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■ REVIEW ■

The Role of Cytokines in Rhinosinusitis

Since the last decade, new insights into inflammatory processes have become possible by investigating the pattern of cytokines in acute and chronic sinus diseases. This review aims to update and discuss the findings of in vitro and in vivo studies concerning the role of cytokines in sinusitis and nasal polyposis. The proinflammatory cytokines interleukin-1β, interleukin-6 and the neutrophil-chemoattractant interleukin-8 may play a major role in acute sinusitis, as shown in viral and allergic rhinitis. In chronic sinusitis interleukin-3 dominates the cytokine profiles, giving support to a variety of inflammatory cells. Interleukin-5 is a key protein in the pathogenesis of nasal polyposis. Activation and survival of eosinophils in nasal polyps are thought to be regulated by interleukin-5. Further investigation of cytokine expression patterns in inflammatory sinus diseases will lead to a better understanding of their pathogenesis and to a development of new therapeutic modality.

Key Words: *Sinusitis; Nasal Polyps; IL-1β; IL-3; IL-5; IL-6; IL-8; Cytokines*

Yang-Gi Min, Kang Soo Lee*

Department of Otorhinolaryngology, Seoul National University College of Medicine, Seoul; Department of Otorhinolaryngology*, Hallym University College of Medicine, Sacred Heart Hospital, Anyang, Korea

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Address for correspondence
Yang-Gi Min, M.D.
Department of Otorhinolaryngology, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea
Tel: +82.2-760-2446, Fax: +82.2-744-9945
E-mail: ygmin@plaza.snu.ac.kr

INTRODUCTION

Rhinosinusitis is a common disease characterized by recurrent or persistent inflammation of the nasal and the paranasal sinus mucosa. It is a typical histologic finding in rhinosinusitis that neutrophils dominate the mucosa. Nasal polyposis is understood as a multifactorial disease and is closely linked to the inflammatory response of rhinosinusitis. Recent literature provides evidence to support the importance of cytokines for orchestrating inflammatory response in rhinosinusitis and nasal polyposis. However, the role of cytokines in the development of rhinosinusitis and nasal polyposis is not well understood. Furthermore, results from the previous studies still remain controversial due to the insufficient characterization of patients, lack of a valid classification of sinus disease, and use of different techniques for investigation (1). The authors' objective is to review the results of previous in vivo and in vitro studies concerning the expression of cytokines in acute and chronic sinusitis with or without nasal polyposis and discuss the role of cytokines.

ACUTE SINUSITIS

Acute sinusitis can be defined as an inflammation of paranasal sinus mucosa less than 3 weeks in duration. There is an evidence that in acute bacterial and viral sinusitis, proinflammatory cytokines play a dominant role in initiating and maintaining the inflammation, which is characterized by neutrophil tissue infiltration (2). All proinflammatory cytokines, interleukin-1β, interleukin-6 and interleukin-8, were elevated in the acute sinusitis mucosa compared to control turbinates, with the rise in interleukin-8, a neutrophil chemoattractant, being statistically significant. None of interleukin-3, interleukin-4, interleukin-13, and interferon (IFN)-γ was upregulated, and granulocyte/macrophage colony-stimulating factor (GM-CSF) and interleukin-5 were not measurable in any of the samples (1, 2). According to these results, the inflammatory cytokines such as interleukin-1β, interleukin-6, and interleukin-8 may play an important role in acute sinusitis. In acute sinusitis, the increased synthesis of interleukin-8 may relate to the prominent tissue neutrophilia seen in the mucosa. It has been suggested that an early release of proinflammatory cytokines may induce such increased synthesis of interleukin-8 (1). These data clearly characterize acute sinusitis as non-specific inflammatory reactions which naturally limit themselves to a few days. However, in the subjects with predisposing hereditary or anatomic factors, these diseases may act as an initial signal for the development of chronic inflammation or as a trigger for chronic immunologic alteration within the mucosa.

CHRONIC SINUSITIS

Chronic sinusitis can be defined as an inflammation of paranasal sinus mucosa present for greater than 12 weeks, although an arbitrary temporal definition has little real value. In the sinus fluid of patients with chronic

sinusitis, main inflammatory cells are neutrophils with only few eosinophils, mast cells, and basophils (3). So far investigations of cytokines have focused on neutrophils in chronic sinusitis. Interleukin-1β mRNA was detected in some extravascular polymorphonuclear cells (PMNs) and in mononuclear lymphocytes in chronic maxillary sinusitis mucosa, with upregulated intercellular adhesion molecule (ICAM)-1 and E-selectin on mucosal microvascular endothelial cells (4). These results suggest that interleukin-1β produced by PMNs induce the expression of ICAM-1 and E-selectin and stimulates the infiltration of PMN in chronic sinusitis. However, in another study only a small proportion of tissue from patients with chronic sinusitis showed the presence of interleukin-1β, ICAM-1, and E-selectin by immunohistochemistry (5).

Although the levels of proinflammatory cytokines are low in chronic sinusitis, interleukin-3 seems to play a dominant role (2). Interleukin-3, which is possibly produced by activated T cells, mast cells and eosinophils in the sinus mucosa, displays multi-colony-stimulating factor (CSF) activities and stimulates the differentiation and activation of macrophages, neutrophils, mast cells, eosinophils, and other cells. Thus, interleukin-3 might be involved in local defense and repair of chronically inflamed sinus mucosa by supporting various cell populations and inducing the release of various mediators. However, the cytokine may also indirectly contribute to fibrosis and constant thickening of the mucosa leading to an obstrtuction of the ostiomeatal complex (2, 6).

We investigated by RT-PCR and Southern blot the expression of various cytokine mRNAs including interleukin-6, interleukin-8, tumor growth factor (TGF)-β, interleukin-4, interleukin-5, and IFN-γ in maxillary sinus mucosa of patients with chronic sinusitis. Interleukin-6, interleukin-8, TGF-β, interleukin-4, interleukin-5, and IFN-γ mRNAs were expressed more frequently in chronic maxillary sinusitis mucosa than they were in normal turbinate mucosa (Table 1) (7). We concluded that these cytokines may be responsible for recruitment of inflammatory cells and for mucosal thickening in chronic sinusitis, and thus for chronicity of the disease. Rhyoo et al. (8) confirmed our results by demonstrating the upregulation of interleukin-8 gene expression in chronic rhinosinusitis. Interleukin-3 is found to be significantly increased in sinus mucosa; however, another study suggested that interleukin-8 play a major role in neutrophil recruitment (9). Different criteria of definition and techniques of investigation may account for this discrepancy.

Table 1. Gene expression of various cytokines in chronic sinusitis and nasal polypopsis

Cytokine	Chronic sinusitis	Nasal polyposis
Interleukin-1β	ND	No difference
TGF-β	Increased	Increased*
Interleukin-4	Increased	Increased
Interleukin-5	Increased	Increased
Interleukin-6	Increased	Increased
Interleukin-8	Increased	Increased
IFN-γ	Increased	Increased

Increased, frequently expressed and relatively higher mean density ratio of positive band compared to control; No difference, no difference between chronic sinusitis mucosa or nasal polyp tissue and normal turbinate mucosa; ND, not determined; *, frequently expressed but no differences in mean density ratio of positive band compared to control

Interleukin-6 is a proinflammatory TH2-type cytokine that stimulates fibroblast proliferation and collagen synthesis in various inflammatory response. Ghaffar et al. (11) examined the interleukin-6 mRNA and immunoreactivity in the sinus epithelial and subepithelial cells of patients with allergy-associated and allergy-unassociated chronic sinusitis by in situ hybridization and immunohistochemistry. In this study, however, there was no difference in interleukin-6 expression between the two groups. Interleukin-12 is a TH1-associated cytokine produced by macrophages/monocytes, which may play a suppressive role in the development of allergic sinonasal responses. Interleukin-12 mRNA and interleukin-12 receptor expression were found to decrease in allergy-associated and allergy-unassociated chronic sinusitis when compared with control (12). This result suggested that interleukin-12 may play a role in the in vivo suppression of the allergic inflammatory response and that the suppressive role may be exerted via the interleukin-12 receptor.

Several recent reports have demonstrated differential activation of distinct cytokine pathways in patients with allergy-associated and allergy-unassociated chronic sinusitis. Hamilos et al. (13) have showed that the most distinguishing cytokines are interleukin-4 and interleukin-5 in allergic subgroup and IFN-γ in nonallergic group. Kotsimbos et al. (14) and Wright et al. (12) have also demonstrated that the upregulation of αinterleukin-5 receptor expression is predominantly associated with allergy-associated chronic sinusitis, whereas the upregulated αGM-CSF receptor expression is predominantly associated with allergy-unassociated chronic sinusitis.

Few studies have reported the roles of cytokines in regulating mucosal remodeling in ostiomeatal unit, the key area of sinus ventilation and drainage (1). Further studies regarding such regulation seems to be crucial to clarify the pathophysiology of chronic sinusitis.

NASAL POLYPOSIS

Although nasal polyposis is believed to be a multifactorial disease, the pathogenesis of this disease is poorly defined. In order to understand this disease, large accu-

mulation of eosinophils in nasal polyps must first be explained, for which three different ways are possible: 1) by increased tissue infiltration of eosinophils, 2) by prolonged survival of these cells, and 3) most likely by a combination of both. Another key question concerns the precise mechanism by which eosinophils contribute to tissue damage, inflammation, and polyp formation (1). To answer these questions, various techniques, such as in situ hybridization, immunohistochemistry, measurement of protein, and biofunctional models have been used in biopsies taken from the diseased tissues. In this section, a survey of the literature is given, together with some of our results. Several recent studies have shown that GM-CSF, interleukin-3, tumor necrosis factor (TNF)-α, macrophage inflammatory protein (MIP)-1α, interleukin-1, and TGF-β mRNA are expressed in nasal polyps. We have demonstrated that interleukin-6, interleukin-8, TGF-β, interleukin-4, interleukin-5 and IFN-γ mRNAs were expressed more frequently in polyp specimens than in normal turbinate mucosa, and all of the polyp specimens revealed a relatively higher mean density ratios for the cytokines than normal turbinate mucosa, except TGF-β (Table 1) (15). Liu et al. (16) and Hamaguchi et al. (17) quantified interleukin-1β and interleukin-1α in nasal polyps and suggested their significance in the pathogenesis. We have recently demonstrated that interleukin-1β was expressed even in normal turbinate tissue as well as in nasal polyp tissue (15). This result poses an interesting question regarding the role of interleukin-1β in normal nasal mucosa in addition to its role in nasal polyposis. Eosinophils were also suggested as the major source of TNF-α and -β1 in nasal polyps, contributing to structural abnormalities such as stromal fibrosis and basement membrane thickening (18). There are at least three functions of TGF-β in nasal polyps including induction of collagen deposition, stimulation of fibroblast proliferation, and inhibition of T cell proliferation (19). TNF-α is known to increase transendothelial migration of eosinophils through the induction of ICAM-1, VCAM-1, and E-selectin (20). TNF-α also stimulates the production of oxygen metabolites that result in toxic cell injury (21). Ohno et al. (22) have detected proteins of GM-CSF in the supernatant of cultured nasal polyp tissue and GM-CSF mRNA in nasal polyp specimens. It has been suggested that polyp tissue expresses more GM-CSF mRNA than turbinate nasal mucosa, and that there is a correlation of the number of activated EG2+ eosinophil and interleukin-3 mRNA with the amount of GM-CSF mRNA-positive cells (23).

Hamilos et al. (24) have recently proposed distinct mechanisms of eosinophilia in nasal polyposis patients with and without allergy. They concluded that the production of TH2-type cytokines, including GM-CSF, interleukin-3, interleukin-4, and interleukin-5, by infiltrating T cells contributes to the allergic mechanism of eosinophilia, whereas the nonallergic mechanism involves GM-CSF, interleukin-3, and IFN-γ. In our study, however, mRNAs of interleukin-4 and interleukin-5, TH2-type cytokines known to be important in the pathogenesis of allergy, were expressed in the nasal polyps from allergy-unassociated subjects, as well as in those from allergic subjects (15, 25). Our results suggest that allergic mechanisms may not play important roles in the pathogenesis of nasal polyp. Furthermore, the results of our study are compatible with those of several other studies (26, 27), suggesting that allergy may not be the cause of nasal polyps.

Eosinophil migration in nasal polyposis

Several studies have demonstrated the importance of cytokines and chemokines in mediating the migration of inflammatory cell in vitro. interleukin-1, interleukin-4, interleukin-5, interleukin-8, RANTES, and eotaxin have been shown to deliver signals that support or cause the selective influx of eosinophils (1). The proinflammatory cytokines interleukin-1β and TNF-α increase transendothelial migration of eosinophils, which is not specific for eosinophils. Interleukin-8 is known to be a chemoattractant for neutrophils, but may also be chemotactic for eosinophils under certain circumstances (28). RANTES induces chemotaxis and transendothelial migration of eosinophil, production of reactive oxygen species, and release of eosinophil cationic protein (ECP) in vitro (29). RANTES immunoreactivity has been reported in nasal polyp homogenates and biopsy specimens, and it has a chemotactic property for eosinophils (30). Our recent in vivo study has shown that the expression of interleukin-5 and RANTES increases in allergic and nonallergic nasal polyp tissue compared with control, and that it is correlated with eosinophil infiltration (31). Nasal epithelial cells are a major source of RANTES, which localizes eosinophils in the tissue. However, Bachert et al. (1) reported that the protein levels of RANTES does not differ between nasal polyps and control tissue, bringing into question the importance of RANTES as a major agent for recruiting eosinophils in nasal polyps. RANTES may be involved in the localization of eosinophils within the area of the polyp or act over a short distance in key areas. Besides RANTES, eotaxin is known to be a selective chemoattractant in vitro which induces eosinophil migration in vivo (32). It may have a role in attracting eosinophils to the site of inflammation and may also contribute to tissue damage by its capacity of inducing the release of reactive oxygen species.

Jahnsen et al. (33) have demonstrated that selective induction of interleukin-4 plays an important role for the preferential recruitment of eosinophils in cultured human

nasal polyp tissue. It has recently been shown that 80% of interleukin-4-positive cells in nasal polyps may represent eosinophil (34). Interleukin-13, interleukin-1 and TNF-α in addition to interleukin-4 can induce the expression of VCAM-1 in vivo and in vitro. Hamilos et al. (35) confirmed the results of Jahnsen's study by reporting the upregulation of VCAM-1 in polyp tissues from both allergic and non-allergic patients. We have also shown that interleukin-4 mRNAs were expressed in all nasal polyp tissues (15, 25). However, Bachert et al. (36) reported that interleukin-4 protein is not detectable in nasal polyp tissue.

Eosinophil survival and the role of interleukin-5

Cytokines such as interleukin-3, interleukin-5, GM-CSF, and IFN-γ have been known to increase the survival of eosinophils by inhibiting the programmed cell death (apoptosis) both in vitro and in vivo (37). Evidence of apoptosis was obtained at days 8-12 of tissue culture in nasal polyp samples, at days 2-3 in control mucosa, and within 24 hr in purified blood eosinophils (38). From these findings, the authors concluded that apoptosis of eosinophils is delayed in nasal polyps compared to that of nasal mucosa or of blood eosinophils. Neutralizing monoclonal antibody (mAb) to interleukin-5 induces eosinophil apoptosis and decreases tissue eosinophilia. Immunohistochemical analysis demonstrated that interleukin-5 is localized in mast cells, lymphocytes, and eosinophils in polyp tissue (39). Eosinophils may be a major source of interleukin-5 in human nasal polyps. Thus, eosinophils may create an autocrine loop for their activation and survival within the tissue (1). At the early stage of nasal polyposis, T cells are the major source of interleukin-5, but with the aging of nasal polyps, the eosinophils may be involved in interleukin-5 synthesis. It has been reported that TGF-β induces the apoptosis of eosinophils (40).

The precise mechanism by which eosinophils cause tissue damage and polyp formation remains to be elucidated. Mediators from these cells are extracellularly deposited in polyps and are raised in body fluids. Eosinophils could contribute to tissue damage and inflammation via various mediators including cytotoxic granule proteins, superoxides, leukotrienes and cytokines (41).

CONCLUSION

In acute sinusitis, proinflammatory cytokines play a dominant role to orchestrate mucosal defense and to limit infection as in viral rhinitis. In chronic sinusitis, interleukin-8, as a neutrophil chemoattractant, and interleukin-3, with multi-CSF activities, are the prominent cytokines. They may be involved in the regulation of local defense and repair, but may also lead to mucosal thickening and obstruction of ostiomeatal complex. Tissue eosinophilia, a typical histologic feature in most nasal polyps, may be explained by increased migration of eosinophils, by prolonged eosinophil survival, or by combination of both. interleukin-5 is the most important cytokine responsible for tissue eosinophilia of nasal polyps, enhancing the activation and survival of eosinophils. Furthermore, eosinophils may be the major source of interleukin-5 in the late stage of the disease, thus creating an autocrine loop for their activation and survival. Further investigation on the role of cytokines in rhinosinusitis and nasal polyps will enlarge the current knowledge about their pathophysiology and will provide new therapeutic modalities.

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