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Invited Mini Review

Oxygen matters: hypoxia as a pathogenic mechanism in rhinosinusitis

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The airway epithelium is the first place, where a defense mechanism is initiated against environmental stimuli. Mucociliary transport (MCT), which is the defense mechanism of the airway and the role of airway epithelium as mechanical barriers are essential in innate immunity. To maintain normal physiologic function, normal oxygenation is critical for the production of energy for optimal cellular functions. Several pathologic conditions are associated with a decrease in oxygen tension in airway epithelium and chronic sinusitis is one of the airway diseases, which is associated with the hypoxic condition, a potent inflammatory stimulant. We have observed the overexpression of the hypoxia-inducible factor 1 (HIF-1), an essential factor for oxygen homeostasis, in the epithelium of sinus mucosa in sinusitis patients. In a series of previous reports, we have found hypoxia-induced mucus hyperproduction, especially by MUC5AC hyperproduction, disruption of epithelial barrier function by the production of VEGF, and down-regulation of junctional proteins such as ZO-1 and E-cadherin. Furthermore, hypoxia-induced inflammation by HMGB1 translocation into the cytoplasm results in the release of IL-8 through a ROS-dependent mechanism in upper airway epithelium. In this mini-review, we briefly introduce and summarize current progress in the pathogenesis of sinusitis related to hypoxia. The investigation of hypoxia-related pathophysiology in airway epithelium will suggest new insights on airway inflammatory diseases, such as rhinosinusitis for clinical application and drug development. [BMB Reports 2018; 51(2): 59-64]

INTRODUCTION

The airway epithelium constitutes the first line of defense against environmental stimuli, in innate immunity by serving as mechanical barriers along with the mucociliary transport (MCT), which is the defense mechanism of the airway (1). Preserving this physiologic role requires sustaining energy production, which is supplied by appropriate oxygenation (2). Several pathologic conditions may lead to decrease in oxygen level in the airway epithelium. In chronic airway diseases such as sinusitis, allergic rhinitis, asthma, and chronic obstructive pulmonary disease, decrease in oxygen tension can occur due to pathologic changes in the microvascular structures or increase in metabolic demands (3). Such diseases commonly represent pathologic characteristics such as infiltration of inflammatory cells, tissue remodeling or mucus hypersecretion (4).

In the upper airway, chronic sinusitis is one of the hypoxia-related diseases. The sinus mucosa is composed of ciliated columnar epithelium intermixed with goblet cells. The cilia of epithelial cells have an essential role in transporting mucus outside of sinus through sinus ostium and maintaining a normal physiologic condition in the paranasal sinuses. Normal mucociliary transport is essential for the maintenance of the airway innate defense, and a decrease of mucociliary transport has been proved in rhinosinusitis. The defect in normal mucociliary transport can develop due to changes in mucus viscosity or any toxicity (5). Hypoxia is another potential factor for sinusitis and we have reviewed the pathogenesis of hypoxia-related sinusitis.

HIF-1α-MEDIATED MUCUS HYPERSECRETION BY HYPOXIA

The mechanical obstruction of the sinus natural opening reduces oxygen tension within the sinus resulting in sinusitis (6). Goblet cell hyperplasia is one of the major histopathologic changes in chronic rhinosinusitis (7). In hypoxic conditions, the hypoxia-inducible factor 1 (HIF-1) is essential for oxygen-related pathophysiology for transcriptional expression of erythropoietin (8), vascular endothelial growth factor (VEGF) (9), heme oxygenase-1 (10), and transferrin (11). HIF-1 is composed of a heterodimer, α and β subunits (12), and HIF-1α activation conducts the extracellular signal-regulated kinase signaling pathway (13). Although hypoxia is an effective inflammatory stimulant (4), the influence of hypoxia on mucus overproduction and its related-mechanism has not been

clearly suggested. The hypoxia-response element (HRE) is commonly present at the proximal promoter and includes one or more HIF-1-binding sites (14). The mutation in the HRE location inactivates the transcriptional response to hypoxia (15, 16). The promoter region of the MUC5AC gene includes a similar sequence to the HRE (17, 18). Therefore, we investigated the promoter region of the MUC5AC gene to understand the mechanism of hypoxia-induced MUC5AC gene in airway epithelium. We have mainly utilized primary human nasal epithelial (HNE) cells, which were cultured and differentiated in the condition of the air-liquid interface system, for *in vitro* experiments (19). Under hypoxic condition, HNE cells induced the expression of MUC5AC mRNA and protein (20). The elevation of HIF-1α expression in HNE cell by hypoxia was also identified and its loss- or gain-of-function experiment confirmed the role of HIF-1α in MUC5AC expression under hypoxic environment. To identify the DNA binding activity of HIF-1α to the MUC5AC promoter under hypoxia, we performed chromatin immuno-precipitation (ChIP) assays and the regulatory HRE region of the MUC5AC promoter was identified to be important in increasing the transcriptional activity of MUC5AC caused by hypoxia (20). Immunohistochemical staining proved strong expression of MUC5AC and HIF-1α in the epithelium in sinusitis mucosa. These data suggest that hypoxic condition in the sinus is associated with sinusitis in terms of MUC5AC overproduction via the HIF-1α-mediated mechanism.

EPITHELIAL BARRIER BY HYPOXIA: VEGF MEDIATED-MECHANISM

The pathophysiology of epithelial disruption have been studied based on several aspects. It was demonstrated that hypoxia contributed to the breakdown of epithelial barrier via VEGFR-1 in retinal epithelium (21). The IL-13 led to disruption of tight junction in bronchial epithelium (22). Rhinovirus infection is a fundamental predisposing factor for subsequent bacterial invasion by dissociating zona occludens-1 (23). To the best of our knowledge, this is the first report to elucidate the role of the hypoxia−HIF−VEGF axis in the regulation of epithelial paracellular permeability in airway epithelium.

VEGF is a protein associated with vascular permeability as well as angiogenesis in endothelial cells and induces fenestrations or caveolae in the endothelial cytoplasm, which result in a vascular leak of plasma protein and tissue edema (24). There exist several reports on hypoxia-induced VEGF secretion (25-27). Furthermore, VEGF overexpression has been reported in several chronic airway inflammatory diseases, such as bronchial asthma, sinusitis, and allergic rhinitis (28-31). Therefore, it would be interesting to understand the role of VEGF in the pathogenesis of sinusitis under hypoxia. We hypothesized that HIF-1α and VEGF might be associated with the pathogenesis of sinusitis by augmenting paracellular permeability in the sinus epithelium. In human airway

epithelial cells, the elevation in VEGF mRNA and protein was identified by hypoxic stimulation; overexpression of HIF-1α under normoxic condition also induced VEGF expression (32). Knockdown of HIF-1α resulted in downregulation of VEGF mRNA and protein level under hypoxic condition. These results imply that VEGF expression under the hypoxic condition is mediated through HIF-1α signaling pathway. The functional assay of the epithelial barrier can be measured by transepithelial electrical resistance (TEER). TEER decreases under the hypoxic condition and can be rescued by the knockdown of HIF-1α or bevacizumab, a monoclonal antibody against VEGF. However, we have not yet confirmed the expression of VEGFR-1 or -2 in primary nasal epithelial cells and further investigations are required to elucidate the signaling pathway including identification of VEGFR.

Disruption of epithelial barrier function is an important histological change resulting in clinical significance. This fact provides a possibility of the development of novel therapeutic agents to improve epithelial barrier function for various airway diseases. Vulnerability to adherence or invasion of pathogens can be increased through the leaky epithelial barrier. We also confirmed higher bacterial passage of nasal epithelium under hypoxic condition compared to normoxia.

EPITHELIAL BARRIER BY HYPOXIA: JUNCTIONAL PROTEINS MEDIATED-MECHANISM

The epithelial barrier function is maintained by tight and adherence junctions. The tight junctions are the most apical complex and disconnect the apical lumen from the basolateral side. ZO-1 is a tight junction component that is present in the upper part of epithelium (33). Adherence junctions are also important for the intercellular adhesion as they provide a docking site for signaling molecules (34, 35). The main component of adherence junction is E-cadherin, a trans-membrane protein that forms calcium-dependent hemophilic intercellular adhesions between epithelial cells (36). In the human nasal mucosa, viral infection leads to loss of junctional complexes, especially ZO-1 with resultant augmentation of intranasal bacterial inoculation in mice (23). In allergic nasal mucosa, the reduction of ZO-1 mRNA has been reported (37). The reduction of ZO-1 but the elevation of E-cadherin was observed in the epithelium of nasal polyp (38). Therefore, the alterations in the levels of ZO-1 or E-cadherin can cause the disruption of the epithelial barrier under various pathological conditions (39).

To prove the effect of hypoxia on barrier function, we investigated the effects of hypoxia on ZO-1 and E-cadherin expression level (40). Hypoxia decreased the expression of ZO-1 and E-cadherin significantly after 8 hours of exposure. The disruption of the epithelial barrier was also proven functionally based on the measurement of TEER. The decreased expression pattern of ZO-1 and E-cadherin was also confirmed in the sinus epithelium of chronic sinusitis which is

a hypoxia-conditioned nasal mucosa. Overall, the exposure to hypoxic conditions cause down-regulation of junction complex molecules and increasing TEER implying the disruption of normal barrier function of nasal epithelia.

HMGB1-MEDIATED INFLAMMATION BY HYPOXIA

High-mobility group box 1 (HMGB1) is a small sized protein, which acts as a DNA chaperone. HMGB1 is secreted into the extracellular space either actively or passively. Release following pro-inflammatory stimulation is an active process and release following apoptosis and necrosis is a passive process. The HMGB1, which is released into the extracellular space, binds to Toll-like receptor (TLR) 2 or TLR 4, and the receptor for advanced glycation end products (RAGE) resulting in activation of proinflammatory signaling pathways (41-43). The HMGB1, which is translocated from the nucleus into the cytoplasm, can be dependent on the posttranslational modifications such as phosphorylation, acetylation, and oxidation; reactive oxygen species (ROS) play important role in this process (41, 42, 44, 45). Recently, we reported the detection of elevated levels of HMGB1 in the nasal lavage fluid collected from chronic rhinosinusitis patients (46). Under hypoxic condition, there exists the possibility that HMGB1 can be translocated from the nucleus into the cytoplasm and released into the extracellular space, thus serving as a

characteristic molecule for hypoxia-associated tissue damage (47, 48). Therefore, we investigated the role of HMGB1 in the progression of upper airway inflammatory diseases under hypoxic condition. Hypoxia induces translocation of HMGB1 from the nucleus into the extracellular area in RPMI 2650 cells and HNE cells. Immunofluorescence assay (ELISA and western blotting) revealed augmentation of cytoplasmic HMGB1 under the hypoxic condition and increased the level of HMGB1 protein in supernatants from HNE cells (49). Hypoxia increases the redox potential of local environment due to alterations in the production of ROS (50). ROS production can be dependent on the oxygen tension because the mild degree of hypoxia induces ROS production, but severe hypoxia decreases ROS production (50). The variations in oxygen concentration differentially affect the redox potential of the HMGB1 structure thus altering the functions of HMGB1. In our experimental setting, hypoxia increased the ROS levels significantly, which was confirmed by the pretreatment of the ROS scavenger, N-acetyl cysteine (NAC) with resultant suppression of hypoxia-induced ROS levels. Immunofluorescence assay revealed a reduction in cytoplasmic translocation of HMGB1, implying the association of HMGB1 with the increase in ROS.

Extracellular secretion of HMGB1 was also determined and pretreatment with NAC decreased the HMGB1 protein level from collected apical supernatants by ELISA and western
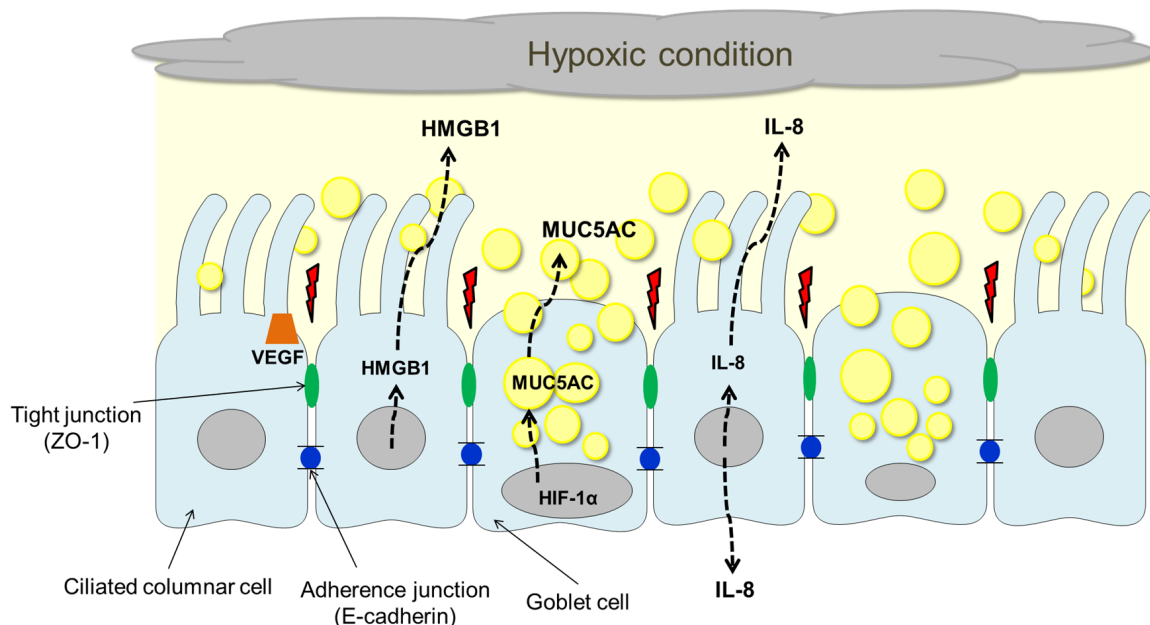
Fig. 1. Hypoxia-induced pathophysiology of upper airway inflammation. Under hypoxic condition, HIF-1α serves as an essential factor mediating MUC5AC overproduction. Hypoxia stimulates HIF-1α-dependent overexpression of VEGF leading to disruption of epithelial barrier function and alteration in adherence (E-cadherin) or junctional (ZO-1) protein. Furthermore, hypoxia induces HMGB1 translocation into the cytoplasm and release of IL-8 through a ROS-dependent mechanism in the airway epithelium.

blotting (49). NADPH oxidase enzymes can generate ROS and dual oxidase (DUOX) 1 and 2. The subtypes of NADPH oxidase enzymes play an important role in the production of ROS in airway inflammation (51). Knockdown of DUOX 2 gene using short hairpin RNA showed (shDUOX2) decreased ROS production in HNE cells but no changes were reported in knockdown of DUOX 1 gene. The shDUOX2-transfected HNE cells also showed a reduction in HMGB1 secretion under hypoxic condition (49). Taken together, it is apparent that DUOX2 but not DUOX1 is essential in hypoxia-induced HMGB1 secretion and DUOX2 can lead to ROS-mediated activation of TLR2 and TLR4 in the upper airway epithelium (51).

The nasal secretions of chronic rhinosinusitis patients may contain mast cell tryptase, neutrophil elastase, eosinophil cationic protein, nitric oxide metabolites, IL-1, IL-5, or IL-8 suggesting that these molecules are involved in the development of chronic inflammation in the upper airway (52-55). HMGB1 binds to several specific cell surface receptors, such as the RAGE, TLR, and act as a cytokine-like protein inducing chemotaxis and cytokine release. We determined HMGB1, TNF-α, IL-1β, and IL-8 in the nasal secretions of chronic rhinosinusitis patients and performed correlation analysis with the Lund-Mackay score, which is a scoring system indicating the severity of sinonasal symptoms. TNF-α was detected in only 21% and IL-1β was detected in 44% of patients with no correlation with symptom severity (46). However, both HMGB1 and IL-8 were detected in all nasal lavage samples from patients and significant correlation was observed with the severity of Lund-Mackay score. Interestingly, the level of HMGB1 was significantly correlated with the level of IL-8 (46). Therefore, we investigated IL-8 in HNE cells under hypoxia and found that IL-8 secretion was increased by hypoxia and suppressed by NAC pretreatment. This finding implies that IL-8 secretion can be dependent on ROS signaling pathway. Furthermore, the treatment of HMGB1 using mammalian recombinant HMGB1 (rHMGB1) induced IL-8 secretion in apical culture supernatants. During the course of employment of anti-HMGB1 blocking antibody to inhibit the function of the secreted HMGB1 protein, IL-8 production was abrogated (49). This observation is very interesting because HMGB1 may be associated with specific cytokines such as IL-6, IL-8, and IL-33 in the nasal epithelium (56, 57). HMGB1 also induces the release of IL-1α, IL-1β, IL-6, IL-8, and TNF-α in macrophages and TNF-α, IL-1β, and IL-8 in neutrophils (58). In endothelial cells, HMGB1 can increase the production of tissue factor, an initial protein involved in the coagulation cascade and regulation of fibrinolysis (59, 60).

CONCLUSION

Analysis of the results of previously reported studies indicated that hypoxia plays an important role in the pathogenesis of upper airway inflammation, especially in the chronic rhinosinusitis (Fig. 1). HIF-1α is an essential factor for oxygen homeostasis in the epithelium and mediates MUC5AC overproduction. HIF-1α mediated VEGF overexpression and alteration of junctional proteins such as ZO-1 and E-cadherin are also important aspects leading to the disruption of the epithelial barrier under hypoxic condition. Furthermore, hypoxia induces HMGB1 translocation into the cytoplasm and release of IL-8 through a ROS-dependent mechanism in the airway epithelium. It is hypothesized that the investigation of hypoxia-related pathophysiology in airway epithelium will suggest a novel therapeutic target for upper airway inflammatory diseases.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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