ORIGINAL RESEARCH

Role of CD23 Activated ERK Signaling Pathway in the Pathogenesis of Eosinophilic Chronic Sinusitis with Nasal Polyps

Ming Xu, MM; Zuyao Chen, MD; Qingshan Jiang, MM; Yongqian Gong, MM; Hongbo Tang, MM

ABSTRACT

Objective • In the context of the rising prevalence of eosinophilic chronic sinusitis accompanied by nasal polyps, this study aims toinvestigate the role of CD23 in the pathogenesis of eosinophilic chronic sinusitis with nasal polyps.

Methods • The cross-sectional study was conducted, 75 patients with chronic sinusitis and nasal polyps treated in our hospital from January 2019 to May 2021 were selected, including 40 cases of eosinophilic patients with the average age of 29.92 years and 35 cases of non-eosinophilic patients with the average age of 30.05 years and 30 patients with the average age of 30.14 years who underwent skull base benign tumor resection in our hospital were selected as the control group, the expression of CD23 in polyp tissue was detected by immunohistochemistry, and the expression of CD23, p-ERK and CCL20 in polyp tissue were detected by Western blot. Specifically, tissue samples were processed and subjected to staining using specific antibodies targeting CD23. The stained sections were then visualized under a microscope to determine the expression levels of CD23. CD23, p-ERK, and CCL20 expressions in polyp tissue were evaluated via Western blot. Total protein was extracted, separated on a gel, transferred to a membrane, and probed with specific antibodies. Chemiluminescence allowed visualization and quantification of protein expressions.

Results • Immunohistochemistry showed that CD23 expression was high in the eosinophilic group but low in the non-eosinophilic and control groups. The relative expression levels of CD23 protein, p-ERK protein, and CCL20 protein in polyp tissue s of the eosinophilic group were (0.892 ± 0.092), (0.733 ± 0.101) and (0.813 ± 0.106), respectively, which were significantly higher than those in non-eosinophilic group and control group ($P < .05$). The relative expression levels of CD23 protein, p-ERK protein, and CCL20 protein in the non-eosinophilic group were (0.461 ± 0.087), 0.412 ± 0.096) and (0.424 ± 0.098), which were significantly higher than those in the control group ($P < .05$). The relative expression level of CD23 protein in the eosinophilic group was positively correlated with the relative expression levels of p-ERK protein and CCL20 protein ($P < .05$). The Lund-Kennedy score in the eosinophilic group was (6.10 ± 1.01), which was significantly higher than that in the non-eosinophilic group ($P < .05$). The relative expression level of CD23 protein in the eosinophilic group was positively correlated with Lund-Kennedy score ($P < .05$).

Conclusion • Eosinophilic chronic sinusitis with nasal polyp mucosal tissue CD23 expression is up-regulated, which is positively correlated with the ERK signaling pathway and disease severity. This study provides valuable insights into potential therapeutic targets that could be explored to develop future treatment modalities. The potential clinical significance of the study is to reveal the important role of CD23 in the pathogenesis of chronic sinusitis with nasal polyps. The upward adjustment of CD23 is positively related to the severity of the disease, which provides valuable guidance for future treatment strategies. This discovery may provide new ways for the development of CD23 treatment methods, so as to better control the progress of the disease of eosinophilic chronic sinusitis with nasal polyps. Further research can explore the molecular mechanism of CD23 regulation, further verify the feasibility of CD23 as the treatment target, and evaluate the potential value of CD23 as a prognostic logo. (*Altern Ther Health Med.* 2023;29(8):638-643).

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INTRODUCTION

Chronic sinusitis with nasal polyps is a chronic inflammatory disease classified into eosinophilic chronic sinusitis with nasal polyps and non-eosinophilic chronic sinusitis with nasal polyps according to eosinophilic infiltration.[1] Chronic sinusitis with nasal polyps is a common chronic upper respiratory disease in the world, especially more common in Asia and North America. It will significantly affect the quality of life of patients, cause symptoms such as breathing discomfort and loss of smell, and may lead to the recurrence of sinusitis and the increase in upper respiratory tract infections. This is of great significance for the formulation

of prevention and treatment strategies and improving the quality of life of patients. Eosinophilic chronic sinusitis with nasal polyps has a high recurrence rate and is difficult to treat.[2] The increase of eosinophilic levels is closely related to type 2 immunity and inflammatory response and may result in IgE-mediated specific allergic reactions locally. Epidemiological studies have revealed that chronic sinusitis with nasal polyps is a prevalent chronic inflammatory disorder affecting a substantial portion of the population. The condition's prevalence rates exhibit regional and demographic variations, with an estimated global prevalence of approximately 2-4%. While the exact cause of chronic sinusitis with nasal polyps remains multifactorial and complex, it has been observed that environmental factors, genetic predisposition, and immune responses contribute to its development. Patients with eosinophilic chronic sinusitis have higher levels of IgE.[3,4] CD23 is a low-affinity receptor for IgE that is expressed on human nasal mucosal epithelial cells, and is involved in the bidirectional transport of IgE and the unidirectional transport of IgE immune complexes. CD23 is involved in developing allergic rhinitis and promotes the recruitment and chemotaxis of eosinophils, leading to local inflammation in nasal polyps.[5] It is unclear Whether CD23 is also present in eosinophilic chronic sinusitis with nasal polyps and its mechanism of action, and further exploration is needed. The combination of CD23 and IgE enhances the symptoms of inflammatory response and allergies, and also participates in regulating the functions of eosinophilic granulocytes and alkaline particle cells. To understand the function of CD23 in -depth, it helps to understand the mechanism of immunity and inflammatory diseases. Although studies have shown that CD23 is involved in allergic rhinitis and inflammation, its existence and role in eosinophilic chronic sinusitis with nose polyps is still unclear. Therefore, this study aims to explore the functions and significance of CD23 in allergic rhinitis and inflammation, as well as the correlation with the reaction of immune response regulation and IGE media, thereby providing new in the development of the treatment of immune and inflammatory diseases Opinions. Through a detailed analysis of the expression and action mechanism of CD23, we hope that we can deeply understand its importance in the development of the disease and provide theoretical and experimental basis for the development of potential drug targets and treatment strategies.

MATERIALS AND METHODS

General information

A total of 75 patients with chronic rhinosinusitis with nasal polyps treated at our hospital from January 2019 to May 2021 were selected, including 40 patients with eosinophilic inflammation (eosinophil count ≥ 70 / high-power field) and 35 patients with non-eosinophilic inflammation (eosinophil count < 70 / high-power field). The theoretical basis of inclusion and exclusion criteria was mainly based on the scientific validity, reliability, and relevance of the purpose of the study. Inclusion criteria were as follows: (1) diagnosis in accordance with the standards of the "Chinese Guidelines for the Diagnosis and Treatment of Chronic Rhinosinusitis (2018)";[6] (2) age >18 years; (3) informed consent obtained from patients and their families. Exclusion criteria were: (1) use of corticosteroids within the past month; (2) concomitant with infectious, allergic, immune system diseases, or other serious illnesses. Additionally, 30 patients who underwent benign tumor resection surgery in the skull base at our hospital were selected as the control group. The clinical general information of the study group and control group is shown in Table 1, and the two groups were comparable. The hospital's ethics committee approved this study.

Specimen collection and preparation

Nasal polyp tissues and inferior turbinate polyp tissues were collected during surgery, rinsed, and trimmed to an appropriate size and thickness. The specimens were fixed with 4% neutral buffered formalin for 24 hours, dehydrated in a gradient alcohol series for 2 hours, and then treated with xylene for 1 hour. The specimens were embedded in paraffin, adjusted to a thickness of 4mm, and sliced. The slices were fixed in a 75°C oven for 1 hour and then subjected to subsequent immunofluorescence staining.

Immunohistochemical detection of CD23 expression

Tissue slices were baked at 60°C for 3 hours, routinely dewaxed, treated with 3% H2O2 for 10 minutes at room temperature, and then incubated with PBS for 3 washes, each for 3 minutes. The slices were treated with citrate solution for antigen retrieval, followed by 3 washes with PBS for 3 minutes each. The slices were incubated overnight with the primary antibody, washed 3 times with PBS for 3 minutes each time, and then incubated with a polymer enhancer at room temperature for 20 minutes. The slices were washed 3 times with PBS for 3 minutes each, then incubated with biotinylated goat anti-human IgG at room temperature for 30 minutes. The slices were washed 3 times with PBS for 3 minutes each, then incubated with SABC reagent at room temperature for 30 minutes. DAB staining was performed, followed by counterstaining with hematoxylin, xylene dehydration, and neutral gum mounting. The slices were observed and recorded under a microscope. The SABC immunohistochemistry kit was purchased from Beijing Zhongshan Biotechnology Co., Ltd.

Western blot Detection

Extract total protein by lysing the tissue: Remove it from the -80°C freezer and place it on ice. Use sterilized ophthalmic scissors to separate the tissue. Add 50 μl of lysis buffer to an EP tube, cut the tissue with ophthalmic scissors, and add 150-250 μl of lysis buffer. Use a sterile stirring rod to grind the tissue until it is homogenized and free of clumps. Crush the tissue with an ultrasound probe on ice for approximately 15-20 seconds each time to avoid generating bubbles. Place

the EP tube in a high-speed centrifuge at room temperature and centrifuge at 12,000 rpm. Use a pipette to extract the supernatant and place it in a new EP tube to obtain the protein, which is then stored in a -80°C freezer for later use.

Separate the protein by SDS-PAGE electrophoresis, transfer it onto a PVDF membrane, wash it with TBST, and block it with 5% skim milk powder at room temperature for 1 hour. Add rabbit anti-human primary antibody working solution (against CD23 protein, p-ERK protein, and CCL20 protein) and incubate overnight at 4°C. Add horseradish peroxidase-labeled goat anti-rabbit secondary antibody working solution and incubate at 37°C for 1 hour. Wash with TBST and develop.

Western blot results were calculated based on quantitative signal intensity analysis. First, immune signals are generated on Western blotting membranes by fluorescein or enzyme substrates, and images are acquired using tools such as a molecular imager. Then, band-like stripes of the target protein, called "bands," were selected from the image, and the signal intensity of the bands was measured using image analysis software. To ensure comparability of results, the signal of an internal standard protein band was also measured as a standard. The relative expression level of the target protein was obtained by dividing the signal intensity of the target protein band by the signal intensity of the internal standard protein band, and this relative expression level is presented as a number. The principle of signal strength calculation is the relationship between the signal strength of the target protein in the image and the relative abundance of its sample. Generally speaking, the higher the signal strength, the higher the level of the target protein in the sample. By comparing the signal intensity of the target protein in different samples, the difference in the relatively expression level can be evaluated. This calculation method is of great significance for studying protein expression regulation, disease diagnosis and drug development.

Disease Severity Assessment[7]

Lund-Kennedy Nasal endoscopy is used to evaluate the severity of the disease, including the following components:

Bilateral nasal polyps (0-4 points): The score is divided into 0-4 points. According to the degree of nasal polyps in the nasal cavity, the higher the score indicates the more serious the nasal polyps.

Spew edema (0-4 points): The score is divided into 0-4 points. According to the degree of edema in the nasal mucosa, the higher the score indicates the more serious the mucosal edema.

Drist (0-4 points): The score is divided into 0-4 points. According to the amount and texture of the nasal endocrine, the higher the score, the more serious the secretion is.

Crus (0-4 points): The score is divided into 0-4 points. According to the number and texture of scabs in the nasal cavity, the higher the score, the more serious the scabs are.

Scar (0-4 points): The score is divided into 0-4 points. According to the degree of scars in the nasal cavity, the higher the score indicates the more serious the scar.

Table 1. Comparison of clinical general data among groups

Group	n	Male/Female	Age (year)	BMI (kg/m²)
Eosinophilic group	40	22/18	29.92 ± 8.33	22.43 ± 2.05
Non-eosinophilic group	35	20/15	30.05 ± 7.90	22.25 ± 2.10
Control group	30	20/10	30.14 ± 8.42	22.15 ± 1.92
F/χ^2		1.044	1.011	0.821
P value		.593	.652	.711

Table 2. Expression of CD23 protein in nasal polyps tissues among different groups

Group	n	CD23 protein relative expression	p-ERK protein relative expression	CCL20 protein relative expression
Eosinophilic group	40	0.892 ± 0.092	0.733 ± 0.101	0.813 ± 0.106
Non-eosinophilic group	35	0.461 ± 0.087[a]	0.412 ± 0.096[a]	0.424 ± 0.098[a]
Control group	30	0.143 ± 0.054[a,b]	0.112 ± 0.068[a,b]	0.109 ± 0.079[a,b]
F		11.291	9.982	10.044
P value		.000	.000	.000

[a]*P* < .05 compared with the eosinophilic group
[b]*P* < .05 compared with the non-eosinophilic group

Table 3. Correlation analysis of CD23 with p-ERK and CCL20 in nasal polyps.

	CD23	
Indicator	r	*P* value
p-ERK	0.879	.000
CCL20	0.783	.000

Statistical Analysis

SPSS 22.0 software was used. Normally distributed metric data were expressed as ($\bar{x} \pm s$), and *t* tests or F-tests were used to analyze intergroup differences. Count data were expressed as frequency or percentage, and the χ^2 test was used to analyze intergroup differences. Pearson correlation analysis was used for correlation analysis. $\alpha = 0.05$. The significance level (α) was set at 0.05, indicating that results with a probability value $P < .05$ were considered statistically significant.

RESULTS

Expression of CD23 in Colonic Polyp Tissues Among Different Groups

Eosinophilic group, non-eosinophilic group and control group, and the number of samples (n) in each group was 40, 35, and 30, respectively. Clinical general data includes gender distribution, age and body mass index (BMI), etc. There was no significant difference in these clinical characteristics between the groups by F-test or χ^2 test ($P > .05$). CD23 expression was mainly observed in epithelial cells, and positive expression appeared as brown-yellow or brown color. CD23 was highly expressed in the eosinophilic group, while it was minimally expressed in the non-eosinophilic and control groups. Refer to Table 1.

Expression of CD23 Protein and Other Proteins in Colonic Polyp Tissues Among Different Groups

The relative expression levels of CD23 protein, p-ERK protein, and CCL20 protein in the eosinophilic group were significantly higher than those in the non-eosinophilic and control groups ($P < .05$). The relative expression levels of CD23 protein, p-ERK protein, and CCL20 protein in the non-eosinophilic group were significantly higher than those in the control group ($P < .05$). Relatively expression levels are

Figure 1. Immunohistochemical staining of CD23. (**A.** Control group, ×200; **B.** Non-eosinophilic group, ×200; **C.** Eosinophilic group, ×400)

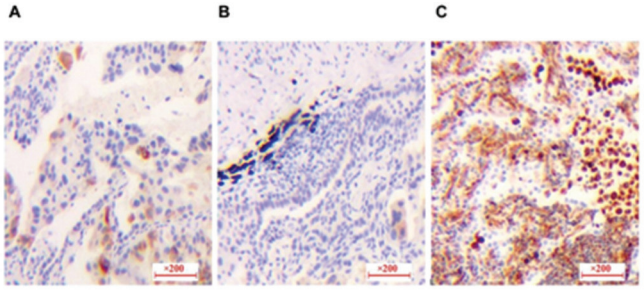


Figure 2. Correlation analysis of CD23 with p-ERK and CCL20.

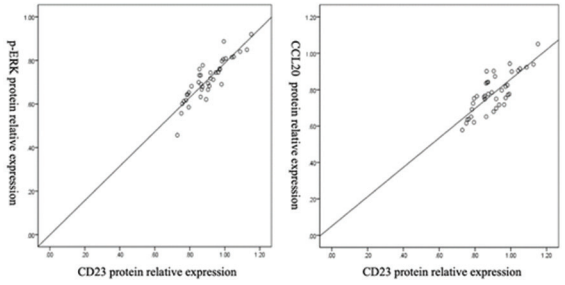
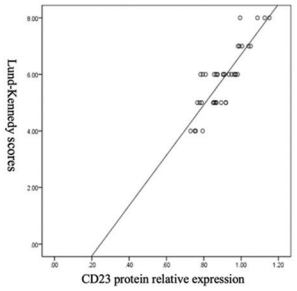


Figure 3. Correlation analysis between CD23 and disease severity.



obtained by the expression level of CD23 protein, P-ERK protein and CCL20 protein under different groups or under different conditions. Refer to Table 2.

Correlation Analysis of CD23 with p-ERK and CCL20

In the eosinophilic group, the relative expression levels of CD23 protein were positively correlated with the p-ERK protein and CCL20 protein (r = 0.879, 0.783, Ps < .05). Refer to Table 3 and Figure 2.

Relationship Between CD23 and Disease Severity

The Lund-Kennedy score of the eosinophilic group (6.10 ± 1.01) was significantly higher than that of the non-eosinophilic group (4.40 ± 0.92), and the difference was statistically significant (t = 7.579, P < .05). The relative expression level of CD23 protein in the eosinophilic group was positively correlated with the Lund-Kennedy score (r = 0.847, P < .05). Refer to Figure 3.

DISCUSSION

The Role of CD23

The pathogenesis of chronic sinusitis with nasal polyps is complex. It involves the interaction of various factors, including increased levels of eosinophils, IgE, mast cells, T lymphocytes, cytokines, and chemokines in the lesion tissues.[8,9] The increase of eosinophils in nasal polyp tissues can lead to allergic reactions, which may be due to the exposure of nasal polyps to allergens, resulting in specific local allergic reactions mediated by IgE, the release of inflammatory mediators and chemokines, immune dysfunction, and the aggregation of various cytokines acting on downstream signaling pathways, further leading to eosinophil aggregation, local tissue edema, and ultimately eosinophilic chronic sinusitis with nasal polyps.[10-12]

CD23 is a low-affinity receptor for IgE, composed of 321 amino acids, and its interaction with IgE may be involved in multiple allergic processes.[13] CD23 can transport IgE-allergen immune complexes in the airways and intestines, and is a key factor in the presentation of IgE-mediated allergens.[14] IgE immune complexes can cause CD23 to cover the surface of B cells, further promoting the formation of CD23-IgE-allergen complexes, making multiple IgE binding sites tightly bound together. When more IgE binds to B cells, these B cells may synthesize new IgE that may become increasingly inhibited.[15,16]

The CD23-ERK-CCL20 Pathway

The results of the immunohistochemical analysis in this study showed that CD23 expression was mainly observed in epithelial cells. Positive expression appeared as light brown or brown color, and CD23 was highly expressed in the eosinophilic group, while only low levels of CD23 expression were observed in the non-eosinophilic group and the control group. This indicates that CD23 expression is closely related to the occurrence of eosinophilic chronic rhinosinusitis with nasal polyps. CD23-IgE complex sites were found in the nasal polyp epithelial cells, suggesting that CD23 expressed in the nasal polyp epithelial cells of patients with eosinophilic chronic rhinosinusitis with nasal polyps may have a function in mediating IgE transcytosis across the epithelium. Non-eosinophilic chronic rhinosinusitis with nasal polyps patients showed only low levels of CD23 expression in the nasal mucosal epithelial cells. At the same time, CD23-mediated transcytosis was enhanced in patients with eosinophilic chronic rhinosinusitis with nasal polyps.

Research has shown[17,18] that CD23 induces degranulation of mast cells and initiates the early phase of allergic rhinitis by facilitating the translocation of IgE and IgE-allergen immune complexes across the epithelium. This, in turn, activates the ERK signaling pathway to promote the downstream chemokines CCL20 and IL-8, leading to the accumulation of various inflammatory cells in the local polyps and participating in the late phase of allergic rhinitis.[19,20] This study aims to investigate whether the CD23-ERK-CCL20/IL-8 signaling pathway is also involved in developing eosinophilic chronic rhinosinusitis with nasal polyps (ECRSwNP). The results of

this study show that the relative expression levels of CD23 protein, p-ERK protein, and CCL20 protein in the eosinophilic polyp group are significantly higher than those in the non-eosinophilic group and the control group ($P < .05$). The relative expression levels of CD23 protein in the eosinophilic group are positively correlated with those of p-ERK protein and CCL20 protein ($P < .05$). The experimental results indicate that CD23, p-ERK, and CCL20 expression is upregulated in polyp tissues of ECRSwNP with eosinophilia. This suggests that the CD23-ERK-CCL20/IL-8 signaling pathway may exist in polyp tissues of ECRSwNP with eosinophilia. The mechanism is thought to be that when IgE-allergen immune complexes act on CD23 in eosinophilic nasal polyps with rhinosinusitis, the ERK signaling pathway is activated, further promoting CCL20 expression, and subsequently, chemotaxis of a large number of immune effector cells and local tissue edema, ultimately leading to the formation of nasal polyps. Therefore, CD23 may also be involved in the delayed onset of eosinophilic chronic rhinosinusitis with nasal polyps. The results of this study show that the Lund-Kennedy score in the eosinophilic group is significantly higher than that in the non-eosinophilic group ($P < .05$), and the relative expression level of CD23 protein in the eosinophilic group is positively correlated with the Lund-Kennedy score. Thus, it can be further inferred that by detecting the expression of CD23, the degree of eosinophilic inflammation with a type 2 immune response and the extent of damage to the lesions of ECRSwNP with nasal polyps can be assessed, providing a new theoretical basis for the diagnosis and treatment of the disease.

Clinical Implications

The clinical levels and related mechanisms of CD23 expression in chronic eosinophilic rhinosinusitis with nasal polyps are not clear. There is a lack of specific clinical treatment, and problems such as poor treatment effects, high surgery rates, and poor prognosis exist. If new regulatory mechanisms for this disease can be discovered, it may provide new targets for specific drug treatment in clinical settings. This study found that CD23 can be a new target for treating eosinophilic chronic rhinosinusitis with nasal polyps, which has certain research value. However, this study had a small sample size and may have some experimental errors. In the next step, it is necessary to increase the sample size and conduct in-depth research to provide more theoretical basis for clinical diagnosis and treatment.

Study Limitations and Future Directions

Certainly, there are several limitations to be acknowledged in this study. Firstly, the relatively small sample size might compromise the statistical power of the analysis, potentially limiting the generalizability of the findings. Secondly, the use of samples solely from a single hospital might introduce selection bias and reduce the external validity of the results. Additionally, due to the cross-sectional design, the study lacks the ability to capture longitudinal trends and causality, which could be better addressed through longitudinal studies.

To enhance the validity of our findings, future studies could consider addressing these limitations. Expanding the sample size and including multiple medical centers would increase the robustness of the results and improve the generalizability. Conducting a longitudinal study design would allow for the exploration of temporal relationships and the identification of potential causal links between CD23 expression and disease progression. Moreover, the inclusion of more comprehensive clinical variables, such as treatment regimens and patient history, could provide a more holistic understanding of the complex interplay between CD23 and chronic rhinosinusitis with nasal polyps.

In conclusion, our study underscores the upregulation of CD23 in eosinophilic chronic rhinosinusitis with nasal polyps and its positive correlation with disease severity and the ERK signaling pathway. While limitations exist, addressing these issues through larger and more diverse samples, longitudinal designs, and comprehensive clinical data could provide a more comprehensive insight into the role of CD23 in the development and progression of this condition.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

MX and HT designed the study and performed the experiments, ZC and QJ collected the data, ZC, QJ and YG analyzed the data, MX and HT prepared the manuscript. All authors read and approved the final manuscript.

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