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Expressions of Lipocalin-2 in nasal tissues and secretions of patients with chronic rhinosinusitis with nasal polyps and correlations with inflammatory factors.

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Keywords: Inflammation Mediators; Lipocalin-2; Nasal polyps; Rhinosinusitis.

Abstract. Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common inflammatory disease of the upper airway. Lipocalin-2, an inflammation-related glycoprotein involved in innate immune regulation, has been linked to several chronic inflammatory disorders, but its role in CRSwNP remains unclear. This study aimed to examine the expression of Lipocalin-2 in nasal tissues and secretions of CRSwNP patients and its relationship with inflammatory factors. Seventy patients diagnosed with CRSwNP between January 2023 and January 2025 were enrolled in the case group, while 60 patients with simple nasal septal deviation served as controls. NP tissues and nasal secretions were collected from CRSwNP patients, whereas inferior turbinate mucosal tissues and nasal secretions were obtained from controls. Levels of Lipocalin-2, interleukin-5 (IL-5), IL-6, and tumor necrosis factor-alpha (TNF-α) were measured and analyzed. Compared with controls, CRSwNP patients showed significantly higher levels of Lipocalin-2 and inflammatory cytokines in nasal secretions ($p<0.05$). Stratification based on Visual Analog Scale (VAS) scores and computed tomography Lund-Mackay (CT L-M) scores indicated that these markers were notably higher in the moderate-to-severe group than in the mild disease group ($p< 0.05$). Lipocalin-2 was positively correlated with IL-5, IL-6, TNF-α, as well as VAS, Lund-Kennedy endoscopy, and CT L-M scores (all $p<0.05$). In summary, Lipocalin-2 is highly expressed in nasal polyp tissues and secretions of CRSwNP patients and closely associated with inflammatory cytokine levels and clinical severity, implying its potential as a biomarker for disease activity in CRSwNP.

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Expresión de Lipocalina-2 en los tejidos nasales y secreciones de pacientes con rinosinusitis crónica con pólipos nasales y su correlación con factores inflamatorios.

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Palabras clave: Mediadores de Inflamación; Lipocalina 2; Pólipos Nasales**;** Rinosinusitis.

Resumen. La rinosinusitis crónica con pólipos nasales (CRSwNP) es una enfermedad inflamatoria frecuente de las vías respiratorias superiores. La lipocalina-2, una glicoproteína asociada a la inflamación e implicada en la regulación de la inmunidad innata, se ha relacionado con diversas enfermedades inflamatorias crónicas; sin embargo, su papel en la CRSwNP aún no ha sido completamente aclarado. El objetivo de este estudio fue investigar la expresión de la lipocalina-2 en los tejidos y en las secreciones nasales de pacientes con CRSwNP, así como su asociación con factores inflamatorios. Setenta pacientes diagnosticados con CRSwNP entre enero de 2023 y enero de 2025 fueron incluidos en el grupo de casos, mientras que 60 pacientes con desviación simple del tabique nasal sirvieron como grupo control. Se recogieron tejidos de pólipos nasales y secreciones nasales de los pacientes con CRSwNP, mientras que en los controles se obtuvieron tejidos de la mucosa del cornete inferior y secreciones nasales. Se midieron y analizaron los niveles de lipocalina-2, interleucina-5 (IL-5), interleucina-6 (IL-6) y del factor de necrosis tumoral alfa (TNF-α). En comparación con los controles, los pacientes con CRSwNP presentaron niveles significativamente elevados de lipocalina-2 y citocinas inflamatorias en las secreciones nasales ($p<0,05$). La estratificación basada en la escala visual analógica (VAS) y en las puntuaciones de la tomografía computarizada Lund-Mackay (CT L-M) mostró que estos marcadores eran notablemente más altos en el grupo con enfermedad moderada a grave que en el grupo con enfermedad leve ($p<0,05$). La lipocalina-2 se correlacionó positivamente con IL-5, IL-6 y TNF-α, así como con las puntuaciones de VAS, Lund-Kennedy endoscópica y CT L-M (todas con $p<0,05$). En conclusión, la lipocalina-2 se expresa de forma elevada en los tejidos de los pólipos nasales y en las secreciones nasales de pacientes con CRSwNP, y se asocia estrechamente con los niveles de citocinas inflamatorias y la gravedad clínica, lo que sugiere su posible utilidad como biomarcador de la actividad de la enfermedad en la CRSwNP.

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INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a common nasal disease characterized by ongoing inflammation and polypoid hyperplasia in the nasal cavity or sinus mucosa, often accompanied by bone damage and mucus retention [1]. The incidence of CRS in China is approximately 8%, with CRSwNP patients making up about one-third of the total cases [2]. CRSwNP has a complex cause involving infection, environmental factors, allergies, and several other elements, with clinical signs like purulent nasal dis-

charge, nasal blockage, and reduced sense of smell, which seriously impact patients' quality of life [3]. In clinical treatment, managing CRSwNP mainly involves medication and surgery, but the disease is often persistent and prone to recurrence due to factors such as low immunity, recurrent infections, and the limited precision of current therapies [4]. The rate of recurrence after surgical removal can be as high as 40-60% [5]. Therefore, it is particularly important to explore new diagnostic and therapeutic targets for CRSwNP to improve patient outcomes.

As a secretory glycoprotein isolated from neutrophils in the early stage, Lipocalin-2 has the typical β-barrel structure of the lipocalin family and participates in many physiological processes, including iron metabolism, cytokine secretion, and extracellular trap regulation through binding to various ligands and receptors. It is also clear that Lipocalin-2 plays a crucial role in tumor cell proliferation and apoptosis, as well as in chronic inflammatory responses [6]. In inflammatory diseases such as asthma and atopic dermatitis, the widespread expression of Lipocalin-2 is positively associated with eosinophil counts and inflammatory factor levels, indicating its strong potential as a target for disease risk [7]. However, systematic clinical studies on the expression pattern of Lipocalin-2 in CRSwNP nasal tissues and secretions, and the mechanisms through which it correlates with inflammatory factors, including interleukin-5 (IL-5) and IL-6, have not yet been conducted.

Given this, an in-depth analysis was conducted on the relationship between Lipocalin-2 expression levels and the characteristics of nasal tissues and secretions from CRSwNP patients, and its correlations with inflammatory factors were explored in the present study.

PATIENTS AND METHODS

Subjects

Seventy patients diagnosed with CRSwNP and visiting our hospital from January 2023 to January 2025 were included in the case group. Additionally, a control group (n=60) consisting of patients with simple nasal septal deviation was established. Demographic and clinical characteristics, such as sex, age, body mass index, and comorbid allergic rhinitis, are summarized in Table 1. There were no statistically significant differences in baseline characteristics between the two groups ($p>0.05$).

Inclusion criteria were as follows: (1) patients in the case group diagnosed with CRSwNP through examinations showing clinical signs, rhinoscopy, and computed tomography (CT), and treated with functional endoscopic sinus surgery; (2) individuals in the control group meeting the diagnostic criteria for nasal septum deviation as specified in the Volume of Otolaryngology Head and Neck Surgery Clinical Practice Guidelines[8], without NP or sinusitis based on clinical examinations; and (3) patients aged 18-65 years. The following exclusion criteria were

Table 1. General data of patients.

Group	n	Gender (male/female)	Age (year)	Body mass index (kg/m^2)	Comorbid allergic rhinitis (n)
Case	70	40/30	42.39±10.24	22.97±2.01	28 (40.00%)
Control	60	36/24	41.92±10.46	22.67±1.97	40 (66.67%)
χ^2/t		0.109	0.258	0.856	0.617
p		0.742	0.797	0.394	0.432

Data are presented as mean ± standard deviation (SD) or number (percentage). Comparisons between groups were performed using the independent-samples t-test for continuous variables and the chi-square (χ^2) test for categorical variables. A p value < 0.05 was considered statistically significant.

applied: (1) patients who had been treated with a large amount of antibiotics, immunosuppressants, or antihistamines in the past month; (2) those with severe cardiac or pulmonary diseases or coagulation disorders; (3) individuals with strict surgical contraindications; (4) those complicated by fungal sinusitis, asthma, or nasal cavity neoplasm; and (5) individuals with serious psychiatric or psychological disorders or who cannot communicate normally. This study was reviewed and approved by the ethics committee of Ningbo Yinzhou No. 2 Hospital, and all patients in both groups signed the informed consent form.

Sample collection and treatment

During surgery, nasal polyps (NP) tissues and nasal secretions were collected from the case group, while inferior turbinate mucosal tissues and nasal secretions were obtained from the control group. NP tissues: The harvested samples were immediately rinsed with 4°C normal saline to remove blood clots and surface impurities. Then, the samples were cut into two tissue blocks of similar size and volume using a sterile scalpel. One tissue block was immersed in 10% (v/v) formalin solution for 12-24 hours for fixation, then embedded in wax. The other was placed in a sterile cryotube for 1-3 hours and then frozen in liquid nitrogen for later use. Nasal secretions: An aseptic cotton swab or cotton pad was gently rotated deep into the nasal cavity and NP for 15 minutes to obtain at least 2 mL of secretions. These were processed in an H1850 centrifuge (Hunan Xiangyi Laboratory Instrument Development Co., Ltd.) at 3,000 rpm for 10 minutes. The supernatant was aspirated and stored in a -80°C freezer.

Detection of Lipocalin-2 and inflammatory factors

Lipocalin-2 expression in tissues: The sections, dipped and embedded in wax, were sequentially hydrated in ethanol and xylene of varying concentrations. Following deparaffinization, a high-temperature, high-pressure retrieval method was used to expose cell and tissue antigens, and a hydrogen peroxide blocking solution was added in drops to inhibit peroxidase activity. Next, goat serum was added dropwise, followed by a 10-minute incubation at room temperature; the supernatant was discarded, and a Lipocalin-2-specific primary antibody was added for overnight incubation at 4°C. The next day, streptavidin-biotin-peroxidase complex solution was added dropwise and incubated for 15 minutes at room temperature, followed by color development with DAB solution, observation under an optical microscope (400×), rinsing, and counterstaining with hematoxylin. Afterward, the sections were placed in an alkaline solution until they turned blue, dehydrated in a graded alcohol series, cleared in xylene, and mounted with neutral resin added dropwise.

The expression levels of Lipocalin-2 in nasal tissues, as well as Lipocalin-2 and inflammatory factors [interleukin-5 (IL-5), IL-6, and tumor necrosis factor-α (TNF-α)] in nasal secretions, were quantified using an ELISA kit (Shanghai Fengshou Biotechnology Co., Ltd.) strictly following the manufacturer's instructions. Specifically, nasal tissue samples were homogenized and processed for ELISA-based measurement of Lipocalin-2, while nasal secretion samples were centrifuged at 300× g at 4°C for 10 minutes; the supernatant was then collected and stored at -80°C in aliquots for testing. Before testing, the kit was brought to room temperature for 30 minutes, and the washing solution (diluted using distilled water at 1:20) and sample diluent [phosphate-buffered saline with Tween-20 (PBST) containing 1% bovine serum albumin (BSA)] were prepared. Next, the standard substance was serially diluted (e.g., Lipocalin-2 standard range: 156-10,000 pg/mL). Then, 100 μL of each sample and standard (nasal secretion supernatants pre-diluted with sample diluent at 1:2-1:10 as needed) were added to a microtiter plate pre-coated with specific an-

tibodies (polyclonal antibody for Lipocalin-2 measurement), followed by incubation at 37°C for 90 minutes and 3 washes with PBST after discarding the liquid (allowing the plate to stand for 30 seconds after each filling, then pat dry). Subsequently, each well was blocked with 200 μL of blocking solution (5% skim milk or 1% BSA/PBS) at 37°C for 2 hours and washed 3 times. Afterward, 100 μL of biotin-labeled detecting antibodies (diluted as specified in the instructions) were added, incubated at 37°C for 60 minutes, and washed 5 times (samples with high background could be washed up to 7 times). Then, 50 μL of TMB chromogenic substrate (A/B solution, 50 μL each) was added for room temperature development, protected from light, for 15 minutes or until positive wells turned light blue. Next, 50 μL of 2 M H_2SO_4 stop buffer was added to each well, and the absorbance (optical density, OD) was immediately measured at 450 nm, with a reference wavelength of 630 nm, using a microplate reader. Finally, target factor concentrations were calculated using the standard curve (four-parameter logistic regression fitting, $R^2 > 0.99$), with a CV value of less than 15% among replicate wells.

Assessment of disease severity

A visual analog scale (VAS) was used for the quantitative evaluation of four clinical symptoms in patients, namely nasal obstruction [9], runny nose, hyposmia, and dizziness and headache. Each item was scored on a 0-2 scale, with a total of 10 points; higher scores indicated more severe symptoms. Additionally, the Lund-Kennedy nasal endoscopy (L-K) score was used to quantify dimensions such as NP area [10], secretions, mucosal edema, and scars, with each item scored 0-2 points and a total score of 0-12 points. The higher the scores, the greater the NP load and the higher the disease activity. Furthermore, the Lund-MacKay sinus computed tomography (L-M) score was applied for standardized scoring based on patients' computed tomography (CT) imaging results [11], where the inflammation in the maxillary sinus, ethmoidal sinus, frontal sinus, and sphenoidal sinus on both sides and the degree of ostiomeatal complex obstruction in patients were mainly observed. Each item was scored 0-2 points, and the total score was 0-24 points, with higher scores representing a wider range of inflammation and a higher degree of the disease.

Statistical analysis

SPSS 24.0 software was adopted for statistical analysis. Measurement data in line with normal distribution were expressed by ($\bar{x} \pm s$) and compared between groups *via* the independent-samples *t*-test. Count data were represented as [n (%)] and subjected to the χ^2 test for intergroup comparison. The correlations of the expression levels of Lipocalin-2, IL-5, IL-6, and TNF-α with the VAS, L-K, and CT L-M scores were identified through Pearson's correlation analysis. $p<0.05$ denoted a statistically significant difference.

RESULTS

Lipocalin-2 expression levels in nasal tissues

The expression level of Lipocalin-2 in nasal tissues was significantly higher in the case group than in the control group ($p<0.05$) (Table 2).

Table 2. Lipocalin-2 expression levels in nasal tissues.

Group	n	Lipocalin-2 (ng/mL)
Case	70	50.36±16.24
Control	60	26.19±9.21
t		10.204
p		<0.001

Data are presented as mean ± standard deviation (SD). Comparisons between groups were performed using the independent-samples t-test.

Levels of Lipocalin-2 and inflammatory factors in nasal secretions from the two groups

The case group showed higher levels of Lipocalin-2, IL-5, IL-6, and TNF-α in nasal

secretions compared to the control group, and these differences were statistically significant ($p<0.05$) (Table 3).

Correlation between Lipocalin-2 and inflammatory factors in nasal secretions obtained from the case group

Pearson's correlation analysis revealed that Lipocalin-2 had positive correlations with IL-5, IL-6, and TNF-α in nasal secretions from the case group ($p<0.05$) (Table 4).

Levels of Lipocalin-2 and inflammatory factors in the case group with different disease severities

Based on the stratification using the VAS score (≤5 points for mild and >5 points for moderate-to-severe) and CT L-M score (≤12 points for mild-to-moderate and >12 points for severe), all indicators were significantly higher in the moderate-to-severe group compared to the mild group ($p< 0.05$) (Table 5).

Correlations of Lipocalin-2 and inflammatory factors with disease severity in the case group

In the case group, the VAS, L-K, and CT L-M scores were positively correlated with the expression levels of Lipocalin-2 and inflammatory factors in patients ($p<0.05$) (Table 6).

DISCUSSION

Classified as an inflammatory disease of the upper respiratory tract secondary to CRS subtypes, CRSwNP is partially caused by abnormal anatomy, genetics, allergic edema, and other factors, with characteristic changes such as inflammatory cell infiltration, stromal edema, and NP growth. Clinically, it manifests as recurrent dizziness and headache, sinus ostium blockage, purulent nasal discharge, and anosmia [12,13]. Although immune responses dominated by T helper type 2 (Th2) inflammation are considered the main drivers of pathological imbalance in CRSwNP, the biological targets that regulate inflammatory factor expression levels remain undefined [14]. Lipocalin-2 is a pro-inflammatory, iron-shuttle molecule associated with neutrophil gelatinase. It participates in biological processes including cell differentiation, apoptosis, defense against bacterial infections, and fatty acid transportation. It also plays a crucial role in iron metabolism, oxidative stress, and inflammation regulation in the human body [15]. A recent study found that Lipocalin-2 can predict and reflect the degree of renal function im-

Table 4. Correlation between Lipocalin-2 and inflammatory factors in nasal secretions from the case group.

Inflammatory factor	Lipocalin-2	
	r	p
IL-5	0.827	<0.001
IL-6	0.465	<0.001
TNF-α	0.597	<0.001

Interleukin-5 (IL-5), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α). *r* indicates Pearson's correlation coefficient.

Table 3. Levels of Lipocalin-2 and inflammatory factors in nasal secretions.

Group	n	Lipocalin-2 (ng/mL)	IL-5 (pg/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)
Case	70	62.15±14.26	46.92±4.52	58.36±14.21	113.68±9.14
Control	60	24.69±8.19	25.64±3.24	43.69±10.24	95.49±8.36
t		17.961	30.380	6.651	11.764
p		<0.001	<0.001	<0.001	<0.001

Data are presented as mean ± standard deviation (SD). Comparisons between groups were performed using the independent-samples t-test. Interleukin-5 (IL-5), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α).

Table 5. Levels of Lipocalin-2 and inflammatory factors in the case group with different disease severities.

Stratification indicator	n	Lipocalin-2 (ng/mL)	IL-5 (pg/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)
VAS score					
≤5 points (mild)	25	48.21±12.35	40.23±3.89	52.14±11.56	105.32±8.23
>5 points (moderate-to-severe)	45	66.89±15.42	51.26±4.71	62.89±13.24	118.97±9.56
t		5.196	9.964	3.401	6.005
p		<0.001	<0.001	0.001	<0.001
CT L-M score					
≤12 points (mild-to-moderate)	32	52.36±13.18	43.56±4.12	55.21±12.34	108.65±8.78
>12 points (severe)	38	68.92±14.89	50.12±4.98	61.54±11.87	119.23±9.01
t		4.639	5.602	2.108	4.750
p		<0.001	<0.001	0.039	<0.001

Data are presented as mean ± standard deviation (SD). Comparisons between subgroups were performed using the independent-samples t-test. Interleukin-5 (IL-5), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α). Visual analog scale (VAS), Lund-MacKay sinus computed tomography (CT L-M).

Table 6. Correlations of Lipocalin-2 and inflammatory factors with disease severity in the case group.

Group	Lipocalin-2		IL-5		IL-6		TNF-α	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
VAS score	0.756	<0.001	0.613	<0.001	0.619	<0.001	0.078	<0.001
L-K score	0.647	<0.001	0.519	0.003	0.492	<0.001	0.069	0.004
CT L-M score	0.597	0.002	0.616	<0.001	0.473	<0.001	0.064	<0.001

r indicates Pearson's correlation coefficient. Correlation analyses were performed using Pearson correlation analysis. Interleukin-5 (IL-5), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α). Visual analog scale (VAS), Lund-Kennedy nasal endoscopy (L-K), Lund-MacKay sinus computed tomography (CT L-M).

pairment, offering clinical advantages like early monitoring, easy assessment, and high specificity [16]. As previously researched, Lipocalin-2 is a key player in the pathology of diseases such as alcoholic fatty liver and malignant tumors. It promotes disease progression by regulating inflammatory expression, mediating iron homeostasis, and participating in signaling pathways, making it a potential target for diagnosis and prevention [17]. However, studies on Lipocalin-2 and inflammatory factors in CRSwNP are still limited.

In this study, the case group exhibited significant increases in the expression level of Lipocalin-2 in nasal tissues as well as the levels of Lipocalin-2, IL-5, IL-6, and TNF-α in nasal secretions, in contrast to the control group, suggesting that Lipocalin-2 and inflammatory factors are highly expressed in the pathogenesis of CRSwNP, exerting a synergistic effect on NP formation. As a multifunctional pro-inflammatory protein, Lipocalin-2 induces the expression of chemokines, including CXCL8 and CCL2, and recruits neutrophils and eosinophils to NP tissues in combination with Th2 inflammatory factors such as IL-5, thereby exacerbating inflammatory infiltration. Moreover, TNF-α, IL-6, and other inflammatory factors can activate T lymphocytes to mediate neutrophil secretion of Lipocalin-2, form a synergistic cycle of inflammatory factors

and Lipocalin-2, and enhance the release of inflammatory signals [18]. The iron-chelating function of Lipocalin-2 can activate the ferroptosis pathway, disrupt the metabolic stability of the nasal mucosa, and elevate intracellular ferrous ion concentration. Besides, inflammatory factors released under oxidative stress activate the NF-κB signaling pathway, which up-regulates the expression of inflammatory factors and Lipocalin-2 again [19]. In addition, owing to its specific structure, Lipocalin-2 is capable of binding to and transporting various lipophilic small molecules including iron and fatty acids, affecting the metabolism of immune cells and polarization of macrophages. Finally, it collaborates with Th2 inflammatory factors to induce epithelial-mesenchymal transition, promote excessive deposition of the fibrous extracellular matrix, and facilitate hyperplasia and invasion of NP tissues. As indicated in the literature, in the diseased skin tissues of patients with psoriasis, keratinocytes exhibit high Lipocalin-2 expression within an activated inflammatory microenvironment, and Lipocalin-2 has synergistic effects with the pro-inflammatory factors TNF-α and IL-8. Once again, it demonstrates the regulatory roles of Lipocalin-2 and inflammatory factors in the disease validation cascade [20]. Through deep investigation, it was uncovered that Lipocalin-2 had positive relations to IL-5, IL-6, and TNF-α, together with significantly positive correlations with the VAS, L-K, and CT L-M scores in CRSwNP patients, suggesting that Lipocalin-2 forms a pathogenic network with inflammatory factors to jointly participate in and reflect the progression of CRSwNP. Combined with correlation analysis results, as a crucial cytokine regulating eosinophil maturation, activation, and tissue migration, IL-5 can work with Lipocalin-2 to recruit eosinophils, transfer them to NP tissues, and release toxic proteins to aggregate local mucosal edema and inflammation, resulting in increased NP size and thickened sinus mucosa, and triggering symptoms such as nasal obstruction and headache. TNF-α and IL-6 form a two-way feedback loop with Lipocalin-2 that continuously activates inflammation-related signaling pathways and accelerates the release of inflammatory mediators such as reactive oxygen species and proteases, thereby up-regulating ICAM-1 and other adhesion molecules, increasing vascular permeability of the nasal mucosa, and amplifying inflammatory responses. Meanwhile, Lipocalin-2 may exacerbate pain sensitization by activating trigeminal nerve endings in the nasal mucosa and promoting the release of neuroinflammatory substances, which directly affect the severity of the patient's subjective symptoms as measured by the VAS score. Existing studies have corroborated a positive correlation between Lipocalin-2 expression levels and the severity of ankylosing spondylitis [21]. In a study of hemorrhagic fever with renal syndrome, Lipocalin-2 is highly expressed in the serum of patients [22]. As demonstrated by the above literature and the present study, Lipocalin-2 is likely a broad-spectrum regulator of chronic inflammatory diseases, and its synergistic effects with inflammatory factors may serve as a potential indicator of clinical phenotypes and disease severity.

In conclusion, Lipocalin-2 exhibits high expression in NP tissues and secretions from CRSwNP patients, and it is not only significantly correlated with levels of inflammatory factors IL-5, IL-6, and TNF-α, but also positively associated with disease severity. This suggests that Lipocalin-2 could become a novel therapeutic target for monitoring disease progression, exploring the pathogenesis, and developing new treatments for CRSwNP. However, this study only identified a correlation between Lipocalin-2 and inflammatory factors, and there is a lack of scientific evidence regarding its regulatory mechanisms and signaling pathways, which can be examined in future research using cell models or animal studies.

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Author's contributions

YL designed this study and significantly revised the paper; YY, JX, and YZ performed this study, analyzed the data, and drafted the paper. All authors have approved the submission and publication of this paper.

Conflict of interest

The authors declare no conflict of interest.

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