet V. HIF-1α influences myeloid cell antigen presentation and response to subcutaneous OVA vaccination. J Mol Med (Berl) 2013; 91: 1199-1205.
9. Ema M, Taya S, Yokotani N, Sogawa K, Matsuda Y, Fujii-Kuriyama Y. A novel bHLH-PAS factor with close sequence similarity to hypoxia-inducible factor 1alpha regulates the VEGF expression and is potentially involved in lung and vascular development. Proc Natl Acad Sci U S A 1997; 94: 4273-4278.
10. Cavadas MA, Nguyen LK, Cheong A. Hypoxia-inducible factor (HIF) network: insights from mathematical models. Cell Commun Signal 2013; 11:42.
11. Minet E, Arnould T, Michel G, Roland I, Mottet D, Raes M, Remacle J, Michiels C. ERK activation upon hypoxia: involvement in HIF-1 activation. FEBS Lett 2000; 468: 53-58.
12. Stroka DM, Burkhardt T, Desbaillets I, Wenger RH, Neil DA, Bauer C, Gassmann M, Candinas D. HIF-1 is expressed in normoxic tissue and displays an organ-specific regulation under systemic hypoxia. FASEB J 2001; 15: 2445-2453.
13. Schofield CJ, Ratcliffe PJ. Oxygen sensing by HIF hydroxylases. Nat Rev Mol Cell Biol 2004; 5: 343-354.
14. Christoph M, Ibrahim K, Hesse K, Augstein A, Schmeisser A, Braun-Dullaeus RC, Simonis G, Wunderlich C, Quick S, Strasser RH, Poitz DM. Local inhibition of hypoxia-inducible factor reduces neointima formation after arterial injury in ApoE-/- mice. Atherosclerosis 2014; 23: 641-647.
15. Zhang M, Gao X, Bai SJ, Ye XM, Zhang J. Effect of pioglitazone on expression of hypoxia-inducible factor 1α and vascular endothelial growth factor in ischemic hindlimb of diabetic rats. Eur Rev Med Pharmacol Sci 2014; 18: 1307-1314.
16. Bai R, Zhao AQ, Zhao ZQ, Liu WL, Jian DM. MicroRNA-195 induced apoptosis in hypoxic chondrocytes by targeting hypoxia-inducible factor 1 alpha. Eur Rev Med Pharmacol Sci 2015; 19: 545-551.
17. Okuyama H, Krishnamachary B, Zhou YF, Nagasawa H, Bosch-Marce M, Semenza GL. Expression of vascular endothelial growth factor receptor 1 in bone marrow-derived mesenchymal cells is dependent on hypoxia-inducible factor 1. J Biol Chem 2006; 281: 15554-15563.
18. Brigati C, Banelli B, di Vinci A, Casciano I, Allemanni G, Forlani A, Borzì L, Romani M. Inflammation, HIF-1, and the epigenetics that follows. Mediators Inflamm 2010; 2010: 263914.

19. Moon EJ, Jeong CH, Jeong JW, Kim KR, Yu DY, Murakami S, Kim CW, Kim KW. Hepatitis B virus X protein induces angiogenesis by stabilizing hypoxia-inducible factor-1alpha. FASEB J 2004; 18: 382-384.

20. Wakisaka N, Kondo S, Yoshizaki T, Murono S, Furukawa M, Pagano JS. Epstein-Barr virus latent membrane protein 1 induces synthesis of hypoxia-inducible factor 1 alpha. Mol Cell Biol 2004; 24: 5223-5234.

21. Stasinopoulos I, O'Brien DR, Bhujwalla ZM. Inflammation, but not hypoxia, mediated HIF-1alpha activation depends on COX-2. Cancer Biol Ther 2009; 8: 31-35.

22. Hellwig-Bürgel T, Stiehl DP, Wagner AE, Metzen E, Jelkmann W. Review: hypoxia-inducible factor-1 (HIF-1): a novel transcription factor in immune reactions. J Interferon Cytokine Res 2005; 25: 297-310.

23. Brahimi-Horn MC, Chiche J, Pouysségur J. Hypoxia and cancer. J Mol Med (Berl) 2007; 85: 1301-1307.

24. Semenza GL. Oxygen homeostasis. Wiley Interdiscip Rev Syst Biol Med 2010; 2: 336-361.

25. Harris AL. Hypoxia--a key regulatory factor in tumour growth. Nat Rev Cancer 2002; 2: 38-47.

26. Wei H, Li F, Fu P, Liu X. Effects of the silencing of hypoxia-inducible Factor-1 alpha on metastasis of pancreatic cancer. Eur Rev Med Pharmacol Sci 2013; 17: 436-446.

27. Gort EH, Groot AJ, van der Wall E, van Diest PJ, Vooijs MA. Hypoxic regulation of metastasis via hypoxia-inducible factors. Curr Mol Med 2008; 8: 60-67.

28. Semenza GL. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. Oncogene 2010; 29: 625-634.

29. Rankin EB, Rha J, Unger TL, Wu CH, Shutt HP, Johnson RS, Simon MC, Keith B, Haase VH. Hypoxia-inducible factor-2 regulates vascular tumorigenesis in mice. Oncogene 2008; 27: 5354-5358.

30. Talks KL, Turley H, Gatter KC, Maxwell PH, Pugh CW, Ratcliffe PJ, Harris AL. The expression and distribution of the hypoxia-inducible factors HIF-1alpha and HIF-2alpha in normal human tissues, cancers, and tumor-associated macrophages. Am J Pathol 2000; 157: 411-421.

31. Griffiths EA, Pritchard SA, Valentine HR, Whitchelo N, Bishop PW, Ebert MP, Price PM, Welch IM, West CM. Hypoxia-inducible factor-1alpha expression in the gastric carcinogenesis sequence and its prognostic role in gastric and gastro-oesophageal adenocarcinomas. Br J Cancer 2007; 96: 95-103.

32. Stoeltzing O, McCarty MF, Wey JS, Fan F, Liu W, Belcheva A, Bucana CD, Semenza GL, Ellis LM. Role of hypoxia-inducible factor 1alpha in gastric cancer cell growth, angiogenesis, and vessel maturation. J Natl Cancer Inst 2004; 96: 946-956.

33. Nakanishi K, Hiroi S, Tominaga S, Aida S, Kasamatsu H, Matsuyama S, Matsuyama T, Kawai T. Expression of hypoxia-inducible factor-1alpha protein predicts survival in patients with transitional cell carcinoma of the upper urinary tract. Clin Cancer Res 2005; 11: 2583-2590.

34. Krishnamachary B, Berg-Dixon S, Kelly B, Agani F, Feldser D, Ferreira G, Iyer N, LaRusch J, Pak B, Taghavi P, Semenza GL. Regulation of colon carcinoma cell invasion by hypoxia-inducible factor 1. Cancer Res 2003; 63: 1138-1143.

35. Liao D, Corle C, Seagroves TN, Johnson RS. Hypoxia-inducible factor-1alpha is a key regulator of metastasis in a transgenic model of cancer initiation and progression. Cancer Res 2007; 67: 563-572.

36. Jiang H, Zhu YS, Xu H, Sun Y, Li QF. Inflammatory stimulation and hypoxia cooperatively activate HIF-1{alpha} in bronchial epithelial cells: involvement of PI3K and NF-{kappa}B. Am J Physiol Lung Cell Mol Physiol 2010; 298: L660-669.

37. Goggins BJ, Chaney C, Radford-Smith GL, Horvat JC, Keely S. Hypoxia and integrin-mediated epithelial restitution during mucosal inflammation. Front Immunol 2013; 4 :272.

38. Palazon A, Goldrath AW2, Nizet V3, Johnson RS. HIF transcription factors, inflammation, and immunity. Immunity 2014; 41: 518-528.

39. Carsten C Scholz and Cormac T Taylor. Targeting the HIF pathway in inflammation and immunity. Curr Opin Pharmacol 2013; 13: 646-653.

40. Hellwig-Bürgel T, Rutkowski K, Metzen E, Fandrey J, Jelkmann W. Interleukin-1beta and tumor necrosis factor-alpha stimulate DNA binding of hypoxia-inducible factor-1. Blood 1999; 94: 1561-1567.

41. Brüne B, Zhou J. Nitric oxide and superoxide: interference with hypoxic signaling. Cardiovasc Res 2007; 75: 275-282.

42. Remels AH, Gosker HR, Verhees KJ, Langen RC, Schols AM. TNF-α-induced NF-κB activation stimulates skeletal muscle glycolytic metabolism through activation of HIF-1α. Endocrinology 2015; 156: 1770-1781.

43. Frede S, Stockmann C, Freitag P, Fandrey J. Bacterial lipopolysaccharide induces HIF-1 activation in human monocytes via p44/42 MAPK and NF-kappaB. Biochem J 2006; 396: 517-527.

44. Jantsch J, Chakravortty D, Turza N, Prechtel AT, Buchholz B, Gerlach RG, Volke M, Gläsner J, Warnecke C, Wiesener MS, Eckardt KU, Steinkasserer A, Hensel M, Willam C. Hypoxia and hypoxia-inducible factor-1 alpha modulate lipopolysaccharide-induced dendritic cell activation and function. J Immunol 2008; 180: 4697-4705.

45. Dehne N, Brüne B. HIF-1 in the inflammatory microenvironment. Exp Cell Res 2009; 315: 1791-1797.

46. Willam C. HIF meets NF-κB signaling. Kidney Int 2014; 85: 232-234.

47. Yang S, Yu M, Sun L, Xiao W, Yang X, Sun L, Zhang C, Ma Y, Yang H, Liu Y, Lu D, Teitelbaum DH, Yang H. Interferon-γ-induced intestinal epithelial barrier dysfunction by NF-κB/HIF-1α pathway. J Interferon Cytokine Res 2014; 34: 195-203.

48. Karin M. Nuclear factor-kappaB in cancer development and progression. Nature 2006; 441: 431-436.

49. Spirina LV, Kondakova IV, Choynzonov EL, Chigevskaya SY, Shishkin DA, Kulbakin DY. Expression of vascular endothelial growth factor and transcription factors HIF-1, NF-kB expression in squamous cell carcinoma of head and neck; association with proteasome and calpain activities. J Cancer Res Clin Oncol 2013; 139: 625-633.

50. Bandarra D, Biddlestone J, Mudie S, Müller HA, Rocha S. HIF-1α restricts NF-κB-dependent gene expression to control innate immunity signals. Dis Model Mech 2015; 8: 169-181.

51. Courtnay R, Ngo DC, Malik N, Ververis K, Tortorella SM, Karagiannis TC. Cancer metabolism and the Warburg effect: the role of HIF-1 and PI3K. Mol Biol Rep 2015; 42: 841-851.

52. Minhajuddin M, Bijli KM, Fazal F, Sassano A, Nakayama KI, Hay N, Platanias LC, Rahman A. Protein kinase C-delta and phosphatidylinositol 3-kinase/ Akt activate mammalian target of rapamycin to modulate NF-kappaB activation and intercellular adhesion molecule-1 (ICAM-1) expression in endothelial cells. J Biol Chem 2009; 284: 4052-4061.

53. Lee SH, Jee JG, Bae JS, Liu KH, Lee YM. A group of novel HIF-1α inhibitors, glyceollins, blocks HIF-1α synthesis and decreases its stability via inhibition of the PI3K/AKT/mTOR pathway and Hsp90 binding. J Cell Physiol 2015; 230: 853-862.

54. Choi YH, Jin GY, Li LC, Yan GH. Inhibition of protein kinase C delta attenuates allergic airway inflammation through suppression of PI3K/Akt/mTOR/ HIF-1 alpha/VEGF pathway. PLoS One 2013; 8: e81773.

55. Land SC, Tee AR. Hypoxia-inducible factor 1alpha is regulated by the mammalian target of rapamycin (mTOR) via an mTOR signaling motif. J Biol Chem 2007; 282: 20534-20543.

56. El Assar M, Sánchez-Puelles JM, Royo I, López-Hernández E, Sánchez-Ferrer A, Aceña JL, Rodríguez-Mañas L, Angulo J. FM19G11 reverses endothelial dysfunction in rat and human arteries through stimulation of the PI3K/Akt/eNOS pathway, independently of mTOR/HIF-1α activation. Br J Pharmacol 2015; 172: 1277-1291.

57. Rodríguez-Jimnez FJ, Alastrue-Agudo A, Erceg S, Stojkovic M, Moreno-Manzano V. FM19G11 favors spinal cord injury regeneration and stem cell self-renewal by mitochondrial uncoupling and glucose metabolism induction. Stem Cells 2012; 30: 2221-2233.

58. Hudson CC, Liu M, Chiang GG, Otterness DM, Loomis DC, Kaper F, Giaccia AJ, Abraham RT. Regulation of hypoxia-inducible factor 1alpha expression and function by the mammalian target of rapamycin. Mol Cell Biol 2002; 22: 7004-7014.

59. Majumder PK, Febbo PG, Bikoff R, Berger R, Xue Q, McMahon LM, Manola J, Brugarolas J, McDonnell TJ, Golub TR, Loda M, Lane HA, Sellers WR. mTOR inhibition reverses Akt-dependent prostate intraepithelial neoplasia through regulation of apoptotic and HIF-1-dependent pathways. Nat Med 2004; 10: 594-601.

60. Imtiyaz HZ, Simon MC. Hypoxia-inducible factors as essential regulators of inflammation. Curr Top Microbiol Immunol 2010; 345: 105-120.

61. Fang HY, Hughes R, Murdoch C, Coffelt SB, Biswas SK, Harris AL, Johnson RS, Imityaz HZ, Simon MC, Fredlund E, Greten FR, Rius J, Lewis CE. Hypoxia-inducible factors 1 and 2 are important transcriptional effectors in primary macrophages experiencing hypoxia. Blood 2009; 114: 844-859.

62. Walmsley SR, Cadwallader KA, Chilvers ER. The role of HIF-1alpha in myeloid cell inflammation. Trends Immunol 2005; 26: 434-439.

63. Campbell EL, Bruyninckx WJ, Kelly CJ, Glover LE, McNamee EN, Bowers BE, Bayless AJ, Scully M, Saeedi BJ, Golden-Mason L, Ehrentraut SF, Curtis VF, Burgess A, Garvey JF, Sorensen A, Nemenoff R, Jedlicka P, Taylor CT, Kominsky DJ, Colgan SP. Trans-migrating neutrophils shape the mucosal micro-environment through localized oxygen depletion to influence resolution of inflammation. Immunity 2014; 40: 66-77.

64. Thompson AA, Elks PM, Marriott HM, Eamsamarng S, Higgins KR, Lewis A, Williams L, Parmar S, Shaw G, McGrath EE, Formenti F, Van Eeden FJ, Kinnula VL, Pugh CW, Sabroe I, Dockrell DH, Chilvers ER, Robbins PA, Percy MJ, Simon MC, Johnson RS, Renshaw SA, Whyte MK, Walmsley SR. Hypoxia-inducible factor 2α regulates key neutrophil functions in humans, mice, and zebrafish. Blood 2014; 123: 366-376.

65. Elks PM, van Eeden FJ, Dixon G, Wang X, Reyes-Aldasoro CC, Ingham PW, Whyte MK, Walmsley SR, Renshaw SA. Activation of hypoxia-inducible factor-1α (Hif-1α) delays inflammation resolution by reducing neutrophil apoptosis and reverse migration in a zebrafish inflammation model. Blood 2011; 118: 712-722.

66. McNamee EN, Korns Johnson D, Homann D, Clambey ET. Hypoxia and hypoxia-inducible factors as regulators of T cell development, differentiation, and function. Immunol Res 2013; 55: 58-70.

67. He LY, Li L, Guo ML, Zhang Y, Zhang HZ. Relationship between CD4+CD25+ Treg and expression of HIF-1α and Ki-67 in NSCLC patients. Eur Rev Med Pharmacol Sci 2015; 19: 1351-1355.

68. Thiel M, Caldwell CC, Kreth S, Kuboki S, Chen P, Smith P, Ohta A, Lentsch AB, Lukashev D, Sitkovsky MV. Targeted deletion of HIF-1alpha gene in T cells prevents their inhibition in hypoxic inflamed tissues and improves septic mice survival. PLoS One 2007; 2: e853.

69. Lukashev D, Klebanov B, Kojima H, Grinberg A, Ohta A, Berenfeld L, Wenger RH, Ohta A, Sitkovsky M. Cutting edge: hypoxia-inducible factor 1alpha and its activation-inducible short isoform I.1 negatively regulate functions of CD4+ and CD8+ T lymphocytes. J Immunol 2006; 177: 4962-4965.

70. Pan F, Barbi J, Pardoll DM. Hypoxia-inducible factor 1: A link between metabolism and T cell differentiation and a potential therapeutic target. Oncoimmunology 2012; 1: 510-515.

71. Dang EV, Barbi J, Yang HY, Jinasena D, Yu H, Zheng Y, Bordman Z, Fu J, Kim Y, Yen HR, Luo W, Zeller K, Shimoda L, Topalian SL, Semenza GL, Dang CV, Pardoll DM, Pan F. Control of T(H)17/T(reg) balance by hypoxia-inducible factor 1. Cell 2011; 146: 772-784.

72. Shi LZ, Wang R, Huang G, Vogel P, Neale G, Green DR, Chi H. HIF1alpha-dependent glycolytic pathway orchestrates a metabolic checkpoint for the differentiation of TH17 and Treg cells. J Exp Med 2011; 208: 1367-1376.

73. Ikejiri A, Nagai S, Goda N, Kurebayashi Y, Osada-Oka M, Takubo K, Suda T, Koyasu S. Dynamic regulation of Th17 differentiation by oxygen concentrations. Int Immunol 2012; 24: 137-146.

74. Deng W, Ren Y, Feng X, Yao G, Chen W, Sun Y, Wang H, Gao X, Sun L. Hypoxia inducible factor-1 alpha promotes mesangial cell proliferation in lupus nephritis. Am J Nephrol 2014; 40: 507-515.

75. Kim HJ, Park JW, Cho YS, Cho CH, Kim JS, Shin HW, Chung DH, Kim SJ, Chun YS. Pathogenic role of HIF-1α in prostate hyperplasia in the presence of chronic inflammation. Biochim Biophys Acta 2013; 1832: 183-194.

76. Brouwer E, Gouw AS, Posthumus MD, van Leeuwen MA, Boerboom AL, Bijzet J, Bos R, Limburg PC, Kallenberg CG, Westra J. Hypoxia inducible factor-1-alpha (HIF-1alpha) is related to both angiogenesis and inflammation in rheumatoid arthritis. Clin Exp Rheumatol 2009; 27: 945-951.

77. Kim M, Neinast MD, Frank AP, Sun K, Park J, Zehr JA, Vishvanath L, Morselli E, Amelotte M, Palmer BF, Gupta RK, Scherer PE, Clegg DJ. ERα upregulates Phd3 to ameliorate HIF-1 induced fibrosis and inflammation in adipose tissue. Mol Metab 2014; 3: 642-651.

78. Kim Y, Kim BH, Lee H, Jeon B, Lee YS, Kwon MJ, Kim TY. Regulation of skin inflammation and angiogenesis by EC-SOD via HIF-1α and NF-κB pathways. Free Radic Biol Med 2011; 51: 1985-1995.

79. Zampell JC, Yan A, Avraham T, Daluvoy S, Weitman ES, Mehrara BJ. HIF-1α coordinates lymphangiogenesis during wound healing and in response to inflammation. FASEB J 2012; 26: 1027-1039.

80. Pawlik MW, Kwiecien S, Pajdo R, Ptak-Belowska A, Brzozowski B, Krzysiek-Maczka G, Strzalka M, Konturek SJ, Brzozowski T. Esophagoprotective activity of angiotensin-(1-7) in experimental model of acute reflux esophagitis. Evidence for the role of nitric oxide, sensory nerves, hypoxia-inducible factor-1alpha and proinflammatory cytokines. J Physiol Pharmacol 2014; 65: 809-822.

81. Feng CC, Ye QL, Zhu Y, Leng RX, Chen GM, Yang J, Cen H, Yang XK, Li R, Xu WD, Pan HF, Ye DQ. Lack of association between the polymorphisms of hypoxia-inducible factor 1A (HIF1A) gene and SLE susceptibility in a Chinese population. Immunogenetics 2014; 66: 9-13.

82. Adunka O, Gstoettner W, Knecht R, Kierner AC. Expression of hypoxia inducible factor 1 alpha and Von Hippel Lindau protein in human middle ear cholesteatoma. Laryngoscope 2003; 113: 1210-1215.

83. Rose F, Grimminger F, Appel J, Heller M, Pies V, Weissmann N, Fink L, Schmidt S, Krick S, Camenisch G, Gassmann M, Seeger W, Hänze J. Hypoxic pulmonary artery fibroblasts trigger proliferation of vascular smooth muscle cells: role of hypoxia-inducible transcription factors. FASEB J 2002; 16: 1660-1661.

84. Xu Y, Zhao Y, Xu W, Luo F, Wang B, Li Y, Pang Y, Liu Q. Involvement of HIF-2α-mediated inflammation in arsenite-induced transformation of human bronchial epithelial cells. Toxicol Appl Pharmacol 2013; 272: 542-550.

85. Shepardson KM, Jhingran A, Caffrey A, Obar JJ, Suratt BT, Berwin BL, Hohl TM, Cramer RA. Myeloid derived hypoxia inducible factor 1-alpha is required for protection against pulmonary Aspergillus fumigatus infection. PLoS Pathog 2014; 10: e1004378.

86. Park SJ, Lee KS, Kim SR, Chae HJ, Yoo WH, Kim DI, Jeon MS, Lee YC. AMPK activation reduces vascular permeability and airway inflammation by regulating HIF/VEGFA pathway in a murine model of toluene diisocyanate-induced asthma. Inflamm Res 2012; 61: 1069-1083.

87. Lee SY, Kwon S, Kim KH, Moon HS, Song JS, Park SH, Kim YK. Expression of vascular endothelial growth factor and hypoxia-inducible factor in the airway of asthmatic patients. Ann Allergy Asthma Immunol 2006; 97: 794-799.

88. Baay-Guzman GJ, Bebenek IG, Zeidler M, Hernandez-Pando R, Vega MI, Garcia-Zepeda EA, Antonio-Andres G, Bonavida B, Riedl M, Kleerup E, Tashkin DP, Hankinson O, Huerta-Yepez S. HIF-1 expression is associated with CCL2 chemokine expression in airway inflammatory cells: implications in allergic airway inflammation. Respir Res 2012; 13: 60.

89. Crotty Alexander LE, Akong-Moore K, Feldstein S, Johansson P, Nguyen A, McEachern EK, Nicatia S, Cowburn AS, Olson J, Cho JY, Isaacs H Jr, Johnson RS, Broide DH, Nizet V. Myeloid cell HIF-1α regulates asthma airway resistance and eosinophil function. J Mol Med (Berl) 2013; 91: 637-644.

90. Lee SH, Lee SH, Kim CH, Yang KS, Lee EJ, Min KH, Hur GY, Lee SH, Lee SY, Kim JH, Shin C, Shim JJ, In KH, Kang KH, Lee SY. Increased expression of vascular endothelial growth factor and hypoxia inducible factor-1α in lung tissue of patients with chronic bronchitis. Clin Biochem 2014; 47: 552-559.

91. Fajardo I, Svensson L, Bucht A, Pejler G. Increased levels of hypoxia-sensitive proteins in allergic airway inflammation. Am J Respir Crit Care Med 2004; 170: 477-484.

92. Lee SY, Chung SM. Neovastat (AE-941) inhibits the airway inflammation via VEGF and HIF-2 alpha suppression. Vascul Pharmacol 2007; 47: 313-318.

93. Lee KS, Kim SR, Park HS, Park SJ, Min KH, Lee KY, Choe YH, Hong SH, Han HJ, Lee YR, Kim JS, Atlas D, Lee YC. A novel thiol compound, N-acetylcysteine amide, attenuates allergic airway disease by regulating activation of NF-kappaB and hypoxia-inducible factor-1alpha. Exp Mol Med 2007; 39: 756-768.

94. Sumbayev VV, Yasinska I, Oniku AE, Streatfield CL, Gibbs BF. Involvement of hypoxia-inducible factor-1 in the inflammatory responses of human LAD2 mast cells and basophils. PLoS One 2012; 7: e34259.

95. de Souza Alves CC, Collison A, Hatchwell L, Plank M, Morten M, Foster PS, Johnston SL, da Costa CF, de Almeida MV, Couto Teixeira H, Paula Ferreira A, Mattes J. Inhibiting AKT phosphorylation employing non-cytotoxic anthraquinones ameliorates TH2 mediated allergic airways disease and rhinovirus exacerbation. PLoS One 2013; 8: e79565.

96. Zhou H, Chen X, Zhang WM, Zhu LP, Cheng L. HIF-1α inhibition reduces nasal inflammation in a murine allergic rhinitis model. PLoS One 2012; 7: e48618.

97. Mo JH, Kim JH, Lim DJ, Kim EH. The role of hypoxia-inducible factor 1α in allergic rhinitis. Am J Rhinol Allergy 2014; 28: e100-6.

98. Huerta-Yepez S, Baay-Guzman GJ, Bebenek IG, Hernandez-Pando R, Vega MI, Chi L, Riedl M, Diaz-Sanchez D, Kleerup E, Tashkin DP, Gonzalez FJ, Bonavida B, Zeidler M, Hankinson O. Hypoxia inducible factor promotes murine allergic airway inflammation and is increased in asthma and rhinitis. Allergy 2011; 66: 909-918.

99. Bachert C, Zhang N, van Zele T, Gevaert P. Chronic rhinosinusitis: from one disease to different phenotypes. Pediatr Allergy Immunol 2012; 23 Suppl 22: 2-4.

100. Hirotsu M, Kikuchi K, Kusunoki T, Kase K, Ono N, Ikeda K. Comparison of bacterial examinations between eosinophilic and neutrophilic chronic rhinosinusitis with nasal polyps. Acta Otolaryngol 2011; 131: 997-1001.

101. Brook I. Bacteriology of acute and chronic ethmoid sinusitis. J Clin Microbiol 2005; 43: 3479-3480.

102. Steinke JW, Woodard CR, Borish L. Role of hypoxia in inflammatory upper airway disease. Curr Opin Allergy Clin Immunol 2008; 8: 16-20.

103. Cohen S, Efraim AN, Levi-Schaffer F, Eliashar R. The effect of hypoxia and cycloxygenase inhibitors on nasal polyp derived fibroblasts. Am J Otolaryngol 2011; 32: 564-573.

104. Pahl A, Szelenyi S, Brune K. Hypoxia induced chemokine expression in nasal epithelial cells: development of an in vitro model for chronic rhinosinusitis. ALTEX 2006; 23: 59-63.

105. Blount A, Zhang S, Chestnut M, Hixon B, Skinner D, Sorscher EJ, Woodworth BA. Transepithelial ion transport is suppressed in hypoxic sinonasal epithelium. Laryngoscope 2011; 121: 1929-1934.

106. Tomlinson LA, Carpenter TC, Baker EH, Bridges JB, Weil JV. Hypoxia reduces airway epithelial sodium transport in rats. Am J Physiol 1999; 277: L881-886.

107. Kim YJ, Cho HJ, Shin WC, Song HA, Yoon JH, Kim CH. Hypoxia-mediated mechanism of MUC5AC production in human nasal epithelia and its implication in rhinosinusitis. PLoS One 2014; 9: e98136.

108. Haight JS, Qian W, Daya H, Chalmers P, Zamel N. Hypoxia depresses nitric oxide output in the human nasal airways. Laryngoscope 2000; 110: 429-433.

109. Jiang S, Dong Z, Zhu D, Yang Z. Local tissue hypoxia and formation of nasal polyps. Chin Med J (Engl) 2003; 116: 243-247.

110. Matsune S, Kono M, Sun D, Ushikai M, Kurono Y. Hypoxia in paranasal sinuses of patients with chronic sinusitis with or without the complication of nasal allergy. Acta Otolaryngol 2003; 123: 519-523.

111. Park WS, Jung WK, Park SK, Heo KW, Kang MS, Choi YH, Kim GY, Park SG, Seo SK, Yea SS, Liu KH, Shim EB, Kim DJ, Her M, Choi IW. Expression of galectin-9 by IFN-γ stimulated human nasal polyp fibroblasts through MAPK, PI3K, and JAK/STAT signaling pathways. Biochem Biophys Res Commun 2011; 411: 259-264.

112. Shin HW, Cho K, Kim DW, Han DH, Khalmuratova R, Kim SW, Jeon SY, Min YG, Lee CH, Rhee CS, Park JW. Hypoxia-inducible factor 1 mediates nasal polypogenesis by inducing epithelial-to-mesenchymal transition. Am J Respir Crit Care Med 2012; 185: 944-954.

113. Chien CY, Tai CF, Ho KY, Kuo WR, Chai CY, Hsu YC, Wang LF. Expression of hypoxia-inducible factor 1alpha in the nasal polyps by real-time RT-PCR and immunohistochemistry. Otolaryngol Head Neck Surg 2008; 139: 206-210.

114. Muluk NB, Atasoy P, Arikan OK, Koc C. Role of vascular endothelial growth factor in the pathogenesis of nasal polyps. J Otolaryngol 2007; 36: 357-366.

115. Zaravinos A, Soufla G, Bizakis J, Spandidos DA. Expression analysis of VEGFA, FGF2, TGFbeta1, EGF and IGF1 in human nasal polyposis. Oncol Rep 2008; 19: 385-391.

116. Wittekindt C, Hess A, Bloch W, Sultanie S, Michel O. Immunohistochemical expression of VEGF and VEGF receptors in nasal polyps as compared to normal turbinate mucosa. Eur Arch Otorhinolaryngol 2002; 259: 294-298.

117. Liu Y, Cui YH, Yu LL, Liu Z, Zhang P. Expression of hypoxia-inducible factor-1alpha in nasal polyps and its correlation with vascular endothelial growth factor and inducible nitric oxide synthase. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2005; 40: 366-370. Article in Chinese

118. Yang L, Dong Z. Expression and the role of HIF-1alpha and VEGF in human nasal epithelial cells. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2008; 22: 341-345. Article in Chinese

119. Park SK, Jang WH, Yang YI. Expression of pro-angiogenic cytokines and their inhibition by dexamethasone in an ex vivo model of nasal polyps. Biochem Biophys Res Commun 2009; 379: 255-260.

120. Moon YM, Kang HJ, Cho JS, Park IH, Lee HM. Nox4 mediates hypoxia-stimulated myofibroblast differentiation in nasal polyp-derived fibroblasts. Int Arch Allergy Immunol 2012; 159: 399-409.

121. Early SB, Hise K, Han JK, Borish L, Steinke JW. Hypoxia stimulates inflammatory and fibrotic responses from nasal-polyp derived fibroblasts. Laryngoscope 2007; 117: 511-515.

122. Lin SK, Shun CT, Kok SH, Wang CC, Hsiao TY, Liu CM. Hypoxia-stimulated vascular endothelial growth factor production in human nasal polyp fibroblasts: effect of epigallocatechin-3-gallate on hypoxia-inducible factor-1 alpha synthesis. Arch Otolaryngol Head Neck Surg 2008; 134: 522-527.

123. Sun D, Matsune S, Ohori J, Fukuiwa T, Ushikai M, Kurono Y. TNF-alpha and endotoxin increase hypoxia-induced VEGF production by cultured human nasal fibroblasts in synergistic fashion. Auris Nasus Larynx 2005; 32: 243-249.

124. Matsune S, Sun D, Ohori J, Nishimoto K, Fukuiwa T, Ushikai M, Kurono Y. Inhibition of vascular endothelial growth factor by macrolides in cultured fibroblasts from nasal polyps. Laryngoscope 2005; 115: 1953-1956.

125. Shun CT, Lin SK, Hong CY, Huang HM, Liu CM. Hypoxia induces cysteine-rich 61, vascular endothelial growth factor, and interleukin-8 expressions in human nasal polyp fibroblasts: An implication of neutrophils in the pathogenesis of nasal polyposis. Am J Rhinol Allergy 2011; 25: 15-8.

126. Payne SC, Early SB, Huyett P, Han JK, Borish L, Steinke JW. Evidence for distinct histologic profile of nasal polyps with and without eosinophilia. Laryngoscope 2011; 121: 2262-2267.

127. Shi LL, Xiong P, Zhang L, Cao PP, Liao B, Lu X, Cui YH, Liu Z. Features of airway remodeling in different types of Chinese chronic rhinosinusitis are associated with inflammation patterns. Allergy 2013; 68: 101-109.

128. Payne SC, Han JK, Huyett P, Negri J, Kropf EZ, Borish L, Steinke JW. Microarray analysis of distinct gene transcription profiles in non-eosinophilic chronic sinusitis with nasal polyps. Am J Rhinol 2008; 22: 5685-5681.

129. Jin J, Chang DY, Kim SH, Rha KS, Mo JH, Shin EC, Kim YM. Role of hypoxia-inducible factor-1α expression in regulatory T cells on nasal polypogenesis. Laryngoscope 2014; 124: E151-159.

130. Onnis B, Rapisarda A, Melillo G. Development of HIF-1 inhibitors for cancer therapy. J Cell Mol Med 2009; 13: 2780-2786.

131. Semenza GL. Targeting HIF-1 for cancer therapy. Nat Rev Cancer 2003; 3: 721-732.

132. Semenza GL. Evaluation of HIF-1 inhibitors as anticancer agents. Drug Discov Today 2007; 12: 853-859.