THE ROLES OF INFLAMMATORY CYTOKINES IN RHINOSINUSITIS

Yang-Gi Min, M.D., Jeong-Whun Kim, M.D.

Department of Otorhinolaryngology, Seoul National University College of Medicine, Seoul, Korea

ABSTRACT

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 (IL)-1 β , IL-6 and the neutrophil-chemoattractant IL-8 may play a major role in acute sinusitis, as shown in viral and allergic rhinitis. In chronic sinusitis IL-3 dominates the cytokine profiles, giving support to a variety of inflammatory cells. IL-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 IL-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 polyposis, IL-1 β , IL-3, IL-5, IL-6, IL-8, cytokine

INTRODUCTION

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. 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 with-

out nasal polyposis and discuss the role of cytokines.

ACUTE SINUSITIS

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. All proinflammatory cytokines, IL-1 β , IL-6 and IL-8, were elevated in the acute sinusitis mucosa compared to control turbinates, with the rise in IL-8, a neutrophil chemoattractant, being statistically significant. None of IL-3, IL-4, IL-13, and IFN- γ was upregulated, GM-CSF and IL-5 were not measurable in any of the samples^{1,2)}. According to these results, IL-1 β , IL-6, and IL-8 may play an important role in acute sinusitis. In acute sinusitis, the increased synthesis of IL-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 IL-8¹⁾. 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

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. IL-1 β mRNA was detected in some extravascular polymorphonuclear cells (PMNs) and in mononuclear lymphocytes in chronic maxillary sinusitis mucosa, with upregulated ICAM-1 and E-selectin on mucosal microvascular endothelial cells⁴⁾. These results suggest that IL-1 β produced by PMNs induces 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 IL-1 β , ICAM-1, and E-selectin by immunohistochemistry⁵⁾.

Although the levels of proinflammatory cytokines are low in chronic sinusitis, IL-3 seems to play a dominant role²⁾. IL-3, which is possibly produced by activated T cells, mast cells and eosinophils in the sinus mucosa stimulates the differentiation and activation of macrophages, neutrophils, mast cells and eosinophils. Thus, IL-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 obstruction of the ostiomeatal complex^{2,6)}.

We investigated by RT-PCR and Southern blot the expression of various cytokine mRNAs including IL-6, IL-8, TGF- β , IL-4, IL-5, and IFN- γ in maxillary sinus mucosa of patients with chronic sinusitis. All of the cytokines were expressed more frequently in

chronic maxillary sinusitis mucosa than they were in normal turbinate mucosa⁷⁾. We concluded that these cytokines may be responsible for recruitment of inflammatory cells and for mucosal thickening in chronic sinusitis. IL-3 is found to be significantly increased in sinus mucosa; however, another study suggested that IL-8 play a major role in neutrophil recruitment⁸⁾. Different criteria of definition and techniques of investigation may account for this discrepancy. IL-6 is a proinflammatory Th2-type cytokine that stimulates fibroblast proliferation and collagen synthesis in various inflammatory response. Ghaffar *et al.*⁹⁾, however, showed that there was no difference in IL-6 expression between the patients with allergy-associated and allergy-unassociated chronic sinusitis. In this study, however, IL-12 is a Th1-associated cytokine produced by macrophages/monocytes, which may play a suppressive role in the development of allergic sinonasal responses. IL-12 mRNA and IL-12 receptor expression were found to decrease in allergy-associated and allergy-unassociated chronic sinusitis when compared with control¹⁰⁾.

Several recent reports have demonstrated differential activation of distinct cytokine pathways in patients with allergy-associated and allergy-unassociated chronic sinusitis. Hamilos *et al.*¹¹⁾ have showed that the most distinguishing cytokines are IL-4 and IL-5 in allergic subgroup and IFN- γ in nonallergic group. Wright *et al.*¹⁰⁾ have also demonstrated that the upregulation of α IL-5 receptor expression is predominantly associated with ACS, whereas the upregulated α GM-CSF receptor expression is predominantly associated with NCS. Few studies have reported the roles of cytokines in regulating mucosal remodeling in ostiomeatal unit, the key area of sinus ventilation and drainage¹⁾. Further studies regarding such regulation seems to be crucial to clarify the pathophysiology of chronic sinusitis.

NASAL POLYPOSIS

In order to understand this disease, large accumulation 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 formation¹¹. 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. Several recent studies have shown that GM-CSF, IL-3, TNF- α , macrophage inflammatory protein (MIP)-1 α , IL-1, and TGF- β mRNA are expressed in nasal polyps. We have demonstrated that IL-6, IL-8, TGF- β , IL-4, IL-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 ¹⁵. Liu *et al.*¹³ quantified IL-1 β and IL-1 α in nasal polyps and suggested their significance in the pathogenesis. We have recently demonstrated that IL-1 β was expressed even in normal turbinate tissue as well as in nasal polyp tissue¹². This result poses an interesting question regarding the role of IL-1 β in normal nasal mucosa in addition to its role in nasal polyposis. Eosinophils were also suggested as the major source of TNF- α and - β 1 in nasal polyps, contributing to structural abnormalities such as stromal fibrosis and basement membrane thickening¹⁴. 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 proliferation¹⁵. TNF- α is known to increase transendothelial migration of eosinophils through the induction of ICAM-1, VCAM-1, and E-selectin¹⁶. TNF- α also stimulates the production of oxygen metabolites that result in toxic cell injury¹⁷. Ohno *et al.*¹⁸ 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 IL-3 mRNA with the amount of GM-CSF mRNA-positive cells¹⁹. In this study IL-5 mRNA was found only in low quantities, whereas IL-5 protein was detected at high

concentrations in nasal polyp samples when compared to other sinus diseases and normal controls in Bachert's report²⁰.

Hamilos *et al.*²¹ 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, IL-3, IL-4, and IL-5, by infiltrating T cells contributes to the allergic mechanism of eosinophilia, whereas the nonallergic mechanism involves GM-CSF, IL-3, and IFN- γ . However, mRNAs of IL-4 and IL-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 in our study^{12,22}. Our results suggest that allergic mechanisms may not play important roles in the pathogenesis of nasal polyp.

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, IL-8, as a neutrophil chemoattractant, and IL-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. IL-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 IL-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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Corresponding address :

Yang-Gi Min, M.D.

Department of Otorhinolaryngology

Seoul National University College of Medicine

28 Yongon-dong, Chongno-ku

Seoul 110-744 Korea

TEL : +82-2-760-2446

FAX : +82-2-745-9945

E-mail : ygmin@plaza.snu.ac.kr