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lnc-THRIL and miR-125b relate to disease risk, severity, and imbalance of Th1 cells/Th2 cells in allergic rhinitis

Ji Song[a], Dan Liu[b]*, Weizhi Yin[b]*

[a]*Department of Otorhinolaryngology, The University-Town Hospital of Chongqing Medical University, Chongqing, China*
[b]*Department of Otorhinolaryngology, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, Huangshi, China*

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Abstract
Objective: Tumor necrosis factor and HNRNPL-related immunoregulatory long noncoding RNA (lnc-THRIL) and its target microRNA (miR)-125b are reported to regulate immune response through several means by participating in allergic rhinitis (AR) pathology. This study aimed to investigate the role of lnc-THRIL and miR-125b in detecting AR risk, and to further explore their correlation with disease severity and cytokines released from T helper type (Th) 1 and Th2 in AR patients.
Methods: A total of 160 AR patients and 80 subjects with severe snoring symptoms (as controls) were recruited. Nasal mucosa samples were collected to measure the expressions of lnc-THRIL, miR-125b, and Th1 and Th2 cytokines by reverse transcription quantitative polymerase chain reaction.
Results: The expression of lnc-THRIL decreased while that of miR-125b increased in AR patients when compared with that of controls, and further receiver operating characteristic curve showed that both could well distinguish AR patients from controls. Furthermore, lnc-THRIL negatively correlated with miR-125b in AR patients. lnc-THRIL was negatively correlated with Individual Nasal Symptom Score (INSS) (including nasal rhinorrhea score, sneezing score, and congestion score) and Total Nasal Symptom Score (TNSS), and miR-125b was positively associated with INSS (including itching score, sneezing score, and congestion score) and TNSS. Moreover, lnc-THRIL was correlated with increased Th1 cytokines (interferon-gamma (IFN-γ) and interleukin (IL)-2) but with decreased Th2 cytokines (IL-4 and IL-10), while miR-125b exhibited opposite trends in AR patients.
Conclusion: lnc-THRIL and its target (miR-125b) relate to disease risk, symptom severity, and Th1/Th2 imbalance of AR, suggesting their potential as biomarkers for AR management.

***Corresponding authors:** Dan Liu, Weizhi Yin, Department of Otorhinolaryngology, Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Edong Healthcare Group, No. 141 Tianjin Road, Huangshigang District, Huangshi 435000, Hubei, China. *Email addresses*: dangri4870608@163.com; zhiqian488860@163.com

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Introduction

Chronic rhinitis is a common respiratory disease featured by nasal symptoms (rhinorrhea, nasal obstruction, sneezing) as well as itching.[1,2] The most common type of chronic rhinitis is allergic rhinitis (AR), which is an allergic disease of the nasal mucosa (NM) formed by a reaction mediated by type-I immunoglobulin E (IgE) after encountering allergens.[3,4] Even though it is not a serious illness, AR can lead to several complications (for instance, it is a major risk factor for poor control of asthma), which affect the quality of life and productivity at work or school.[5] Hence, AR management is important, and investigation of the potential biomarkers for AR is helpful.

Tumor necrosis factor and HNRNPL-related immunoregulatory long noncoding RNA (lnc-THRIL) were firstly reported in 2014 with a length of approximately 2 kb, which is required for the expression of a wide variety of cytokines, especially TNF-α, by interacting with hnRNPL to form a functional complex that binds to the promoter of target genes in human macrophages.[6,7] lnc-THRIL has been reported to mediate immunity or inflammation by regulating multiple pathways, including activating the phosphoinositol 3 kinase/protein kinase (PI3K/AKT) signaling pathway in rheumatoid arthritis (RA),[8] "sponging" the microRNA (miR)-424/ROCK2 axis in sepsis-induced acute lung injury, and regulating nuclear factor-kappa B (NF-κB) p65 signaling in cerebral ischemia–reperfusion injury.[9] lnc-THRIL exerts a regulatory role in lipopolysaccharide-induced inflammatory injury through direct sponging of miR-125b.[10] Also, lnc-THRIL and miR-125b have important roles in signal transduction by toll-like receptors (TLRs). TLR activation is involved in stimulation of immunity and inflammatory response.[11,12] A persistent inflammatory response within the respiratory tract is closely involved with AR pathogenesis.[13] miR-125b has been reported to regulate autophagy as well as the epithelial barrier in AR, and acts as a biomarker in AR patients.[14,15] It has been hypothesized that lnc-THRIL and miR-125b might be of clinical value in AR patients.

We investigated the correlation of expression of lnc-THRIL and miR-125b with AR risk. Furthermore, we explored their association with disease severity and the cytokines released by T helper type 1 (Th1) and Th2 cells in AR patients.

Materials and Methods

Ethical approval of the study protocol

The study protocol was approved by the Ethics Review Board of The University Town Hospital, Chongqing Medical University. Written informed consent was obtained from all participants.

Inclusion and exclusion criteria

The criteria for AR patients were: (1) age > 18 years; (2) diagnosed as having AR in reference to the guidelines for the diagnosis and management of allergic and nonallergic rhinitis set by the British Society for Allergy and Clinical Immunology[16]; (3) agreed to collection of their NM tissues.

The exclusion criteria for AR patients were: (1) AR complicated with chronic rhinosinusitis, bronchial asthma, nasal polyposis, or nasal abnormalities; (2) history of severe respiratory disease; (3) currently suffering from a severe infection; (4) had a solid tumor, hematological malignancy, or autoimmune disease; (5) current smoker.

The eligible criteria for healthy controls (HCs) were: (1) no history of AR, asthma, or other allergic diseases; (2) no history of severe respiratory diseases, inflammatory diseases, severe infections, autoimmune diseases, or solid tumors; (3) not suffering from allergic symptoms; (4) willing to provide NM samples.

Participants

Between March 2019 and October 2020, we recruited 160 AR consecutive patients admitted to our hospital. In addition, 80 people suffering from severe snoring were enrolled as HCs.

Collection of data and samples

After recruitment, the demographic information of all participants was documented. For AR patients, the severity of rhinitis symptoms was evaluated using the Individual Nasal Symptom Score (INSS) and Total Nasal Symptom Score (TNSS), as described previously.[17] NM samples were collected under local anesthesia. The serum level of IgE antibodies was measured routinely by enzyme-linked immunosorbent assays in our hospital. Expression of lnc-THRIL and miR-125b in NM samples was measured by real-time reverse-transcription quantitative polymerase chain reaction (RT-qPCR). Besides, levels of Th1 cell–associated cytokines (interferon-γ, interleukin [IL]-2), as well as levels of Th2 cell–associated cytokines (IL-4, IL-10), were also quantified by RT-qPCR.

RT-qPCR

After collection of NM samples, expression of lnc-THRIL, miR-125b, interferon-γ, IL-2, IL-4, and IL-10 was determined by RT-qPCR. Total RNA was extracted from NM samples using RNeasy Protect Mini Kit (Qiagen, Hilden, Germany) and then reverse-transcribed using the PrimeScript™ RT kit (Perfect Real Time; Takara Biotechnology, Shiga, Japan). Subsequently, qPCR was conducted using KOD SYBR® qPCR Mix (Toyobo, Osaka, Japan) to quantify expression of lnc-THRIL, miR-125b, interferon-γ, IL-2, IL-4, and IL-10. In addition, expression of lnc-THRIL, miR-125b, interferon-γ, IL-2, IL-4, and IL-10 was calculated using the $2^{-\Delta\Delta Ct}$ method. Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an internal reference for lncRNA and mRNA, and U6 for miRNA. The primer sequences used in RT-qPCR were listed in Supplementary Table 1.

Statistical analyses

Comparisons were made using the Student's t-test, chi-square test, and Mann–Whitney U-test. Analyses of receiver operating characteristic (ROC) curves were applied to

Table 1 Clinical characteristics.

Items	Controls (N = 80)	AR patients (N = 160)	P
Age (years), mean ± SD	29.6 ± 8.0	29.3 ± 7.1	0.762
Gender, No. (%)			0.645
Male	47 (58.7)	89 (55.6)	
Female	33 (41.3)	71 (44.4)	
Serum IgE (IU/mL), median (IQR)	22.3 (15.8-33.2)	313.8 (172.3-496.4)	<0.001
IFN-γ mRNA, median (IQR)	0.985 (0.640-1.460)	0.475 (0.270-0.668)	<0.001
IL-2 mRNA, median (IQR)	1.000 (0.583-1.330)	0.355 (0.240-0.590)	<0.001
IL-4 mRNA, median (IQR)	0.995 (0.475-1.638)	3.005 (2.053-4.328)	<0.001
IL-10 mRNA, median (IQR)	1.000 (0.618-1.470)	3.195 (1.960-4.388)	<0.001
INSS, mean ± SD			
Nasal rhinorrhea score		1.8 ± 0.9	
Itching score		1.9 ± 0.8	
Sneezing score		2.0 ± 0.9	
Congestion score		1.9 ± 0.9	
TNSS, mean ± SD		7.6 ± 1.8	

AR: Allergic rhinitis; IFN-γ: Interferon-gamma; IgE: Immunoglobulin E; IL-2: Interleukin 2; IL-4: Interleukin 4; IL-10: Interleukin 10; INSS: Individual nasal symptom score; IQR: Interquartile range; SD: Standard deviation; TNSS: Total nasal symptom score

estimate the ability of expression of lnc-THRIL and miR-125b to identify different participants. Correlations of two variables were evaluated by Spearman's rank correlation test. SPSS 24.0 (IBM, Armonk, NY, USA) and Prism 6.01 (GraphPad, San Diego, CA, USA) were used, respectively, to complete statistical analyses and graph plotting. $P < 0.05$ was considered significant.

Results

Clinical characterics of AR patients and HCs

The mean age of AR patients and HCs was 29.3 ± 7.1 years and 29.6 ± 8.0 years, respectively. Of the AR patients, 89 (55.6%) were males and 71 (44.4%) were females. Of the HCs, 47 (58.7%) were males and 33 (41.3%) were females. There was no significant difference in age ($P = 0.762$) or sex ($P = 0.645$) between AR patients and HCs. However, increased serum levels of IgE (313.8 [172.3-496.4] IU/mL vs 22.3 [15.8-33.2] IU/mL, $P < 0.001$), IL-4 (3.005 [2.053-4.328] vs 0.995 [0.475-1.638], $P < 0.001$), and IL-10 (3.195 [1.960-4.388] vs 1.000 [0.618-1.470], $P < 0.001$), and decreased serum levels of interferon-γ (0.475 [0.270-0.668] vs 0.985 [0.640-1.460], $P < 0.001$) and IL-2 (0.355 [0.240-0.590] vs 1.000 [0.583-1.330], $P < 0.001$), were observed in AR patients compared with those in HCs. For AR patients only, the scores for nasal rhinorrhea, itching, sneezing, and congestion were 1.8 ± 0.9, 1.9 ± 0.8, 2.0 ± 0.9, and 1.9 ± 0.9, respectively. Meanwhile, the TNSS score was 7.6 ± 1.8. The detailed information of patient characteristics is shown in Table 1.

Expression of lnc-THRIL and miR-125b

lnc-THRIL expression was decreased in AR patients compared with that in HCs (0.390 [0.190-0.638] vs 0.975 [0.633-1.433], $P < 0.001$) (Figure 1A). Analyses of ROC curves showed that lnc-THRIL expression could be used to distinguish AR patients from HCs (area under the ROC curve [AUC]: 0.847; 95% CI: 0.797-0.897) (Figure 1B). miR-125b expression was increased in AR patients compared with that in HCs (2.910 [1.823-4.303] vs 0.935 [0.620-1.375], $P < 0.001$) (Figure 1C). Analyses of ROC curves showed that miR-125b expression could be used to distinguish AR patients from HCs (AUC: 0.912; 95% CI: 0.877-0.947 [Figure 1D]). lnc-THRIL expression was negatively correlated with miR-125b expression in AR patients ($r = -0.561$, $P < 0.001$) (Figure 2).

Correlation of expression of lnc-THRIL and miR-125b with disease severity in AR patients

lnc-THRIL expression was negatively correlated with scores for nasal rhinorrhea ($r = -0.210$, $P = 0.008$) (Figure 3A), sneezing ($r = -0.173$, $P = 0.029$) (Figure 3C), congestion ($r = -0.232$, $P = 0.003$) (Figure 3D), as well as the TNSS ($r = -0.362$, $P < 0.001$) (Figure 3E), but was not correlated with the itching score ($r = -0.147$, $P = 0.064$) (Figure 3B). miR-125b expression was positively correlated with the scores for itching ($r = 0.169$, $P = 0.033$) (Figure 3G), sneezing ($r = 0.167$, $P = 0.035$) (Figure 3H), congestion ($r = 0.226$, $P = 0.004$) (Figure 3I), as well as the TNSS ($r = 0.352$, $P < 0.001$) (Figure 3J), but was not correlated with the nasal rhinorrhea score ($r = 0.139$, $P = 0.080$) (Figure 3F).

Correlation of expression of lnc-THRIL and miR-125b with Th1 cell- and Th2 cell-associated cytokines in AR patients

lnc-THRIL expression was positively correlated with expression of interferon-γ ($P < 0.001$) (Figure 4A) and IL-2 ($P < 0.001$) (Figure 4B). miR-125b expression was negatively correlated with expression of interferon-γ ($P < 0.001$) (Figure 4C) and IL-2 ($P < 0.001$) (Figure 4D). lnc-THRIL expression

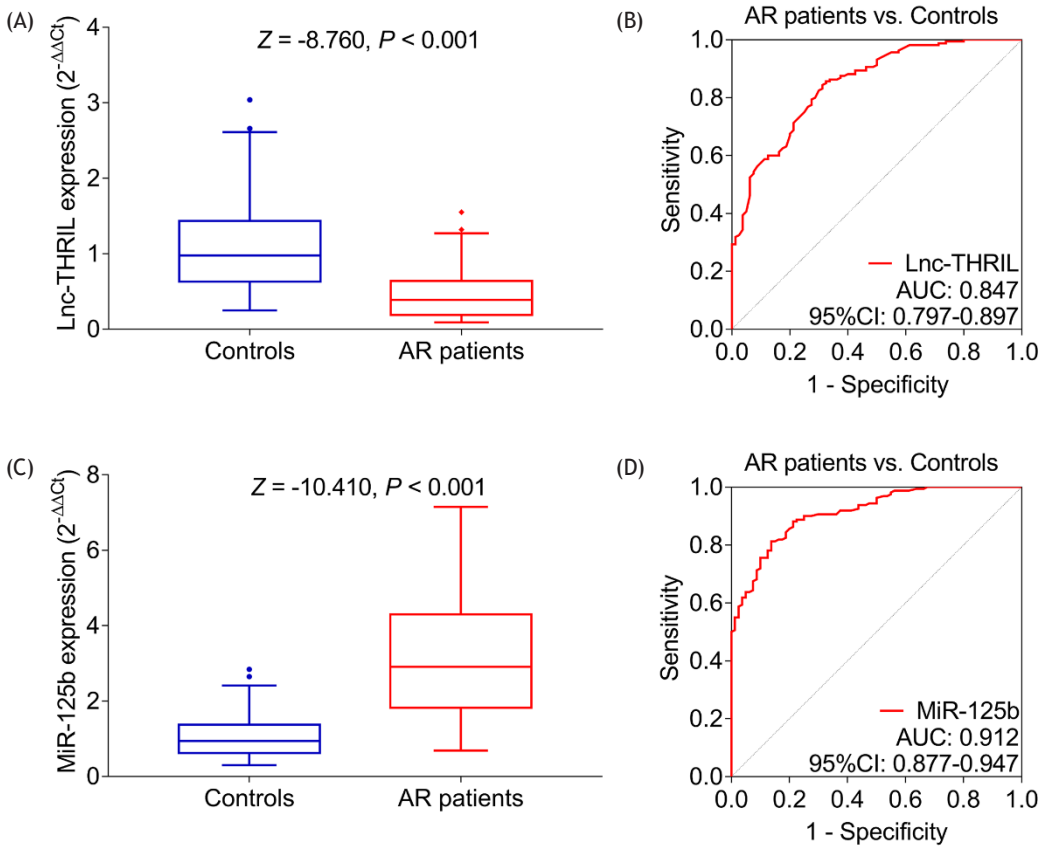

Figure 1 Correlation of expression of lnc-THRIL and miR-125b with AR risk. Comparison of lnc-THRIL expression between AR patients and healthy controls (A). Use of lnc-THRIL expression to distinguish AR patients from healthy controls (B). Comparison of miR-125b expression between AR patients and healthy controls (C). Use of miR-125b expression to differentiate AR patients from healthy controls (D). lnc-THRIL, tumor necrosis factor, and HNRNPL-related immunoregulatory long noncoding RNA; miR-125b, microRNA 125b; AR, allergic rhinitis.

was negatively correlated with expression of IL-4 ($P < 0.001$) (Figure 5A) and IL-10 ($P < 0.001$) (Figure 5B). miR-125b expression was positively correlated with expression of IL-4 ($P < 0.001$) (Figure 5C) and IL-10 ($P < 0.001$) (Figure 5D).

Discussion

lnc-THRIL was first found to modulate lipopolysaccharide-mediated TNF-α expression. Recent studies have demonstrated the role of lnc-THRIL in regulating physiological and pathological immune and inflammatory processes via various mechanisms.[8-10,18,19] For example, abnormal expression of lnc-THRIL has been observed in blood samples of RA patients compared with that in HCs, and lnc-THRIL regulates cell growth and inflammatory response in fibroblast-like synoviocytes in RA cases by mediating the PI3K/AKT signaling pathway, thereby promoting RA development.[8] Animal studies have indicated that the PI3K/AKT signaling pathway is an important mediator of AR, and that suppression of PI3K/AKT activity in mast cells exhibits an antiallergic function in AR management.[20] Until now, it is hard to illuminate the direct correlation between AR and lnc-THRIL. We speculate that lnc-THRIL might be related to AR due to that: (1) lnc-THRIL regulates the inflammatory response via regulating the PI3K/AKT signaling pathway which has been proved to be an important mediator of AR; (2) lnc-THRIL sponges to miR-125b in the molecular level, while the latter one has been found to serve as a biomarker in several allergic diseases including AR. Thus, lnc-THRIL might be correlated with AR.

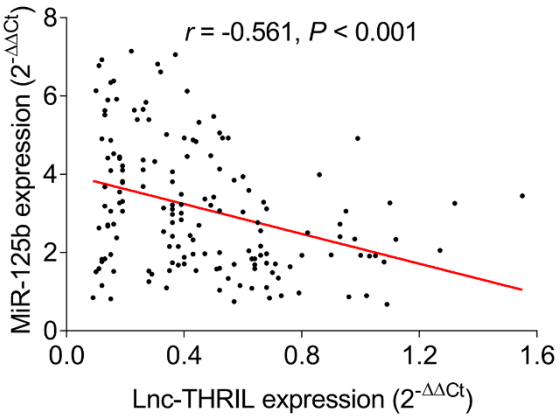

Figure 2 lnc-THRIL expression was negatively correlated with miR-125b expression in AR patients. lnc-THRIL, tumor necrosis factor, and HNRNPL-related immunoregulatory long noncoding RNA; miR-125b, microRNA 125b; AR, allergic rhinitis.

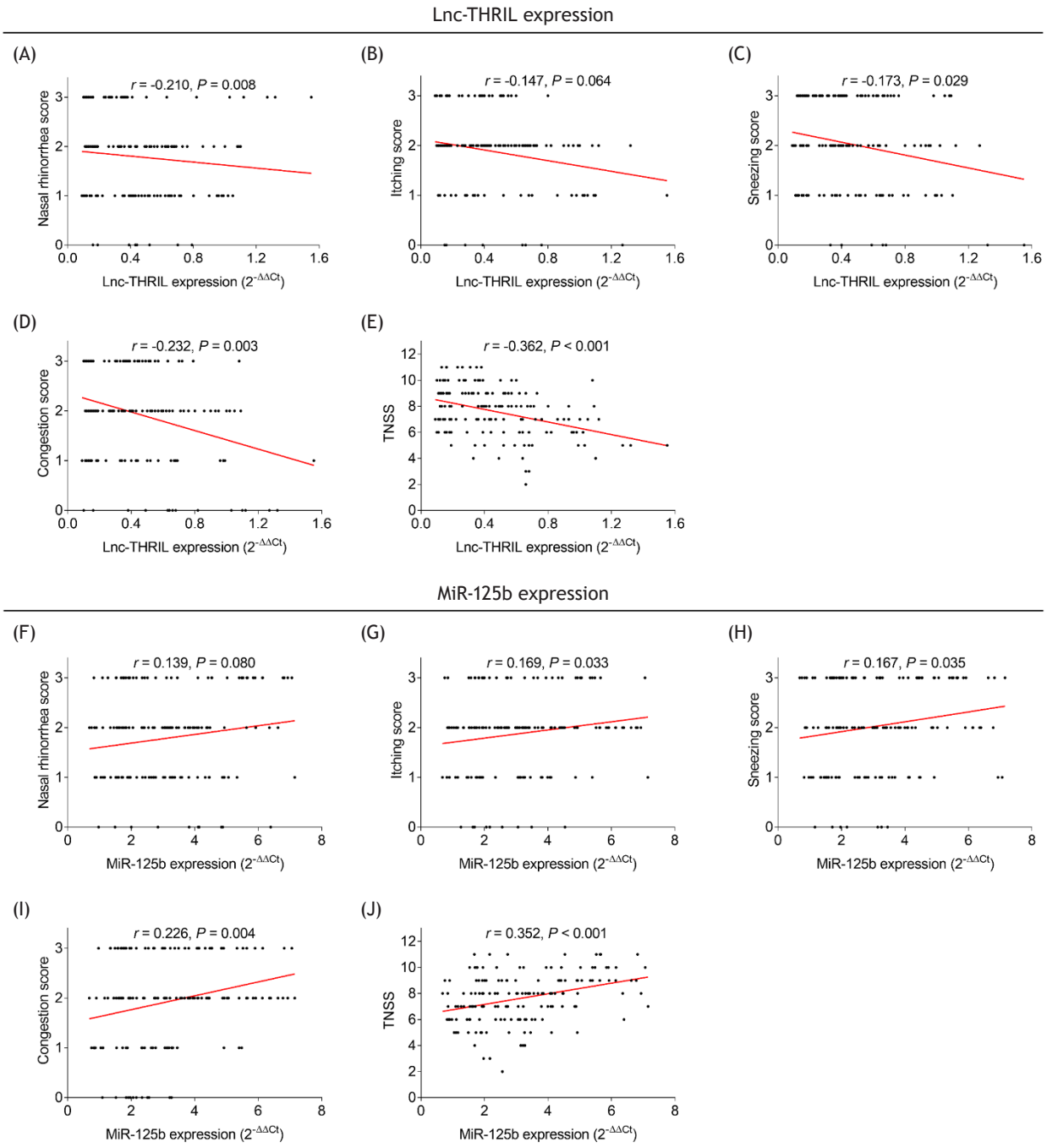

Figure 3 Expression of lnc-THRIL and miR-125b was correlated with disease severity in AR patients. Correlation of lnc-THRIL expression with the nasal rhinorrhea score (A), itching score (B), sneezing score (C), congestion score (D), and TNSS (E). Correlation of miR-125b expression with the (F), itching score (G), sneezing score (H), congestion score (I), and TNSS (J). lnc-THRIL, tumor necrosis factor, and HNRNPL-related immunoregulatory long noncoding RNA; miR-125b, microRNA 125b; AR, allergic rhinitis; TNSS, Total Nasal Symptom Score.

The regulatory role of miR-125b on expression of tight junction–related proteins, autophagy of epithelial cells and, therefore, the function of the nasal epithelial barrier against allergen infiltration in AR pathogenesis, has been revealed.[15] Also, the potential value of miR-125b as a biomarker has been found in several allergic diseases, including AR and asthma.[21] We speculated that lnc-THRIL expression might be correlated with miR-125b expression in AR patients, and that both of them might be of clinical value in AR management.

lnc-THRIL expression was downregulated in AR patients compared with that in HCs. miR-125b expression was upregulated in AR patients compared with that in HCs. Expression of lnc-THRIL and miR-125b was helpful for distinguishing AR patients from HCs, which suggested that lnc-THRIL and miR-125b had a close association with AR risk. There are

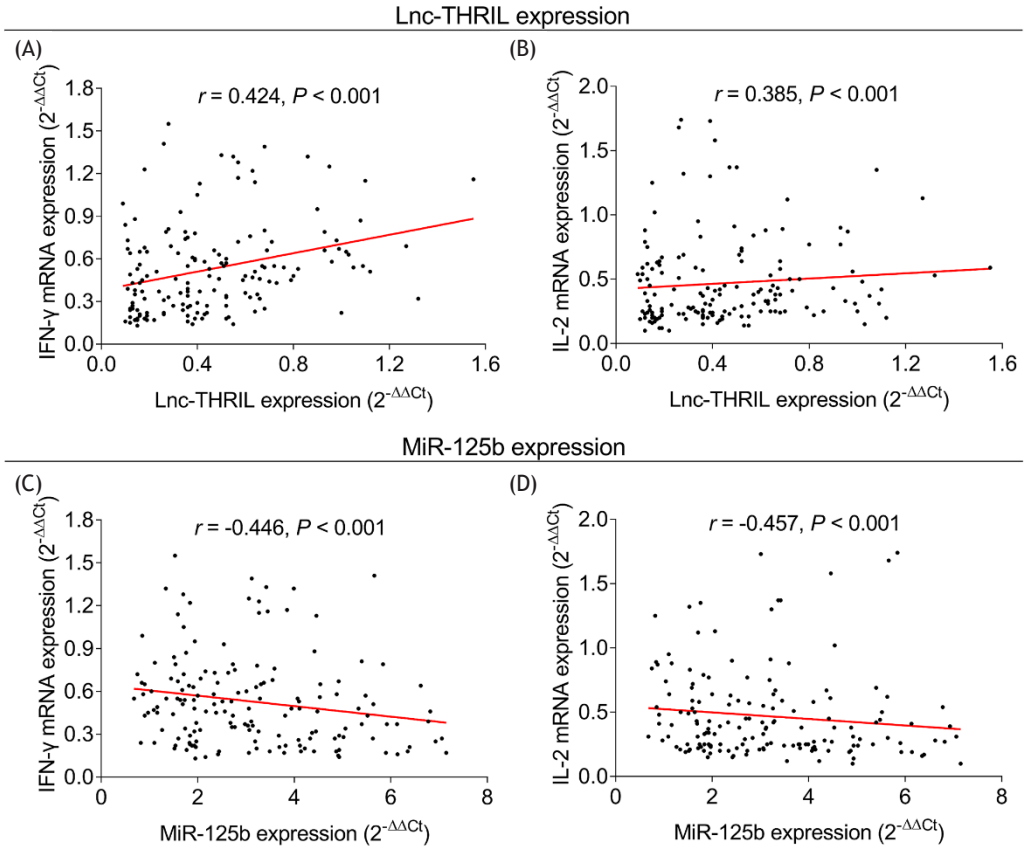

Figure 4 Expression of lnc-THRIL and miR-125b was correlated with release of Th1 cell-based cytokines in AR patients. Correlation of lnc-THRIL expression with levels of interferon-γ (A) and IL-2 (B) in AR patients. Correlation of miR-125b expression with expression of interferon-γ (C) and IL-2 (D) in AR patients. lnc-THRIL, tumor necrosis factor, and HNRNPL-related immunoregulatory long noncoding RNA; miR-125b, microRNA 125b; AR, allergic rhinitis; Th1, T helper type 1; Th2, T helper type 2; IFN-γ, interferon-gamma; IL-2, interleukin 2; IL-10, interleukin 10.

two main reasons for these findings. First, studies have suggested that lnc-THRIL might have an inhibitory role in regulating TLR signaling. lnc-THRIL has been shown to be involved in an imbalance between the number of Th1 and Th2 cells, and to result in a reduced risk of AR occurrence.[11,22] Thus, lnc-THRIL expression was downregulated in AR patients compared with that in HCs and could be used to predict AR risk. Second, miR-125b might promote allergen-induced autophagy via interaction with C-X-C motif chemokine receptor type (CXCR)4 and Forkhead box protein P3 in nasal epithelial cells, thereby leading to dysfunction of the epithelial barrier and increased AR risk.[15] Based on these speculations, we conducted further analyses to explore the correlation between lnc-THRIL and miR-125b: lnc-THRIL was negatively associated with miR-125b in AR patients.

We wished to further investigate the clinical implications of lnc-THRIL and miR-125b in AR management, so we evaluated their correlation with disease severity. We found that lnc-THRIL expression was negatively associated with the TNSS as well as the scores for nasal rhinorrhea, sneezing, and congestion in AR cases. miR-125b expression was positively correlated with the TNSS as well as the scores for itching, sneezing, and congestion in AR patients. These findings might be explained as follows: First, lnc-THRIL might regulate TLR signaling and provide a shift of the balance in Th1 cells/Th2 cells by enhancing the response of Th1 cells which would lead to alleviation of allergic inflammatory disorders and AR symptoms;[11,22] therefore, lnc-THRIL negatively correlates with the disease severity of AR patients. Second, lnc-THRIL might target miR-125b to inactivate CXCR4. This phenomenon would lead to reduced autophagy and enhance the function of the epithelial barrier, which would alleviate AR severity.[15] Third, Lin et al. suggested an interaction between lnc-THRIL and miR-125b in the inflammatory response.[10] Therefore, lnc-THRIL might mediate production of proinflammatory moieties and reduce the capacity of the immune response to bacterial lipopolysaccharide after exposure to a stimulus by regulating miR-125b expression in macrophages. This action would provide an enhancing effect on inflammatory cascades and promote AR severity.[11] However, the underlying mechanism of lnc-THRIL and miR-125b in AR must be explored more deeply.

We undertook further studies to determine the correlation of expression of lnc-THRIL and miR-125b with cytokines secreted from Th1 and Th2 cells in AR patients. lnc-THRIL was associated with increased expression of Th1 cell-based cytokines and decreased expression of Th2 cell-based cytokines, whereas miR-125b presented the opposite trend. Hence, increased expression of lnc-THRIL, but decreased expression of miR-125b, could restore the balance of Th1

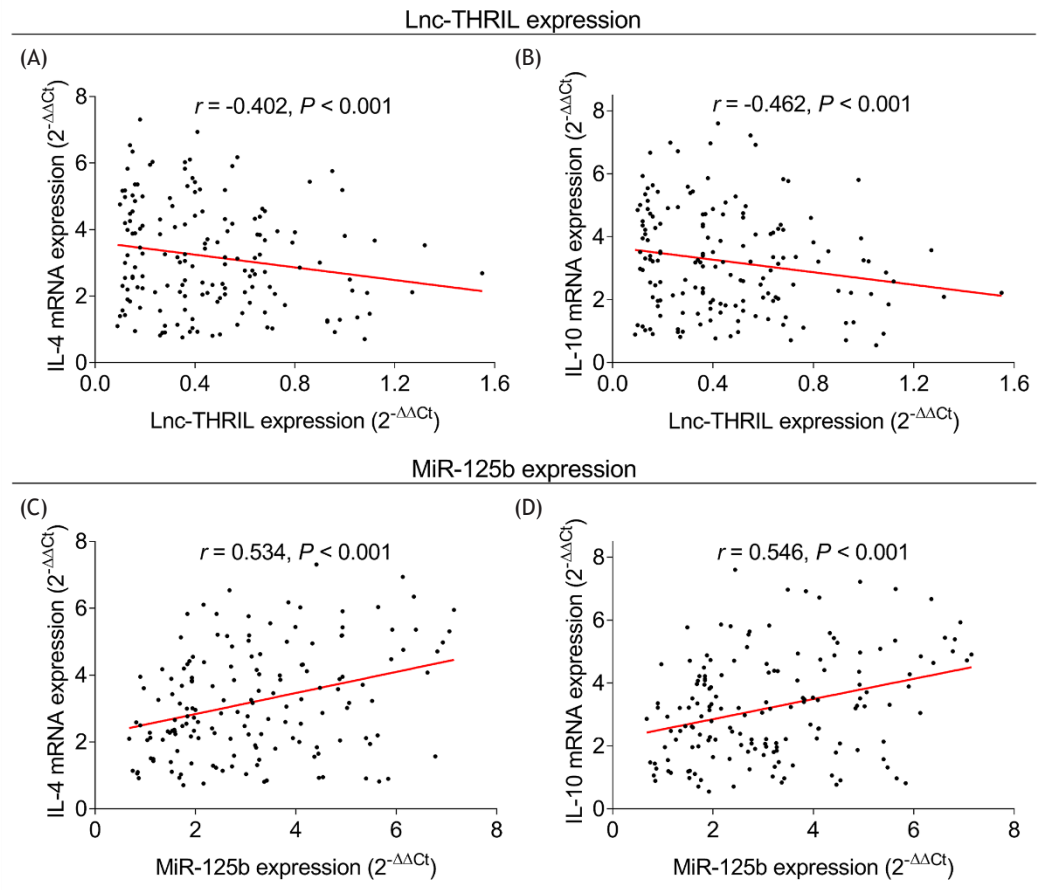

Figure 5 Expression of lnc-THRIL and miR-125b was correlated with release of Th2 cell-based cytokines in AR patients. Correlation of lnc-THRIL expression with levels of IL-4 (A) and IL-10 (B) in AR patients. Correlation of miR-125b expression with levels of IL-4 (C) and IL-10 (D) in AR patients. lnc-THRIL, tumor necrosis factor, and HNRNPL-related immunoregulatory long noncoding RNA; miR-125b, microRNA 125b; AR, allergic rhinitis; Th2, T helper type 2; IL-4, interleukin 4; IL-10, interleukin 10.

cells/Th2 cells in AR patients. There may be two reasons for these observations. First, lnc-THRIL might activate the production of interferon-γ and IL-2 by regulating miR-125b. This action induces the expansion of regulatory T cells and triggers conversion toward a balance of Th1 cells/Th2 cells in AR patients.[21] Second, miR-125b has been reported to be associated with an imbalance in T-regulatory cells/Th17 cells in inflammatory diseases.[23] Therefore, miR-125b might inhibit T-cell differentiation and regulate the production of cytokines from Th2 cells, further impairing that imbalance of Th1 cells/Th2 cells.

Our study had two main limitations. First, it was a single-center study, which may have resulted in a selection bias. Second, the study cohort was small, which diminished the statistical power of our analyses. The underlying molecular mechanisms of lnc-THRIL and miR-125b in AR need further investigation using cellular and animal studies.

Conclusion

lnc-THRIL and its target (miR-125b) correlate with disease risk, symptom severity, and imbalance in Th1 cells/Th2 cells in AR. lnc-THRIL and miR-125b could be biomarkers in AR management.

Acknowledgment

Not applicable.

Conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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Supplementary

Supplementary Table 1 Sequences of primers.

Items	Forward primer (5′-3′)	Reverse primer (5′-3′)
lnc-THRIL	AACTTCACAGGAACACTACACAAGA	TAGGCAACAGAGCAAGACTTCATC
Interferon-g	GTATTGCTTTGCGTTGGACA	GAGTGTGGAGACCATCAAGGA
IL-2	GCACCTACTTCAAGTTCTACAAAGAA	AAAGGAAATATACTTACATTAATTCCATTCAAAATCATCTG
IL-4	AGCAGTTCCACAGGCACAAG	CTCTGGTTGGCTTCCTTCACA
IL-10	TGTTGCCTGGTCCTCCTGACT	GCCTTGATGTCTGGGTCTTGGTT
GAPDH	GAGTCCACTGGCGTCTTCAC	ATCTTGAGGCTGTTGTCATACTTCT
miR-125b	ACACTCCAGCTGGGTCCCTGAGACCCTAAC	CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGTCACAAGT
U6	CTCGCTTCGGCAGCACA	AACGCTTCACGAATTTGCGT

GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; IL-2: Interleukin 2; IL-4: Interleukin 4; IL-10: Interleukin 10; lnc-THRIL: Tumor necrosis factor and HNRNPL-related immunoregulatory long noncoding RNA; miR: MicroRNA