Role of Eotaxin-3 in Chronic Rhinosinusitis with Nasal Polyps

ZhaoWei Gu, MD¹, MingZhu Jin, MD¹, and ZhiWei Cao, PhD¹

Abstract

Chronic rhinosinusitis with nasal polyps (CRSwNP) is connected to a chronic inflammatory process with the activation of different immune components. Eotaxin-3, acidic mammalian chitinase (AMCase), and interleukin (IL)–13 as focal immune factors have been detected in CRSwNP, but their importance and relationship are still being investigated. This study aims to detect the expression of AMCase, IL-13, and eotaxin-3 in the mRNA level and investigate their roles and relationships in CRSwNP. Twenty-four subjects with eosinophilic CRSwNP and 11 controls were included in the study. Tissues were obtained by endoscopic sinus surgery. Target genes were detected by real-time reverse transcription–polymerase chain reaction. AMCase, eotaxin-3, and IL-13 were detected in all CRSwNP and controls. The expression of AMCase, eotaxin-3, IL-13, and mRNA was significantly higher in patients with CRSwNP than in the control group. There was a significantly positive correlation not only between AMCase and eotaxin-3 but also between IL-13 and eotaxin-3 in CRSwNP. Increased AMCase, IL-13, and eotaxin-3 might lead to the Th2 inflammatory cascade reaction.

Keywords

eotaxin-3, acidic mammalian chitinase, IL-13, CRSwNP

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Materials and Methods

After obtaining approval from the China Medical University–affiliated Shengjing Hospital Institutional Review Board, 41 eosinophilic CRSwNP patients were included in the study. Of the 41 CRSwNP patients without asthma or an aspirin sensitivity, 13 noneosinophilic CRSwNP patients were excluded because they had a mean eosinophil number of less than 10 per high power field (HPF) in at least 5 fields, and 4 patients with nasal allergy were excluded to avoid experiment error. Disease extent was also evaluated by computed tomography (CT) images using the Lund-Mackay scoring system. Nasal polyps were obtained from the middle meatus at the beginning of endoscopic sinus surgery (ESS). The control tissues were obtained from the uncinate or ethmoid sinus in 11 patients with cerebrospinal fluid leak but without any evidence of sinus disease. The CRSwNP patients and the control patients did not receive steroids, nonsteroidal anti-inflammatory drugs, antihistamines, or macrolide antibiotics 4 weeks before the biopsy. mRNA of eotaxin-3, AMCase, and IL-13 was detected by real-time polymerase chain reaction (PCR) methods. Primer sequences are listed in Table 1.

Results

The mean Lund-Mackay score in eosinophilic CRSwNP was 16.5 points (range, 8–23 points). AMCase, eotaxin-3, and IL-13 mRNA were detected in all patients with nasal polyps and the control group. The expression ratio of AMCase mRNA was $118.89\pm29.72$ in the nasal polyps group and $2.20\pm0.39$ in the control group. The expression ratio of eotaxin-3 mRNA was 403077

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41.82 ± 14.61 and 1.11 ± 0.37, respectively. The expression ratio of IL-13 mRNA was 85.73 ± 41.58 and 6.04 ± 1.98, respectively. Using the Mann-Whitney test, the expression of AMCase, eotaxin-3, and IL-13 mRNA was significantly higher in the nasal polyps group than in the control group (P < .01) (Figure 1). There was a statistically significant positive correlation between the expression of AMCase and eotaxin-3 (R = .837, P < .01) and between IL-13 and eotaxin-3 (R = .692, P < .01) in the nasal polyps group. There was no correlation between IL-13 and AMCase (R = .383, P = .064) in the nasal polyps group, whereas there was no statistically significant positive correlation in the control group.

Discussion

AMCase produced by mammals acts as an innate immune effector to target potential chitin-containing pathogens and plays an important role in the pathogenesis of allergy and asthma. CRSwNP is characterized by chronic inflammation with eosinophilic infiltration, which is analogous to asthmatic inflammation. Our study found that IL-13 and AMCase mRNA were significantly higher in patients with CRSwNP than in controls, which is approximately concordant with previous studies.3,4 Overexpression of AMCase may be a signal for the activation of the Th2 inflammatory pathway in epithelial cells.

Recently, cytokine and chemokine research has rapidly expanded our understanding of inflammatory responses. Specific cytokines and chemokines appear to play critical roles in the pathogenesis of CRSwNP. Eotaxin-3 as a potent eosinophil chemoattractant may lead to eosinophil recruitment and activation. Several studies have showed overexpression of eotaxin-3 in protein levels in CRSwNP, which confirms the level of mRNA in our study. It is likely that the production of eotaxin-3 could provide a signal for the concentration and activation of eosinophils and T cells in Th2-driven inflammatory processes.

Administration of anti-AMCase sera in the aeroallergen challenge model caused a marked decrease in the expression of eotaxin and eotaxin-2 and dose-dependent decreases of tissue eosinophilia and lymphocyte accumulation in Th2 inflammation.2 Otherwise, enhanced expression of eotaxin-3 by IL-13 is likely operational through the transcription factor STAT6 in eosinophilic esophagitis.5 Inflammation reaction is a hallmark of these diseases. Our study found a statistically significant positive correlation not only between the expression of AMCase and eotaxin-3 but also between IL-13 and eotaxin-3.

From the above, we hypothesize that in CRSwNPs, AMCase produced by epithelial cells in the stimulation of chitin-contained pathogens may not only inactivate such pathogens directly but also may activate resident cells or inflammatory cells to produce eotaxin-3 and IL-13. IL-13 further enhances the production of AMCase and eotaxin-3, which can promote infiltration and activation of eosinophilia and lead to the Th2 inflammatory cascade reaction. Two pathways may enhance the expression of eotaxin-3: one from AMCase to eotaxin-3 and the other from IL-13 and eotaxin-3.

Otherwise, eotaxin-3 is a highly specific ligand for CC chemokine receptor-3 (CCR3), which is selectively expressed in eosinophils, basophils, and Th2 cells. There are already several studies researching the antagonists of CCR3 to attenuate the inflammatory reaction. The exact expression condition and the role of CCR3 antagonists in CRSwNP need further research.
Conclusion

Increased AMCase, IL-13, and eotaxin-3 may lead to a Th2 inflammatory cascade reaction and are important factors in the pathogenesis of CRSwNP. Further studies are needed to determine the potential roles of AMCase, IL-13, and eotaxin-3 as therapeutic targets in CRSwNP.

Author Contributions

ZhaoWei Gu, collection and analysis of the data; MingZhu Jin, collection and analysis of the data; ZhiWei Cao, design of the study.

Disclosures

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References