MicroRNA-150-5P regulates Th1/Th2 cytokines expression levels by targeting EGR2 in allergic rhinitis*

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Abstract

Background: MiR-150-5p is one of the miRNAs in the expression profile of miRNAs, and in many previous studies, it has been shown that miR-150-5p may play an important role in peripheral blood dendritic cells (DCs) of allergic rhinitis (AR) patients. We sought to investigate the role and mechanism of miR-150-5p in regulating DC function by modulating EGR2 and influencing T cell derivation to promote AR development.

Methods: The expression of miR-150-5p and EGR2 in AR patients was examined by real-time quantitative polymerase chain reaction (qRT-PCR), the expression of IL-4 cytokines in the supernatant of AR patients was tested by enzyme-linked immunosorbent assay (ELISA), and the expression of eosinophils in the supernatant of AR patients was measured by HE staining. The expression of EGR2 was detected by immunohistochemistry and fluorescent m-immunohistochemistry.

Results: MiR-150-5p expression was up-regulated and EGR2 expression was down-regulated in peripheral blood DCs from AR patients. miR-150-5p upregulated DCs, which promoted T-cell differentiation. miR-150-5p further regulated EGR2, which suppressed DCs and caused alteration of T-cell differentiation, in turn triggering the occurrence of AR.

Conclusion: MiR-150-5p and its target gene EGR2 are involved in the development of AR, and DCs foster T-cell differentiation in peripheral blood of AR patients.

Key words: miR-150-5p, allergic rhinitis, EGR2, dendritic cells, T cells

Introduction

Allergic rhinitis (AR) is one of the diseases of the immune system and is a common allergic disease characterised by paroxysmal sneezing, runny nose, nasal congestion and nasal itching in susceptible individuals when exposed to inhalant allergens such as pollen, moulds and dust mites. It is mainly mediated by IgE antibodies, predominantly Th2, involving mast cells and dendritic cells and other related cells [1]. AR currently affects 10-30% of the world's population [2], with a prevalence of 10-40% in China [3], and the incidence is increasing year on year as the population lives under stress and environmental pollution. It is not only a health hazard, but also a major weighted risk factor for several diseases such as asthma. The conventional pharmacological or surgical treatment of AR is difficult to treat [4]. Consequently, there is an impending need to find new therapeutic targets for the prevention and therapy of AR.

MicroRNAs (miRNAs) can influence inflammation by regulating the proliferation, differentiation and activation of dendritic cells (DCs) [5]. miRNAs are a group of endogenous non-coding RNAs that regulate gene expression and are small, highly conserved 18-24 nucleotide non-coding RNAs that repress target genes at the post-transcriptional level by degrading mRNA [6]. It has been shown that miR-150-5p is a key regulator of T-cell activation in severe aplastic anaemia [7]. We previously investigated the miRNA expression profile of mature mDCs in CRS, including miR-150-5p, which was confirmed by quantitative real-time polymerase chain reaction (qRT-PCR), and as well as demonstrated that miR-150 expression is increased in AR patients [8]. It is, however, unclear how miR-150-5p regulates DCs in allergic diseases, particularly in AR. Consequently, we predicted the target genes

of miR-150-5p.

Early growth response proteins (EGR) are among the members of the immediate early response factor (IEX) family of transcription factors, which are predominantly involved in the regulation of cell growth, proliferation, differentiation and apoptosis [9]. The major family members are EGR1, EGR2, EGR3 and EGR4, all of which share a common Cys2His2 zinc finger structural domain that binds to DNA. This construct binds to GCG G/T GGG CG sequences in the promoter regions of other genes and hence exerts its regulatory role at the transcriptional level. There are no directly relevant literature reports on the role of EGR2 in allergic rhinitis. It has been found that early growth response 2 (EGR2) is upregulated during positive selection of T cells [10]; in addition, it is also expressed during the developmental stages of other lymphocytes and plays a mobile but equally important role in the development of B cells and natural killer T cells (NKT) [11]. Furthermore, EGR2 governs IL-17 expression and Th17 differentiation over negative regulation of Batf [12]. However, the role of EGR2 in AR is unclear.

DCs are bone marrow-derived cells that are spawned by lympho-myelopoiesis and are among the most powerful pathogen-presenting cells in the respiratory airways [13]. In our preliminary study, we have analysed and studied multilayered cells in detail. Mature DCs move to sub-lymphatic organs and innitiate the division of T cells. Activation by the pathogen on DCs induces the production of pro-inflammatory cytokines, which activate and induce the differentiation of naieve T cells into cells such as Th1, Th2 and Th17 types. Recent work has demonstrated that DCs in the nasal mucosa of AR patients are through their ability to influence T cell differentiation and polarisation, suggesting that DCs play a crucial role in the development and persistence of inflammation in AR patients [14-16]. Therefore, we hypothesize that miR-150-5p may regulate the allergenic properties of DCs by targeting EGR2, affecting DCs to induce T cell polarisation, which in turn leads to the development of AR. This research investigated the role of miR-150-5p in enhancing the development of AR and its possible mechanisms. EGR2 as the target gene of miR-150-5p was used as the main line of research, and the regulation of miR-150-5p in DCs was used as the entry point. The aim of this study was to evaluate the clinical question of the potential of miR-150-5p as a predictor of AR. In addition, through the regulation of DCs by EGR2, we aimed to investigate the regulatory role of miR-150-5p mediating the functional effects of EGR2 on DCs and T cells in the pathogenesis of AR and to clarify the role of miR-150-5p in the pathogenesis of AR. This study has important clinical value by establishing a control strategy for AR and provides a new target for the treatment of AR.

Materials and methods

Patients and specimens

A total of 30 individual patients were recruited for this research between August 2021 and December 2022. All patients were declared on the grounds of medical history, nasal endoscopy, and allergen intradermal test. According to the diagnostic criteria of the 2022 Chinese Guidelines for the Treatment of Allergic Rhinitis, the named attendees were divided into an AR group (20 patients: 10 males and 10 females) and a healthy control group (10 patients: 6 males and 4 females). The exclusion of the AR and healthy control groups were as listed below: 1) systemic use of glucocorticoids, anti-tissue inflammatory drugs, leukotrienes, and non-steroidal anti-inflammatory drugs during the 1 month period prior to the operation; 2) smoking or history of smoking >10 packs/year in the last year; 3) combined diseases such as chronic sinusitis, posterior nasal polyps, fungal sinusitis, inflammatory or cystic fibrosis diagnosis; 4) exposure to immunotherapy against any allergen, such as current desensitisation or after treatment; 5) allergic reaction to any medication performed within the last 2 weeks; 6) being pregnant. An intraoperative specimen of nasal mucosa was taken from a section of the inferior middle turbinate. Based on the examination results, the study subjects were separated into two groups: Normal Control and Allergic Rhinitis. Written informed consent was obtained from all subjects and the study was approved by the Ethics Committee of the Third Affiliated Hospital of Zunyi Medical University.

Quantificational real-time polymerase chain reaction (qRT-PCR)

Before extraction of RNA, nasal mucosa specimens from patients were obtained and stored frozen in a minus 80° refrigerator. Total RNA was recovered from each patient's sample after the Trizol reagent was withdrawn from the freezer and equilibrated to room temperature according to the reagent manufacturer's instructions. OD260/OD280 data for RNA density were read to determine the mass and concentration of total RNA, which read between 1.8 and 2.2 to fulfill experimental requirements. Using the extracted total RNA as a template, complementary DNA (cDNA) was synthesised using the reverse Scription kit according to the manufacturer's instructions. EGR2 was used as the homologous reference gene for miR-150-5P, and glyceraldehyde dehydrogenase 3 phosphate (GAPDH) was used as the exogenous reference gene for the other genes. The relative expression of each gene was calculated using the $2^{-\Delta\Delta CT}$method.

Enzyme-linked immunosorbent assay (ELASA)

Because IL-4 is the predominant cytokine in Th2 cells, it also drives the production of other pro-allergic cytokines (e.g., IL-13 and IL-2) by Th5 cells in allergic diseases. IL-4 also promotes the development of mDCs and participates in the migration of Th2 cells and eosinophils to sites of inflammation. In addition, IL-4 activates B cells to synthesise IgE and induces proliferation of cup cells, triggering airway hyperresponsiveness and mucus hypersecretion. The supernatant was taken at room temperature

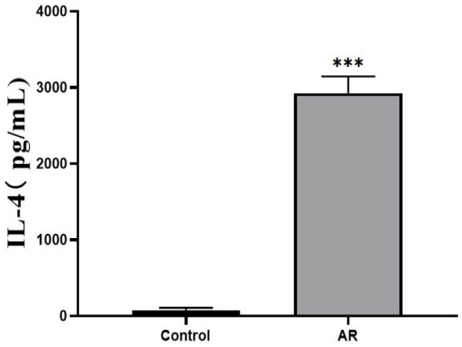

Figure 1. IL-4 expression in the normal control and AR patient groups. Control: normal group; AR: allergic rhinitis group. ***P < 0.001. N = 20 in AR group, N = 10 in control group.

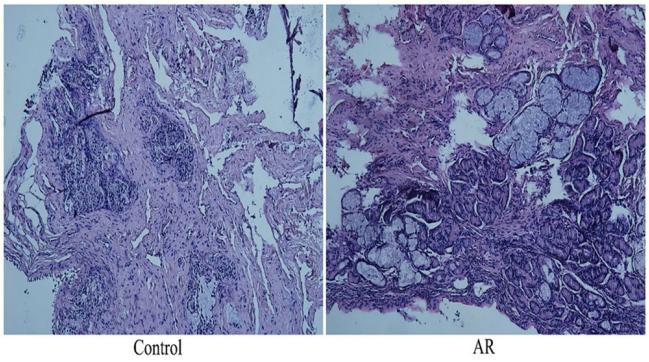

Figure 2. The extent of eosinophil infiltration in the normal control and AR patient groups. Control: the normal group; AR: the allergic rhinitis group. Representative images are shown for all groups. ×40 magnification. N = 20 in AR group, N = 10 in control group.

and then centrifuged at 4°C x 1500g for 10min. The ELISA kit was used to the quantification of cytokines, such as IL-4, in the serum according to the manufacturer's structure. Results are expressed as repeat sequences in pg/ml.

Histological analysis

The middle turbinates of human samples were excised and immediately frozen in 4% paraformaldehyde for 24-48 hours. Tissue samples were dehydrated in a graded series of ethanol and embedded in paraffin. A 4-μm thick section of nasal mucosa tissue was cut and stained with haematoxylin and eosin (H&E) for histopathological examination.

Nasal mucosal tissue immunohistochemistry (IHC) and immunofluorescence (IF)

Nasal mucosal tissue samples were paraffin embedded, fixed and sectioned as previously described. After antigen repair by microwave using sodium citrate (pH 6.0) followed by the addition of an appropriate amount of endogenous peroxidase blocker, the sections were then closed with goat serum for 1 hr at 37°C and the samples were incubated with primary antibody (EGR2) for 1 hr at 37°C or overnight at 2-8°C. The enzyme-labelled monoclonal antibody mouse/rabbit IgG polymer was then added dropwise and incubated for 20 minutes at room temperature. Sections were re-stained with hematoxylin using diaminobenzidine (DAB) as a chromogenic agent. For immunofluorescence, fluorescent secondary antibodies diluted in 1% BSA were used and incubated for 1 hour at 37°C in a wet box protected from light. Sections were then sealed with an anti-fluorescence quencher containing DAPI (4',6-diamidino-2-phenylindole) and photographed for microscopic observation. For female controls, incubation was performed using PBS instead of the specific primary antibody.

Statistical analysis

All statistical analyses were performed by one-way ANOVA using GraphPad Prism 8.0 software. values of $P<0.05$ indicate statistically significant differences (*$P<0.05$, **$P<0.01$, ***$P<0.001$). For all charts, the mean ± SEM is shown.

Results

IL-4 expression in normal control and AR patient groups

A previous study found that miR-150-5p, which is up-regulated in expression, regulates DCs, which promote T cell proliferation and differentiation. To elucidate the effect of EGR2 on T cells, we measured the expression level of IL-4 in the peripheral blood of control and AR patients by ELISA. The results showed that the expression level of IL-4 in the AR group was higher than that in the control group (Figure 1).

To observe the effect of pathological changes in the nasal mucosa in the control and AR patient groups

Next, we explored the effect of miR-150-5p-mediated EGR2 on pathological alterations in the nasal mucosa. The pathological changes of the nasal mucosa from the control and AR groups were analysed by using hematoxylin and eosin (H&E) staining for histopathological examination. As shown in Figure 2, the mucous membrane of the turbinate was swollen and eosinophilic infiltration was evident in the AR group, while no mucous membrane swelling or eosinophil infiltration was evident in the control group. These results suggest that miR-150-5p-mediated EGR2 may be involved in the process of immune cell infiltration in the nasal mucosa of AR patients and provide a certain basis for the subsequent immunohistochemical experiments.

miR-150-5p and EGR2 expression in the nasal mucosa of AR patients

To examine whether miR-150-5P and EGR2 are implicated in AR, we employed QRT-PCR to assay the manifestation of miR-150-5p

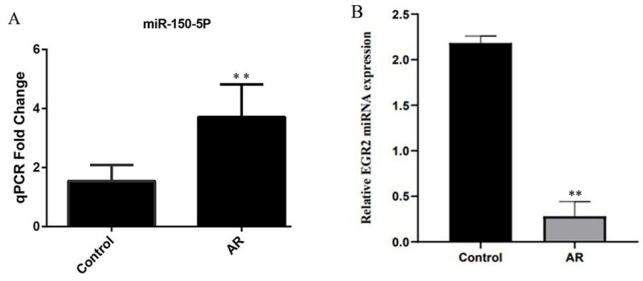

Figure 3. Expression of miR-150-5p and EGR2 mRNA in the nasal mucosa of AR patients and healthy controls. Expression of (A) miR-150-5P and (B) EGR2 by RT-QPCR. Each symbol represents a separate individual. Data are expressed as mean ± SEM. **P<0.01. N = 20 in AR group, N = 10 in control group.

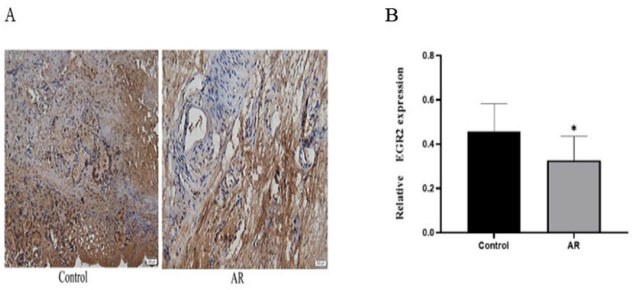

Figure 4. Immunohistochemical staining to detect EGR2 expression in the control and AR groups. A) brownish yellow indicates the expression level of EGR2; B) quantitative analysis of EGR2 expression level in the two groups. Control: normal group; AR: allergic rhinitis group. *P < 0.05. N = 20 in AR group, N = 10 in control group. Rulers: 200μm.

and EGR2 in the nasal mucosa of clinical specimens. As shown in Figure 3, The expression of miR-150-5p was significantly higher in AR patients than in normal controls, while the expression of EGR2 was significantly lower than in normal controls (P<0.01), implying their possible engagement in the pathogenesis and development of AR.

To elucidate the correlation between EGR2 expression levels and the progression of AR disease

To further investigate the effect of miR-150-5p-mediated EGR2 on the pathogenesis of AR and the relationship between EGR2 and AR disease development, firstly, the expression level of EGR2 in the AR group was found to be lower than that in the control group by immunohistochemical staining (Figure 4); secondly, it was further found by fluorescence immunohistochemistry that EGR2 was localized in the cytoplasm, and the expression level of EGR2 in the AR group was also lower than that in the control group (Figure 5). Finally, it is clear from the above experiments that miR-150-5p mediates the negative regulation of EGR2 and DCs in AR, which in turn affects T cell differentiation and EGR2 expression levels negatively correlate with the development of AR disease.

Discussion

Our former work has demonstrated that MiR-150-5p is uplifted in peripheral blood DCs from patients with CRS and that EGR2 down regulates this expression through DC-Th axis expression [17]. In this study, we hypothesized that the development of AR is associated with changes in the expression of miR-150-5p and EGR2. We provide several lines of evidence to support our findings that miR-150-5p and its identified target EGR2 play an important role in the development of AR. First, we observed and validated the fact that miR-150-5p expression is upregulated in DCs from peripheral blood of AR patients, based on qRT-PCR, and that miR-150-5p does not affect DC maturation. Secondly, by ELISA, we identified the regulatory role of miR-150-5p in DCs from AR patients and determined that EGR2 negatively regulates miR-150-5p to regulate DC function and affect T cell differentiation. Thirdly, in previous studies we have identified EGR2 as a target gene of miR-150-5p by bioinformatics analysis, Western blot analysis and luciferase reporter gene analysis.

We have observed that miR-150-5p expression is upregulated in the peripheral blood of AR patients (Figure 3A). Consequently, we hypothesized that AR development is associated with miR-150-5p. There are many mechanisms regarding the development of AR. Previous studies have endeavoured to further clarify the pathogenesis of AR. It has been shown that miRNAs can be involved in and shape the inflammatory pattern of AR patients [18]; it has also been shown that miRNAs can act as major post-transcriptional regulators in the control of most cellular processes, and since a single miRNA can target multiple mRNAs, often dysregulation of miRNA expression in the same pathway may alter specific cellular responses and lead to the development of various diseases [19]. miR-150-5p is a primary modulator of the evolution and polarization of various immune cells and is widely engaged in coordinating inflammatory responses [20]. Thus, miR-150 is also involved in regulating the differentiation and immune response of B cells, T cells and NK/iNKT cells [21]. DCs are antigen-presenting cells and key players in the initiation and regulation of the immune response [22]. miRNAs regulate the development and function of DCs; miR-150 regulates the immune inflammatory response of DCs.

Our study also found that the expression level of EGR2 was lower in the AR group than in the control group (Figure 3B). As shown in the figure, we found a negative regulatory role for EGR2 with miR-150-5p in AR, which plays an important role in T cell differentiation through regulation of DCs and induces naive T cell polarisation through DCs. As upregulation of miR-150-5p expression promotes the production of pro-inflammatory cytokines (IL-6, IL-17, IL-1β and TNF-α) [23]. Decreased cytokine secretion by Th1 cells and increased cytokine secretion by Th2 cells are the main mechanisms leading to AR, and an imbalance

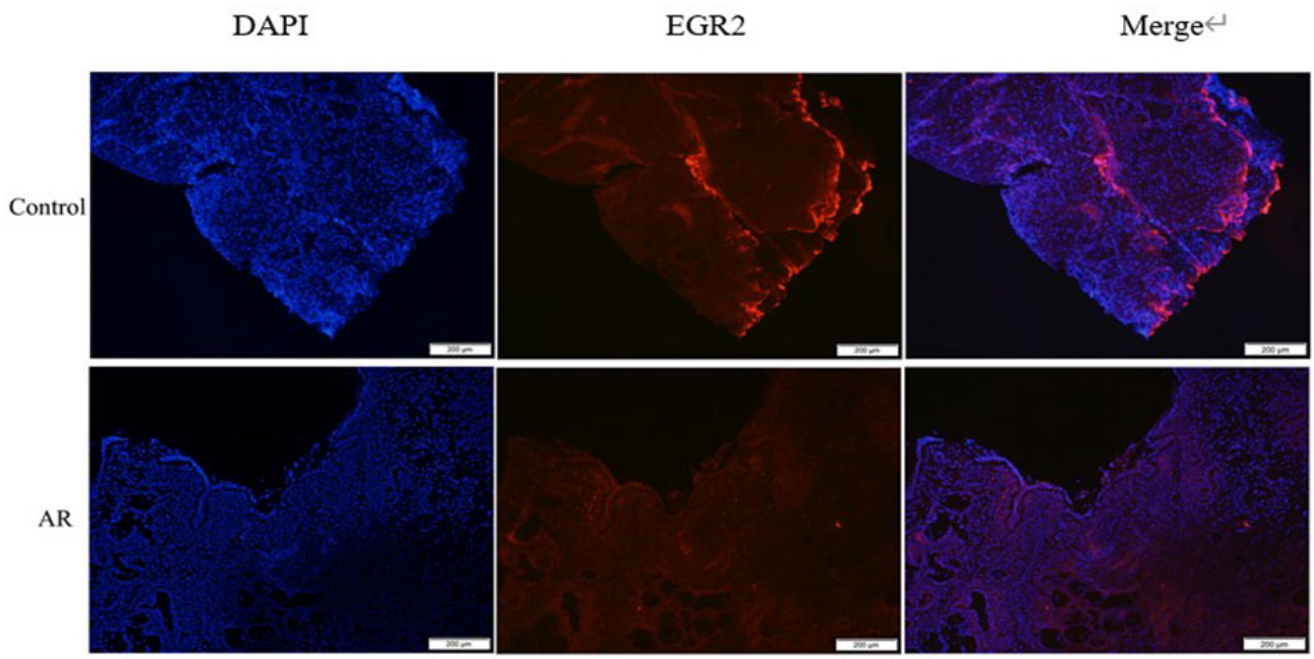

Figure 5. Fluorescent immunohistochemical staining to detect EGR2 expression in the control and AR groups. Blue: nucleus; red: EGR2. Control: normal group; AR: allergic rhinitis group. N = 20 in AR group, N = 10 in control group. Rulers: 200μm.

between helper T cells (Th17) and regulatory T cells (Treg) is also involved in the pathogenesis of AR (24). Naive helper T cells can differentiate into at least four major subpopulations, including Th 1, Th 2, Treg and Th17, and they are involved in enhancing the clearance of certain intracellular pathogens [25]. DCs play a key role in the control of helper T cell 2 (Th2) cell-dependent disease [26]. Our previous databases also suggest that EGR2 is a target gene of miR-150-5p and may be involved in the development of AR.

Our previous experiments have demonstrated that EGR2 is a physiological target of miR-150-5p and that it reduces EGR2 expression levels at post-transcriptional levels in CRS patients [17]. We therefore hypothesized that EGR2 expression may be associated with allergic disease; EGR2 may negatively regulate DC function by regulating miR-150-5p, which in turn affects T cell function. We chose EGR2 as the target gene of miR-150-5p because protein blotting experiments revealed changes in the expression of EGR2, whereas the expression of other candidates (ATP6V1H, ELOVL3 and TADA 1) was not altered. The above studies suggest that up-regulated miR-150-5p can down-regulate EGR2 and further affect DC. Recent studies have found that EGR2 can act as a biomarker and link T cell activation to deleterious immune inflammatory signals [27]. It is a highly protected zinc finger transcription factor and is part of the multigene EGR family, which plays a critical role in the regulation of monocyte/macrophage destiny polarisation and proliferation [28]. Furthermore, our preliminary study predicted EGR2 to be a specific target gene of miR-150-5p by bioinformatic analysis. EGR2 promotes adaptive immune responses while controlling inflammation and preventing the development of autoimmune diseases and is important for maintaining T-cell immune function [29]. We investigated the biological effects and potential mechanisms of miR-150-5p and EGR2 in AR by examining the expression of miR-150-5p as well as EGR2 in AR patients. miR-150-5p was upregulated in AR patients compared to levels in controls (Figure 3A).

Our previous study by gene chip screening that EGR2 is expressed in AR, and the relationship that EGR2 is the target gene of miR-150-5p has been verified by dual luciferase reporter gene assay and protein blotting experiments. Meanwhile, IL-4 is the predominant cytokine in Th2 cells and drives the production of other pro-allergic cytokines (e.g., IL-13 and IL-2) by Th5 cells in allergic diseases. IL-4 also promotes the development of mDCs and is involved in the migration of Th2 cells and eosinophils to sites of inflammation. In addition, IL-4 activates B cells to synthesise IgE and induces proliferation of cup cells, triggering airway hyperresponsiveness and mucus hypersecretion. Therefore, we measured the expression levels of IL-4 in the peripheral blood of patients in the control and AR groups by ELISA (Figure 1). The results showed that the expression level of IL-4 in the AR group was higher than that in the control group. From Figure 2, the mucous membrane of the turbinate was swollen and eosinophil infiltration was evident in the AR group, while no mucous membrane swelling and eosinophil infiltration were evident in the control group. These results may tentatively indicate that miR-150-5p-mediated EGR2 promotes the infiltration of immune

cells in the nasal mucosa of AR patients. As shown in Figure 4A, preliminary immunohistochemical staining revealed that EGR2 was expressed in both the AR and control groups, and further quantitative analysis revealed that the expression level of EGR2 was lower than that of the control group (Figure 4B); in addition, fluorescence immunohistochemistry revealed that EGR2 was localized in the cytoplasm, and the expression level of EGR2 in the AR group was also lower than that of the control group (Figure 5). From the above experiments, it was initially clear that miR-150-5p mediated the negative regulation of EGR2 with DCs in AR, which in turn affected T cell differentiation and EGR2 expression levels negatively correlated with the development of AR disease. This suggests that when the expression of miR-150-5p is upregulated it will downregulate the expression level of EGR2, which in turn affects the function of DCs, thus affecting the differentiation of naive T cells to Th2 cells, leading to an imbalance in the balance between Th1 and Th2, which in turn is involved in the development of AR. EGR2 is essential for the preservation of T cell homeostasis and its control of the development of autoimmune diseases [30].

At present, further clarification of the mechanisms regulating the allergic response to AR is needed as the pathogenesis of AR remains controversial; hence, extra studies are needed to define the most appropriate targeted AR treatment strategies. The following questions can be further addressed based on our findings. Are there differentially expressed common and specific miRNAs in the nasal sinus mucosa and peripheral blood of AR patients, and can AR be prevented and treated by intervention of differential miRNA expression in the DC-Th axis? Based on the above discussion, our results suggest that miR-150-5p is upregulated in DCs from AR patients and that this expression is downregulated via the DC-Th axis via EGR2 expression, which may provide a new treatment option for AR therapy.

Conclusion

The present study suggests that as miR-150-5p overexpression significantly reduces the expression of EGR2, it may lead to the influence of EGR2 on the differentiation of Th0 cells to Th2 cells, resulting in a Th1/Th2 imbalance, which may in turn lead to an increase in the secretion of Th2 cytokines (e.g.IL-4, IL-5, IL-13, etc.), which is involved in the development of AR. Our findings provide potential new biomarkers and therapeutic targets for the treatment of AR and point to potential directions for future research. The main limitation of this study is that the function of EGR2 in DCs is still unclear, and the role and impact of EGR2 in the regulation of DCs needs to be further investigated.

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Authorship contribution

HF and LZ were mainly responsible for specimen collection; HJ and XL were mainly responsible for completing the relevant experimental content; ZM mainly provided theoretical knowledge and technical guidance.

Conflict of interest

All authors declare no conflict of interest.

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References

1. Bousquet J, Anto JM, Bachert C, et al. Allergic rhinitis. Nat Rev Dis Primers. 2020;6(1): 95.
2. Gani F, Cottini M, Landi M, et al. Allergic rhinitis and COVID-19: friends or foes? Eur Ann Allergy Clin Immunol. 2022;54(2): 53-59.
3. Tugrul S, Senturk E, Dogan R, et al. Effect of allergic rhinitis on the outcomes of diode laser dacryocystorhinostomy. Am J Otolaryngol. 2021;42(6): 103127.
4. Bernstein DI, Schwartz G, Bernstein JA. Allergic rhinitis: mechanisms and treatment. Immunol Allergy Clin North Am. 2016;36(2): 261-278.
5. Zhu Y, Liu Y, Zhu X, et al. Upregulation of miR-155 regulates group 2 innate lymphoid cells by targeting c-maf in allergic rhinitis. Eur J Pharmacol. 2020;887: 173564.
6. Ho PTB, Clark IM, Le LTT. MicroRNA-Based diagnosis and therapy. Int J Mol Sci. 2022;23(13):7167.
7. Li Y, Yu J, Wang F, et al. MiR-150-5p regulate T cell activation in severe aplastic anemia by targeting Bach2. Cell Tissue Res. 2021;384(2): 423-434.
8. Ma ZX, Tan X, Shen Y, et al. MicroRNA expression profile of mature dendritic cell in chronic rhinosinusitis. Inflamm Res. 2015;64(11): 885-893.
9. O'donovan KJ, Tourtellotte WG, Millbrandt J, et al. The EGR family of transcription-regulatory factors: progress at the interface of molecular and systems neuroscience. Trends Neurosci. 1999;22(4): 167-173.
10. Lawson VJ, Weston K, Maurice D. Early growth response 2 regulates the survival of thymocytes during positive selection. Eur J Immunol. 2010;40(1): 232-241.
11. Li S, Symonds AL, Zhu B, et al. Early growth response gene-2 (Egr-2) regulates the development of B and T cells. PLoS One. 2011;6(4): e18498.
12. Miao T, Raymond M, Bhullar P, et al. Early growth response gene-2 controls IL-17 expression and Th17 differentiation by negatively regulating Batf. J Immunol. 2013;190(1): 58-65.
13. Collin M, Bigley V. Human dendritic cell subsets: an update. Immunology. 2018;154(1): 3-20.

14. Patente TA, Pinho MP, Oliveira AA, et al. Human dendritic cells: their heterogeneity and clinical application potential in cancer immunotherapy. Front Immunol. 2018;9: 3176.
15. Liu H, Xia J, Chen Y, et al. Immunosuppressive regulation of dendritic cells and T Cells in allergic rhinitis by semaphorin 3A. Am J Rhinol Allergy. 2021;35(6): 846-853.
16. Peng YQ, Chen DH, Xu ZB, et al. IL-33 receptor expression on myeloid and plasmacytoid dendritic cells after allergen challenge in patients with allergic rhinitis. Int Immunopharmacol. 2021;101(Pt B): 108233.
17. Ma Z, Shen Y, Zeng Q, et al. MiR-150-5p regulates EGR2 to promote the development of chronic rhinosinusitis via the DC-Th axis. Int Immunopharmacol. 2018;54: 188-197.
18. Zhang XH, Zhang YN, Liu Z. MicroRNA in chronic rhinosinusitis and allergic rhinitis. Curr Allergy Asthma Rep. 2014;14(2): 415.
19. Weidner J, Bartel S, Kilic A, et al. Spotlight on microRNAs in allergy and asthma. Allergy. 2021;76(6): 1661-1678.
20. Zhuang Y, Peng H, Mastej V, et al. MicroRNA regulation of endothelial junction proteins and clinical consequence. Mediators Inflamm. 2016;2016: 5078627.
21. Huang X L, Zhang L, Li JP, et al. MicroRNA-150: A potential regulator in pathogens infection and autoimmune diseases. Autoimmunity. 2015;48(8): 503-510.
22. Zhu J, Yao K, Guo J, et al. miR-181a and miR-150 regulate dendritic cell immune inflammatory responses and cardiomyocyte apoptosis via targeting JAK1-STAT1/c-Fos pathway. J Cell Mol Med. 2017;21(11): 2884-2895.
23. Jiang H, Zhu M, Wang H, et al. Suppression of lncRNA MALAT1 reduces pro-inflammatory cytokines production by regulating miR-150-5p/ZBTB4 axis through JAK/STAT signal pathway in systemic juvenile idiopathic arthritis. Cytokine. 2021;138: 155397.
24. Wei P, Hu GH, Kang HY, et al. An aryl hydrocarbon receptor ligand acts on dendritic cells and T cells to suppress the Th17 response in allergic rhinitis patients. Lab Invest. 2014;94(5): 528-535.
25. Read KA, Powell MD, Sreekumar BK, et al. In vitro differentiation of effector CD4(+) T helper cell subsets. Methods Mol Biol. 2019;1960: 75-84.
26. Han M, Ma J, Ouyang S, et al. The kinase p38alpha functions in dendritic cells to regulate Th2-cell differentiation and allergic inflammation. Cell Mol Immunol. 2022;19(7): 805-819.
27. Jung IY, Bartoszek RL, Rech AJ, et al. Type I interferon signaling via the EGR2 transcriptional regulator potentiates CAR T cell-intrinsic dysfunction. Cancer Discov. 2023; 13(7):1636-1655.
28. Doncel-Perez E, Mateos-Hernandez L, Pareja E, et al. Expression of Early Growth Response Gene-2 and regulated cytokines correlates with recovery from Guillain-Barre Syndrome. J Immunol. 2016;196(3): 1102-1107.
29. Taefehshokr N, Miao T, Symonds ALJ, et al. Egr2 regulation in T cells is mediated through IFNgamma/STAT1 and IL-6/STAT3 signalling pathway. Pathol Res Pract. 2020; 216(12): 153259.
30. Kim TD, Jung HR, Seo SH, et al. MicroRNA-150 modulates intracellular Ca (2+) levels in naive CD8(+) T cells by targeting TMEM20. Sci Rep. 2017;7(1): 2623.

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