Long Non-coding RNAs and mRNAs Expression Profiles of Monocyte-Derived Dendritic Cells From PBMCs in AR

Yumei Zhou†, Xuemei Chen†, Yanfei Zheng†, Rongmin Shen†, Shuxian Sun†, Fei Yang†, Jiayu Min†, Lei Bao†, Yan Zhang†, Xiaoshan Zhao‡, Ji Wang* and Qi Wang†

Objective: The objective of this study is to explore the long non-coding RNAs (lncRNAs) and messenger RNAs (mRNAs) expression profiles of monocyte-derived dendritic cells (DCs) obtained from peripheral blood mononuclear cells (PBMCs). DCs are known to play a major role in the regulating function of allergic rhinitis (AR).

Methods: PBMCs were separately isolated from the human peripheral blood of patients with AR and normal person (NP). The mixed lymphocyte reaction (MLR) assay was used to evaluate the function of DCs. Flow cytometry was used to determine the immune regulatory function of immature DCs (imDCs) and mature DCs (mDCs). lncRNAs and mRNAs in the NP group (DCs isolated from NP) and the test group (DCs isolated from patients with AR) were identified via chip technology and bioinformatic analyses. Moreover, bioinformatic analyses were employed to identify the related biological functions of monocyte-derived DCs and construct the functional networks of lncRNAs and mRNAs that are differentially expressed (DE) in imDCs and mDCs.

Results: MLR was significantly higher in the mDCs group than that in the imDCs group. CD14 was highly expressed in imDCs, whereas HLA-DR, CD80, and CD86 were highly expressed in mDCs ($p < 0.001$). We identified 962 DE lncRNAs and 308 DE mRNAs in the imDCs of NP and patients with AR. Additionally, there were 601 DE lncRNAs and 168 DE mRNAs in the mDCs in the NP and test groups. Quantitative RT-qPCR was used to study the significant fold changes of lncRNAs and mRNAs. The Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis found 16 significant regulated pathways in imDCs and 10 significant regulated pathways in mDCs, including the phagosome, cell adhesion signaling pathway, and inflammatory mediator regulation of TRP channels pathway.

Conclusion: Our research studied the lncRNA and mRNA expression profiles of monocyte-derived DCs and demonstrated the functional networks that are involved in monocyte-derived DCs-mediated regulation in AR. These results provided possible molecular mechanisms of monocyte-derived DCs in the immunoregulating function and laid the foundation for the molecular therapeutic targets of AR.

Keywords: monocyte-derived dendritic cells, allergic rhinitis, long non-coding RNA, immunoregulation, mRNA
BACKGROUND

Allergic rhinitis (AR) is a very common allergic disease that affects 10–40% of the global population (Bousquet et al., 2008). Its remarkable prevalence and relapses put an extensive burden on its patients and the society. Furthermore, AR negatively impacts the quality of life of patients with AR. There had been a marked increase in the prevalence of AR during the past years (Wang et al., 2016). AR turns into asthma if it is not treated in time, and the adequate treatment of AR can alleviate the severity of asthma (Leynaert et al., 2004). Researchers have illustrated that mast cell infiltration, lymphocytes imbalance, and goblet cell hyperplasia are involved in the pathogenesis of AR (Ouyang et al., 2010; Poggi et al., 2012). AR, which is a type I allergic disorder that is mediated by IgE humoral immune response, is accompanied by an influx of eosinophils and T helper 2 cells that secrete pro-inflammatory cytokines, namely, IL-4, IL-5, and IL-13 (Wilson et al., 2005). Abnormal innate and adaptive immune responses play a major role in the pathogenesis of AR.

Dendritic cells (DCs), which are the most important antigen-presenting cells (APCs) that send signals to the T cells, mainly participate in the pathogenesis of many diseases with immunoregulatory mechanisms, such as AR. DCs link the innate and adaptive immune responses. The peripheral blood mononuclear cells (PBMCs) have a round nucleus (Delves, 2016). PBMCs include lymphocytes, monocytes, and DCs. In humans, the frequencies of these DCs vary among individuals. PBMCs are divided into various functional subtypes with respect to the specific cytokine expression profiles, surface markers, and the transcription factors. Phenotypic and functional assessments of PBMC research lay the foundation of the human immune system research; hence, the knowledge that population is represented in the peripheral blood and how they act with other immune cells is essential. Additionally, the results from human PBMC studies (Schiekofer et al., 2003; Tacconi et al., 2004; Chang et al., 2014) cannot be neglected. Therefore, it is important to know the progression of AR along with its expression profiles in PBMCs, especially DCs.

Long non-coding RNAs (lncRNAs), over 200 nt in length, is a type of RNA that does not a protein coding function (Ulitsky and Bartel, 2013). These RNAs have been regarded as indispensable epigenetic regulators and are probably involved in the cell's biological behaviors (Kopp and Mendell, 2018). For example, they are involved in regulating the homeostasis of the immune system (Wang et al., 2014; Du et al., 2017). However, it is critical to find out whether lncRNA can immunoregulate DC in the progression of AR.

The combination of lncRNA–messenger RNA (mRNA) expression profiles and functional networks is adopted to analyze the DC-mediated regulation functions. These results improve our understanding of lncRNAs in the immunoregulatory function of monocyte-derived DCs and indicate the potential targets for the curative treatment of AR.

MATERIALS AND METHODS

Subjects

Patients with AR visited doctors in the outpatient service in the Guo Yi Tang of Beijing University of Chinese Medicine. In this study, there were 24 subjects: 12 males and 12 females. They were divided into two groups: the AR group (patients with AR, 12 subjects: five males and seven females) and NP group (normal persons, 12 subjects: four males and eight females). With support/approval from the Ethics Committee of Beijing University of Chinese Medicine, this study was conducted while adhering to the principles of the Declaration of Helsinki. Patients in the AR group were positive for skin puncture test, including pollen, food, dust mites, paint, or molds as well as in specific IgE. Two weeks before study recruitment, these patients with AR received no topical or systemic corticosteroid therapy. We chose the study participants with no history of smoking or other immune system disorders, such as rheumatoid arthritis, systemic lupus erythematosus, and scleroderma.

Isolation of PBMCs and Generation of DCs

The whole blood samples obtained from the two groups were stored in vacuum tubes with heparin, and PBMCs were isolated from these samples by lymphocyte separation solution (Tianjin Haoyang Biological Manufacture Co., Ltd.). Mononuclear cells were seeded in 12-well plates with the RPMI 1640 medium that contains 10% heat-inactivated fetal calf serum (FCS, Gibco, Germany) and 2 mM of l-glutamine (R10 medium, Sigma, St. Louis, MO, United States). After incubation at 37°C for 2 h, the non-adherent cells were removed and the adherent cells were cultured within the medium containing 100 ng/ml of rhGM-CSF and 100 ng/ml of rhIL-4 (R&D Systems, Minneapolis, MN, United States). On the sixth day, 50 ng/ml of TNF-α (R&D Systems, Minneapolis, MN, United States) was added into the samples; the method had the same protocol in the study of Andrea et al. (2005). Immature DCs (imDCs) were collected on the fifth day, and the mature DCs (mDCs) were collected on the seventh day.

Mixed Lymphocyte Reaction (MLR)

After being treated with 25 μg/mL of mitomycin at 37°C for 30 min, the DCs were placed at the concentrations of 2 × 10⁸ cells per well at a quantity of 200 μl and incubated with non-adherent PBMCs obtained from the same healthy people. These samples were later stimulated by lymphocytes in the concentration proportions of 1:10, 1:50, and 1:100. Thereafter, the samples were mixed and incubated with non-adherent PBMC from the same healthy persons at the same concentrations in triplicate. The cells were treated with 10% fetal bovine serum. Then, 10 μl of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) solution (5 mg/ml, medium dilution, Sigma–Aldrich Chemical Co., St. Louis,
MO, United States) was added to each well, and the cells were incubated for 72 h in the incubator. Then, 150 µl of DMSO was added followed by the addition of enzymes after 4 h. The absorbance was detected using a spectrophotometer at 570 nm.

**DC Surface Marker Expression Analysis in imDCs and mDCs**
The CD14 (PerCP-Cy 5.5, BD Biosciences, United States), HLA-DR (APC, BD Biosciences, United States), and isotype mouse IgG2a-PE (PE, BioLegend, United States) were added in the samples of imDCs. Moreover, CD86-APC, CD80-PE, and isotype mouse IgG1–FITC (BioLegend, United States) were added in the samples of mDCs. The cells were then suspended with precooled PBS, counted under a microscope, and centrifuged at 1000 g for 5 min. Data were acquired using a FACSCalibur cytometer (BD Biosciences, United States) and the ratios of CD14+, HLA-DR+, CD80+, and CD86+ DCs were determined.

**RNA Extraction, Labeling, Chip Hybridization, and Scanning**
The RNA extraction, labeling, chip hybridization, and scanning were all finished following the use of Agilent Human LncRNA–mRNA profiling chip (4*180K, Design ID: 062918). All the chip results were detailed according to the processes of software operations. The screening criteria were to increase or decrease the fold change value ≥ 2.0 and p-value < 0.05.

**Gene Ontology (GO) and Pathway Enrichment Analysis**
The GO and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were used to study the differentially expressed (DE) mRNAs. The results of the target gene analysis of LncRNA and the mRNA expression results on the chip need to be correlated so that the upregulated and downregulated DE genes can be investigated. The corrected p-value < 0.05 by calculating the FDR and FDR < 0.05 was selected as the threshold.

**LncRNA–mRNA-Weighted Co-expression Network**
The correlation of the LncRNA–mRNA expression in the imDCs and mDCs was calculated. Then, the relationship pairs of LncRNA and mRNA based on the abovementioned criteria (p-value < 0.05, FDR < 0.05) were screened. The co-expression network of LncRNAs and mRNAs was constructed, and the co-expression network of LncRNAs and mRNAs was then established.

**FIGURE 1** Morphology of dendritic cells and the functional activity of DCs were assayed by autologous MLR. (A,B) imDCs and mDCs, mDCs have a more structure of dendrites. (C) MLR was determined by the stimulation index. $2 \times 10^6$ ml−1 DCs and lymphocytes were cultured with the medium for 72 h, and then DCs were collected and autologous MLR was performed. The control group was stimulated with 25 mg/L mitomycin as controls. ***P < 0.001.
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FIGURE 2 | Flow cytometric analysis showing the percentage of CD14, HLA-DR, CD80, and CD86 in DCs. (A,B) The flow cytometric analysis showed that percentage of CD14 in NP group was lower than that in AR group (p = 0.0008). (C,D) The flow cytometric analysis showed that percentage of HLA-DR in NP group was lower than that in AR group. (E,F) The flow cytometric analysis showed that percentage of CD80 in NP group was lower than that in AR group. (G,H) The flow cytometric analysis showed that percentage of CD86 in NP group was lower than that in AR group. ***P < 0.001, **P < 0.01.

Real-Time PCR Verification of DE Genes
Quantitative RT-qPCR was used to investigate the different expressions of imDCs’ and mDCs’ genes between the patients with AR and NP. The total RNA was extracted from imDCs and DCs according to the kit for cells. In all, 20 µg of total RNA was converted into cDNA by using oligo (dT) and reverse transcriptase (Thermo, United States) to analyze the qPCR results. The thermal cycler conditions were set as follows: amplification at 95°C for 10 min, 95°C for 15 s, 60°C for 60 s, 40 cycles of denaturation (15 s, 94°C), 15 s at 95°C, and a combined process of annealing and extension (1 min, 60°C). Supplementary Table S1 shows the primers for these genes.

Statistical Analysis
The SPSS 22.0 software was used for statistical analysis in this study. Results were expressed as mean ± standard deviation. The relationship of lncRNAs and mRNAs was determined by the Spearman’s correlation coefficient. p-values < 0.05 were considered significant values for this study.

RESULTS
Allogeneic T-Cell Proliferation Experiment
In allergenic mixed lymphocyte reaction (MLR), the levels of T-cell proliferation were increased with the proportion of T cells.
DCs in the patients with AR have a stronger stimulation ability than NP as shown in Figures 1A–C. When the ratio of DC cells to T cells was 1:50 and 1:100, the difference was significant (p < 0.001).

**Immunophenotype of DCs in Patients With AR and NP**

We evaluated the percentages of CD14, HLA-DR, CD80, and CD86 in the DCs. The immunophenotypic characteristics of DCs in patients with AR were compared with that of NP, as shown in Figure 2. The CD14 concentration of imDCs was lower in patients with AR than that in the NP group. The mean percentage of CD14+ DCs in the patients with AR was 0.84 ± 0.25% (median: 0.78%), and it was significantly lower than the value in the NP group (p = 0.0008), where the mean percentage of these cells was 0.012 ± 0.013% (median: 0.017%) (Figures 2A,B).

The mean proportion of HLA-DR+ mDCs in the patients with AR was 44.25 ± 8.64% (median: 44.8%) and was higher (p = 0.0006) than the NP group, where the mean percentage of these cells was 95.3 ± 3.84% (median: 99.0%) (Figures 2C,D).

The mean proportion of CD80+ mDCs in the patients with AR was 72.15 ± 7.64% (median: 67.78%) and was
TABLE 1 | The characteristics of mRNAs with the largest fold change in imDCs.

| GeneName                                      | Genbank Accession | FC (abs) | Regulation |
|-----------------------------------------------|-------------------|----------|------------|
| Fatty acid 2-hydroxylase                      | NM_024306         | 2.7454393| Up         |
| Uncharacterized LOC645984                     | AK095436          | 2.289749 | Up         |
| Shisa homolog 9 (Xenopus laevis)              | NM_001145205      | 2.3817623| Down       |
| NK2 homeobox 1                                | NM_003317         | 2.2437493| Down       |
| Sodium channel, voltage-gated, type VII, alpha| NM_002976         | 3.4931335| Down       |
| Nucleolar and spindle associated protein 1    | NM_016359         | 2.0980568| Up         |
| Ventral anterior homeobox 1                   | NM_000139         | 2.798632 | Down       |
| Chromosome 20 open reading frame 132          | NM_213631         | 2.831788 | Up         |
| Programmed cell death 1 ligand 2              | NM_0025239        | 3.0216887| Down       |
| Solute carrier family 29 (nucleoside transporters), member 1 | NM_001078177 | 2.2991307| Up         |
| Very low density lipoprotein receptor         | NM_001018056      | 2.4887624| Down       |
| Tropomyosin 2 (beta)                          | NM_00013129       | 2.175945 | Down       |
| Uncharacterized LOC100131129                  | AK095436          | 2.1942973| Up         |
| Peptidyl arginine deiminase, type II          | NM_0007365        | 3.0724247| Up         |
| CD300 molecule-like family member f           | NM_139018         | 2.5870113| Up         |
| Programmed cell death 1 ligand 2              | NM_0025239        | 2.921507 | Down       |
| CD36 molecule (thrombospondin receptor)       | NM_0001001547     | 2.167322 | Down       |
| Suppression of tumorigenicity 5               | NM_0005418        | 2.673464 | Up         |
| T-cell acute lymphocytic leukemia 1           | NM_0003189        | 2.3056405| Up         |
| Fc receptor-like B                            | NM_001002901      | 2.311816 | Up         |

The mean proportion of CD86+ mDCs in the patients with AR was 62.15 ± 7.64% (median: 64.69%) and was higher (p = 0.006) than the control group, where the mean percentage of these cells was 92.3 ± 5.84% (median: 95.12%) (Figures 2G,H).

Identification of DE lncRNAs and mRNAs in imDCs

In total, 308 DE mRNAs, including 175 upregulated mRNAs and 133 downregulated mRNAs, were found in the imDCs of patients with AR and NP. A clustergram (Figure 3A) and volcano plots (Figure 3C) are used to depict DE mRNAs. Table 1 shows 67 mRNAs with the largest fold changes. The list contains several genes, including HLA-C, MARCO, KIR2DS3, ITGAV, CD36, and IFNBI. Additionally, 168 DE mRNAs, including 77 upregulated mRNAs and 91 downregulated mRNAs, were found in the mDCs of patients with AR. Figures 4A,C show the clustergram and volcano plots of the DE mRNAs, respectively. Table 2 shows the 10 mRNAs with the greatest variation, and several genes, such as HLA-B, F11R, HLA-DQB1b, HLA-DQB1, and PTAFR, are also shown.

In total, 962 DE lncRNAs, including 434 upregulated and 528 downregulated lncRNAs, were found in patients with AR and NP. The clustergram (Figure 3B) and volcano plots (Figure 3D) show DE lncRNAs. In total, 601 lncRNAs, including 200 upregulated and 401 downregulated lncRNAs, were found in the DE mDCs of the patients with AR. The clustergram in Figure 4B and the volcano plots in Figure 4D show the DE lncRNAs. Tables 1, 3 show the top 10 lncRNAs of imDCs and mDCs with the largest fold changes. The pathways, including interferon-gamma-mediated signaling pathway, membrane repolarization, and peptide antigen binding, that contribute to the phagocytosis function in imDCs and antigen-presenting function of mDCs were also identified.

Interaction, Co-expression Network Analysis of DE mRNAs in Patients With AR

Figure 5A shows the interactions of proteins that were coded by DE mRNAs in imDCs. Additionally, Figure 5B shows the co-expression network between DE lncRNAs and mRNAs. TRIM69 has the maximum target mRNAs including 58 DE mRNAs, and SIDT2 has the maximum co-expressed lncRNAs. Table 2 shows the top 10 co-expression pairs in imDCs. lncRNAs exert their biological function as ceRNAs (Wilfried et al., 2016).

We identified 268 target genes after analyzing the possible DE lncRNAs target genes in imDCs. Figure 5C shows the target genes with a combined score of more than 0.9. HLA-C was the target gene of AC108142.1-005, and CD36 was the target gene of FR264384. Moreover, IFNBI was the target gene of MIR3150-210. The Venn diagram analysis showed that 95 mRNAs were coincided between the 166 DE mRNAs and the 95 DE lncRNA target genes (Figure 5D). The 95 DE lncRNAs were all included in the 166 DE mRNAs.

Figure 6A shows the interaction proteins that were coded by DE mRNAs in mDCs. In this network, HLA-B, HLA-DQB1, HLA-DQB2, PTAFR, and F11R are important genes that interact with many other DE mRNAs. Furthermore, Figure 6B shows the co-expression network of DE lncRNAs and mRNAs. TRIM77P has the maximum target numbers including 39 DE mRNAs, in
which FAM153A and ZNF396 have the maximum co-expressed lncRNAs. Table 4 shows the top 10 co-expression pairs of mDCs.

Additionally, we also investigated the possible presence of DE lncRNA target genes in mDCs. In our study, 99 target genes were identified in these DE lncRNAs. Figure 6C shows the target genes with the combined score of more than 0.9. In the figure, HLA-B has three target genes of lincRNAs, namely, DHRS3, FCHO2, and linc-PRR5-1. Figure 6D shows that 42 mRNAs coincided between the 95 DE mRNAs and the 42 DE lncRNA target genes in the Venn diagram analysis. Moreover, the 42 DE lncRNAs were included in the 95 DE mRNAs. It also includes some known inflammatory-related molecules.

Validation of DE mRNA and lncRNA Expression Levels by RT-qPCR

RT-qPCR was used to evaluate DE mRNAs and lncRNAs to verify our RNA chip results. We randomly detected three lncRNAs and 10 mRNAs. MARCO, KIR2DS3, F11R, HLA-B, HLA-C, NON-HSAG046717, and NON-HSAT089067 were
TABLE 2 | The top 10 co-expression of mRNA and lncRNA in imDCs.

| mRNA       | Gene   | lncRNA  | Gene   | Correlation coefficient | P-value |
|------------|--------|---------|--------|-------------------------|---------|
| NM_018208  | ETNK2  | NON-HSAT008926 | ETNK2  | 0.9970621              | 3.24775E–10 |
| NM_005891  | ACAT2  | NON-HSA045301 | NON-HSA045301 | 0.9953173 | 2.09182E–09 |
| NM_128985  | TRIM69 | NR_104175.1 | LOCO00799 | −0.9914054 | 2.36259E–08 |
| BX580802   | GPR17  | FR351114 | FR351114 | 0.9064622 | 3.31169E–08 |
| NM_002977  | SCN9A  | NON-HSA029733 | NON-HSA029733 | 0.9882097 | 8.33527E–08 |
| NM_014485  | HPGDS  | NON-HSA097445 | HPGDS  | 0.9877657 | 9.6583E–08 |
| AK131565   | LOC100132368 | ENST00000588609 | LIN0098-004 | 0.9883888 | 1.47941E–07 |
| NM_006005  | NDUF9  | NON-HSA101913 | RP11-1113N2.4 | 0.9860654 | 1.62207E–07 |
| XM_001719518 | LOC100128869 | NON-HSA042749 | NON-HSA042749 | −0.985726 | 1.78529E–07 |
| NM_032772  | ZNF503 | ENST00000438293 | LINC00906-004 | 0.9853318 | 1.98986E–07 |

TABLE 3 | The characteristics of mRNAs with the largest fold change in mDCs.

| Gene Name                                      | Accession no. | Fold change | Regulation |
|------------------------------------------------|---------------|-------------|------------|
| Armadillo repeat containing 9                  | NM_025139     | 2.1053998   | Up         |
| Cat eye syndrome chromosome region, candidate 2 | NM_031413     | 2.1667209   | Down       |
| Semenogelin II                                  | NM_003008     | 2.2934558   | Up         |
| Polycystic kidney disease 1 like 1             | NM_138295     | 3.8540776   | Up         |
| Rho guanine nucleotide exchange factor (GEF) 35| NM_001003702  | 2.662969    | Up         |
| Sushi domain containing 4                      | NM_017892     | 3.1600573   | Down       |
| ST6 beta-galactosamide alpha-2,6-sialyltransferase 1 | NM_173216     | 2.504244    | Up         |
| Chromosome 2 open reading frame 71             | NM_001029883  | 2.1819167   | Up         |
| Dehydrogenase/reductase (SDR family) member 3  | NM_004753     | 2.1267188   | Up         |
| Sterile alpha motif and leucine zipper containing kinase AZK | NM_016653 | 2.2057335 | Up |
| Chromosome 5 open reading frame 62             | NM_032947     | 2.0991956   | Up         |
| Transmembrane protein ENSP00000343375         | BC031304      | 2.0238611   | Down       |
| Family with sequence similarity 101, member B  | NM_182705     | 2.506473    | Up         |
| Olfactory receptor, family 2, subfamily T, member 8 | NM_001005522  | 2.5608928   | Down       |
| Sorbin and SH3 domain containing 1             | NM_001034954  | 2.0617623   | Down       |
| Transmembrane protease, serine 6               | BC039082      | 2.2889757   | Down       |
| DEAD (Asp-Glu-Ala-Asp) box polypeptide 6       | NM_004397     | 2.0167336   | Up         |
| spondin 2, extracellular matrix protein         | NM_012445     | 2.7114112   | Up         |
| HLA-DBQ1                                       | NM_001243961  | 2.154       | Down       |

DISCUSSION

In our research, we used rhGM-CSF, rhIL-4, and TNF-α to induce the mDCs from PBMCs. The generation of human monocyte-derived DCs from whole blood was recognized by all the scientists (Wilfried et al., 2016). We investigated phenotypic and functional features of DE DCs in vitro from patients with AR and the NPs. Besides that, we used RT-qPCR to confirm these findings. Our KEGG pathway analysis (Tables 5, 6) indicates that interferon-gamma-mediated signaling pathway, membrane repolarization, and peptide antigen binding pathways contribute to the phagocytosis function in imDCs, and the antigen-presenting function in mDCs contributes to the immunoregulatory function of DCs in AR.

Dendritic cells play a central role in allergic inflammation (Froidure et al., 2016). The latest in vitro techniques allow the in vitro differentiation of DCs (Thurner et al., 1999). Their ability to induce the proliferation of T cells in the MLR assay is commonly used for evaluating their functions (Cao et al., 2004). In MLR experiment, the stimulation index of mDCs was significantly higher than that of the imDCs. In our study, the expression of HLA-DR, CD80, and CD86 in patients with AR is indeed upregulated than that in NP, which is a sign of improved mDCs antigen presentation in patients with AR. This result is in accordance with a previous study by KleinJan et al. (2006). In the study, CD14 in the NP group was higher than that in patients with AR. CD14 is the marker of monocytes whose expression decreases gradually during DC differentiation from monocytes. In fact, CD80 and CD86 are important co-stimulating factors that affect the proliferation of T lymphocytes in the DCs (Duperrier et al., 2000; Ebner et al., 2001; Andreia et al., 2005;
FIGURE 5 | Interaction and co-expression network analysis, analysis of lncRNA target mRNAs in imDCs. (A) Interactions between DE mRNAs. Purple indicates upregulated genes, and green indicates downregulated genes. (B) Co-expression network of DE lncRNAs and DE mRNAs. (C) DE lncRNAs and their target genes with a combined score larger than 0.9 are shown. Yellow indicates upregulated genes, and blue indicates downregulated genes. (D) Venn diagram showing DE mRNAs and target genes of DE lncRNAs.

Wilfried et al., 2016). DCs are the most efficient APCs. It can present the antigens to the T cells for stimulating the adaptive immune response.

More number of studies have focused on exploring the mRNA expressed in DCs, but none have been conducted to reveal which and how mRNA affects DCs in patients with AR. To investigate
the mechanism of DCs’ functions in patients with AR, the mRNA expression profile was determined and bioinformatics analysis was performed in our study. In total, 308 mRNAs were identified in the analysis. Among these DE genes, HLA-C, ITGAV, MARCO, CD36, IFNB1, and KIR2DS3 were found to be most significantly upregulated in the imDCs’ network. HLA-C plays an important role in promoting differential DC maturation (Raj et al., 2011). ITGAV is the expression of DC-specific transmembrane protein. MARCO promotes TLR activation, which validates a major role of MARCO in mounting an inflammatory response (Haydn et al., 2014). ImDCs play an important role in the phagocytosis of apoptotic...
TABLE 4 | The top 10 co-expression of mRNA and lncRNA in mDCs.

| mRNA     | Gene       | IncRNA  | Gene       | Correlation coefficient | P-value |
|----------|------------|---------|------------|-------------------------|---------|
| NM_012445| SPON2      | NON-HSA037252 | NON-HSA037252 | 0.9947499 | 3.30E-09 |
| NM_138782| FCHO2      | NON-HSAT102095 | FCHO2      | 0.9945368 | 3.87E-09 |
| AK311167 | LOC100132352 | TCONS_2_00028804 | lnc-ANKRD20A4-2 | 0.9832951 | 3.34E-07 |
| NM_003162| STRN       | ENST00000562064 | CTD-2015G9.2-001 | 0.9825929 | 3.93E-07 |
| NM_001034954 | SORBS1 | TCONS_00010265 | lnc-FASTKD3-1 | 0.9794563 | 7.60E-07 |
| NM_001463| FRZB       | NRL_038973.1 | FAM170B-AS1 | 0.9797894 | 1.04E-06 |
| NM_001979| EPHX2      | NON-HSAT021480 | AP000445.1  | −0.9769811 | 1.18E-06 |
| AB018295 | FAM153A    | NON-HSAT002078 | linc-LPHN2-2 | 0.974958 | 1.71E-06 |
| NM_007048 | BTN3A1   | NON-HSAT142393 | RP11-429P3.2 | 0.9737392 | 2.02E-06 |
| NM_182487 | OLFML2A | FR052374 | FR052374  | 0.9723832 | 2.46E-06 |
| NM_001146162 | TRIM77P | ENST00000541885 | RP11-439H13.2-001 | 0.9723254 | 2.48E-06 |

FIGURE 7 | Validation of DE mRNAs and lncRNAs. (A,B) DE mRNAs were confirmed by qPCR. (C) DE lncRNAs were confirmed by qPCR. Ligand 1, MACO, the scavenger receptor; Ligand 2, KIR2DS3, a type of killer cell immunoglobulin-like receptors (KIRs); Ligand 3, F11R, a cell adhesion molecule found on the surface of human platelets; Ligand 4 and Ligand 5, HLA-B and HLA-C are all a type of human Leukocyte Antigen (HLA) class I molecules; Ligand 6, ITGAV, integrin subunit alpha v; Ligand 7, CD36, a membrane glycoprotein present on platelets, mononuclear phagocytes, adipocytes, hepatocytes, myocytes, and some epithelia; Ligand 8, IFNB1, interferon beta, a secreted cytokine; Ligand 9, PTAIR, platelet-activating factor receptor; Ligand 10, HLA-DQB1, human leukocyte antigen DQB1. **P < 0.01, * P < 0.05.

TABLE 5 | Pathways KEGG analysis of imDCs.

| Pathway                          | Count | P-value  | Corrected P-value | Gene                                    |
|----------------------------------|-------|----------|--------------------|-----------------------------------------|
| Vitamin digestion and absorption| 3     | 0.00377492 | 0.35867536 | PLB1/SLC19A1/SCARB1                     |
| Butanoate metabolism            | 3     | 0.005268382 | 0.35867536 | AACS/ACADS/ACAT2                       |
| Hypertrophic cardiomyopathy     | 3     | 0.005764726 | 0.35867536 | TPM2/TPM1/MYH7/ITGAV/IGF1              |
| Dilated cardiomyopathy          | 5     | 0.00755082 | 0.35867536 | TPM2/TPM1/MYH7/ITGAV/IGF1              |
| Aldosterone synthesis and secretion | 5   | 0.008223347 | 0.35867536 | CACNA1/CAKNJ5/PRAKCB/SCARB1/POMC       |
| GnRH secretion                  | 4     | 0.008686888 | 0.39078267 | CACNA1/CAKNJ5/PRAKCB/PIK3R3            |
| Aldosterone-regulated sodium reabsorption | 3 | 0.011502085 | 0.39078267 | PRKCB/PK3R3/IGF1                       |
| Phagosome                       | 6     | 0.013026696 | 0.39078267 | C1R/ITGAV/SCARB1/MARCO/CD36/HLA-C     |
| Glioma                          | 4     | 0.015303573 | 0.408095286 | PRKCB/PK3R3/CDK6/IGF1                  |
| Fat digestion and absorption    | 3     | 0.017291278 | 0.414990664 | SCARB1/CD36/ACAT2                      |
| Valine, leucine, and isoleucine degradation | 3 | 0.022152058 | 0.479306938 | AACS/ACADS/ACAT2                      |
| Cholesterol metabolism          | 3     | 0.025762258 | 0.479306938 | LRPAP1/SCARB1/CD36                     |
| Natural killer cell-mediated cytotoxicity | 5 | 0.025962459 | 0.479306938 | IFNB1/PRKCB/PIK3R3/KIR2DS3/HLA-C      |
| Terpenoid backbone biosynthesis | 2     | 0.031653591 | 0.54232982 | MMP14/RUNK2/PRKCB/PDE4D               |
| Inflammatory mediator regulation of TRP channels | 4 | 0.038448883 | 0.574011496 | HLA-C                                  |
| Parathyroid hormone synthesis, secretion, and action | 4 | 0.046842901 | 0.574011496 | HLA-C                                  |
cells, in particular, CD36 (Albert et al., 1998). Additionally, the GO analysis demonstrated specific molecular functions, for example, binding of transforming growth factor-beta, signaling pattern recognition receptor activity, and pattern recognition receptor activity, thereby indicating the critical role of these cytokines in the immunoregulatory functions of imDCs. The KEGG analysis identified 17 signaling pathways of the DE mRNAs, wherein interferon-gamma-mediated signaling pathway, membrane repolarization, and peptide antigen binding were the pathways with the significant differences that contributed to the phagocytosis function of imDCs (Figures 3E,F). This result is consistent with that of a previous study (Lambrecht, 2001). Although research works have been conducted to determine the functions of imDCs in AR, the

### TABLE 6 | Pathways of mDCs with the largest significant difference in KEGG analysis.

| Pathway                                      | Count | P-value       | Corrected P-value | Gene                          |
|----------------------------------------------|-------|---------------|--------------------|-------------------------------|
| Neuroactive ligand–receptor interaction      | 6     | 0.008916046   | 0.526895235        | PTAFR, POMC, OPRM1, MCHR2, GNRH1, MLNR |
| Allograft rejection                          | 2     | 0.017316097   | 0.526895235        | HLA-DQB1, HLA-B               |
| Graft-versus-host disease                    | 2     | 0.020925187   | 0.526895235        | HLA-DQB1, HLA-B               |
| Type I diabetes mellitus                     | 2     | 0.021872484   | 0.526895235        | HLA-DQB1, HLA-B               |
| Other types of O-glycan biosynthesis         | 2     | 0.025835563   | 0.526895235        | ST6GAL1, LFNG                 |
| Arginine and proline metabolism              | 2     | 0.028984793   | 0.526895235        | AMD1, ALDH7A1                 |
| Autoimmune thyroid disease                   | 2     | 0.032279732   | 0.526895235        | HLA-DQB1, HLA-B               |
| Glutathione metabolism                       | 2     | 0.036890685   | 0.526895235        | GSTM3, G6PD                   |
| Viral myocarditis                            | 2     | 0.04050554    | 0.526895235        | HLA-DQB1, HLA-B               |
| Cell adhesion molecules                      | 3     | 0.044652139   | 0.526895235        | HLA-DQB1, HLA-B, F11R         |
| Retinol metabolism                           | 2     | 0.050761992   | 0.544537736        | DHRSS3, ALDH1A1               |

### TABLE 7 | GO analysis of DE mRNA in imDCs.

| Term                                        | Domain             | Count | P-value       | Corrected P-value |
|---------------------------------------------|--------------------|-------|---------------|-------------------|
| Apoptotic cell clearance                     | Biological process | 5     | 4.48014E-05   | 4.48014E-05       |
| Vascularogenesis                            | Biological process | 6     | 0.000164507   | 0.000164507       |
| Response to fatty acid                      | Biological process | 6     | 0.000263738   | 0.000263738       |
| Phospholipid metabolic process              | Biological process | 13    | 0.000319148   | 0.000319148       |
| Glycosphospholipid metabolic process        | Biological process | 11    | 0.000323952   | 0.000323952       |
| Oligodendrocyte differentiation             | Biological process | 6     | 0.000454451   | 0.000454451       |
| Actin filament-based movement               | Biological process | 7     | 0.00047494    | 0.00047494        |
| Glycerolipid metabolic process              | Biological process | 12    | 0.000748476   | 0.000748476       |
| Negative regulation of tumor necrosis factor production | Biological process | 5     | 0.000792316   | 0.000792316       |
| Carbohydrate derivative transport           | Biological process | 5     | 0.000792316   | 0.000792316       |
| Synaptic vesicle membrane                   | Cellular component | 5     | 0.000264902    | 0.000264902       |
| Excocytic vesicle membrane                  | Cellular component | 5     | 0.000264902    | 0.000264902       |
| Integral component of synaptic vesicle membrane | Cellular component | 3     | 0.000805305    | 0.000805305       |
| Presynaptic cytosol                         | Cellular component | 2     | 0.000855871    | 0.000855871       |
| Presynapse                                  | Cellular component | 11    | 0.000892316    | 0.000892316       |
| Cell leading edge                           | Cellular component | 10    | 0.0009798418   | 0.0009798418      |
| Integral component of organelle membrane    | Cellular component | 6     | 0.000895744    | 0.000895744       |
| Excocytic vesicle                           | Cellular component | 6     | 0.000895744    | 0.000895744       |
| Melanosome membrane                         | Cellular component | 2     | 0.000909825    | 0.000909825       |
| Chitosome                                   | Cellular component | 2     | 0.000909825    | 0.000909825       |
| Transforming growth factor beta binding     | Molecular function | 4     | 7.69207E-05    | 7.69207E-05       |
| 1-Phosphatidylinositol binding              | Molecular function | 3     | 0.000452198    | 0.000452198       |
| Lipoprotein particle receptor activity      | Molecular function | 3     | 0.000452198    | 0.000452198       |
| Signaling pattern recognition receptor activity | Molecular function | 3     | 0.000824225    | 0.000824225       |
| Pattern recognition receptor activity       | Molecular function | 3     | 0.000889099    | 0.000889099       |
| Amyloid-beta binding                        | Molecular function | 5     | 0.001167764    | 0.001167764       |
| Lipase activity                             | Molecular function | 5     | 0.005214971    | 0.005214971       |
| Intrinsic transcription regulatory region sequence-specific DNA binding | Molecular function | 2     | 0.005236034    | 0.005236034       |
| Intrinsic transcription regulatory region DNA binding | Molecular function | 2     | 0.005236034    | 0.005236034       |
| Lipoprotein particle binding                 | Molecular function | 3     | 0.006313499    | 0.006313499       |
TABLE 8 | GO analysis of DE mRNA in mDCs.

| Term                                              | Domain            | Count | P-value          | Corrected P-value |
|---------------------------------------------------|-------------------|-------|------------------|-------------------|
| Interferon-gamma-mediated signaling pathway        | Biological process| 5     | 0.000105145      | 0.000105145       |
| Regulation of membrane repolarization             | Biological process| 3     | 0.000897665      | 0.000897665       |
| SA node cell to atrial cardiac muscle cell migration| Biological process| 2     | 0.001143106      | 0.001143106       |
| Cellular response to interferon-gamma             | Biological process| 5     | 0.001152483      | 0.001152483       |
| Atrial cardiac muscle cell membrane repolarization| Biological process| 2     | 0.001392464      | 0.001392464       |
| Cerebral cortex cell migration                     | Biological process| 3     | 0.001490903      | 0.001490903       |
| Telencephalon development                         | Biological process| 6     | 0.001681684      | 0.001681684       |
| Response to interferon-gamma                      | Biological process| 5     | 0.001981297      | 0.001981297       |
| Membrane repolarization                           | Biological process| 3     | 0.002157971      | 0.002157971       |
| Regulation of macrophage cytokine production      | Biological process| 2     | 0.002280906      | 0.002280906       |
| MHC protein complex                               | Cellular component| 3     | 0.000314384      | 0.000314384       |
| Integral component of luminal side of endoplasmic reticulum membrane | Cellular component| 3     | 0.000491764      | 0.000491764       |
| Luminal side of endoplasmic reticulum membrane    | Cellular component| 3     | 0.000491764      | 0.000491764       |
| Side of membrane                                  | Cellular component| 8     | 0.000689806      | 0.000689806       |
| Clathrin-coated endocytic vesicle membrane        | Cellular component| 3     | 0.001274169      | 0.001274169       |
| Plasma membrane protein complex                   | Cellular component| 8     | 0.002912282      | 0.002912282       |
| ER to Golgi transport vesicle membrane            | Cellular component| 3     | 0.003192827      | 0.003192827       |
| MHC class II receptor activity                    | Cellular component| 2     | 0.003242854      | 0.003242854       |
| Alpha-actinin binding                             | Cellular component| 3     | 0.003995823      | 0.003995823       |
| Actinin binding                                   | Cellular component| 3     | 0.006941689      | 0.006941689       |
| Protein phosphatase 2A binding                    | Molecular function| 3     | 0.000313848      | 0.000313848       |
| Lipopolysaccharide binding                        | Molecular function| 3     | 0.000491764      | 0.000491764       |
| Peptide antigen binding                           | Molecular function| 3     | 0.000491764      | 0.000491764       |
| Oxidoreductase activity, acting on the aldehyde or oxo group of donors, NAD or NADP as acceptor | Molecular function| 8     | 0.000689806      | 0.000689806       |
| Oxidoreductase activity, acting on the aldehyde or oxo group of donors | Molecular function| 3     | 0.001274169      | 0.001274169       |
| Protease binding                                  | Molecular function| 8     | 0.002912282      | 0.002912282       |
| Growth factor receptor binding                    | Molecular function| 3     | 0.003192827      | 0.003192827       |
| MHC class II receptor activity                    | Molecular function| 2     | 0.003242854      | 0.003242854       |
| Alpha-actinin binding                             | Molecular function| 3     | 0.003995823      | 0.003995823       |
| Actinin binding                                   | Molecular function| 3     | 0.006941689      | 0.006941689       |

TABLE 9 | lncRNAs in imDCs with the largest fold change.

| lncRNA_Accession | FC (abs) | Regulation | Chromosome | Strand | Start | End | Class | Size |
|------------------|----------|------------|------------|--------|-------|-----|-------|------|
| TCONS_l2_000303438 | 6.1069527 | Down       | chrX       | –      | 5571461 | 5644346 | lncRNA | 72885 |
| NON-HSAT016934   | 5.6184836 | Down       | chr10      | –      | 127823936 | 127843874 | lncRNA | 19938 |
| TCONS_l2_0001274 | 5.147873  | Up         | chr1       | –      | 65450890  | 65451399 | InRNA  | 519   |
| NON-HSAT016934   | 4.9528494 | Down       | chr10      | +      | 127772904 | 127792637 | lncRNA | 19053 |
| NON-HSAT09748     | 4.6156665 | Down       | chr18      | +      | 66817065  | 66832387 | InRNA  | 15322 |
| NON-HSAO053933    | 4.34199   | Up         | chrX       | –      | 2484070   | 2527190  | InRNA  | 43120 |
| NON-HSAO029733    | 4.2480536 | Down       | chr2       | +      | 16705481  | 16705524 | InRNA  | 362   |
| NON-HSAT03933     | 4.0038888 | Down       | chr3       | +      | 189885384 | 189038493 | InRNA  | 53109 |
| NON-HSAOG053933   | 3.8807297 | Down       | chr3       | +      | 189885384 | 189038493 | InRNA  | 53108 |
| NON-HSAO053855    | 3.8563106 | Down       | chrY       | –      | 21034387  | 21239448 | InRNA  | 205061 |

role of IFNB1 and KIR2DS3 in imDCs was not known in AR (Tables 7, 8).

The imDCs migrate to the lymphoid organs that will be matured in the future. They present captured Ag to the naïve T cells (Banchereau and Steinman, 1998). Hence, the imDCs and mDCs had different functions in the presented Ag. In our study, we focused on the immature and mature stages of DCs. In the mDC' mRNA analysis, 168 mRNAs were identified. Among these DE genes, HLA-B, HLA-DQB1, HLA-DQB2, PTAFR, and F11R were the most significantly upregulated genes in mDCs. HLA-B is the major histocompatibility complex (class I) antigens that present the processed antigens. HLA-DQB1 is the major histocompatibility complex (class II) antigens that have been identified as useful biomarkers of...
candidacy for effective allergy immunotherapy in patients with AR (Yanming et al., 2019). This result indicates that these cytokines affect the antigen-presenting process in the mDCs. We can determine from the KEGG analysis that there are 12 signaling pathways related to DE mRNAs. The cell adhesion molecules were the useful pathways that contribute to the antigen-presenting function in mDCs (Figures 4E, F), which is consistent with a previous study (Roche and Furuta, 2015). Although many genes have been identified to play an important role in mDCs, but the mechanisms by which HLA-DQB2, PTAFR, and F11R affect mDC in AR are unknown (Tables 9, 10).

Long non-coding RNA is an important component in the mRNA expression profiles (Kopp and Mendell, 2018). Several studies have shown that the differentiation of DCs is closely related to lncRNAs (Pin et al., 2014; Majid et al., 2020). It is confirmed from our studies that lncRNA may play a key role in the development of DC. Our data showed that 172 lncRNAs of imDCs and 104 lncRNAs of mDCs were significantly expressed in patients with AR as compared to that in NP by at least twofold changes. This result helps in studying the AR-related global transcriptome.

Long non-coding RNAs do not have a protein coding function, but they can be used as a new modulator, such as cis- or trans-gene regulating expression, demethylation-promoting effect, and mRNA-processing control were the major mechanisms (Sone et al., 2007; Wahlestedt, 2013; Qiao et al., 2016). To analyze the functions of lncRNAs, mRNA–lncRNA was used to create a co-expression profile to predict the potential functions of the DE lncRNAs of patients with AR. We found that the DE lncRNAs were all included in the results of mRNA–lncRNA chip results.

We used RT-qPCR to validate the mRNA–lncRNA chip results with only one randomly selected transcript, and found that the RT-qPCR results are consistent with the chip results in better understanding the role of lncRNA in the pathogenesis of DC-mediated AR.

In summary, our study proved that several mRNAs and lncRNAs of DC affect a certain process of AR pathogenesis by regulating the target genes. This result points out the direction for future studies on determining and explaining the functions and mechanisms of AR-related mRNA and lncRNA, and provides new therapeutic targets for patients with AR.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author/s.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by the medical and experimental animal ethics committee of Beijing University of Traditional Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

**AUTHOR CONTRIBUTIONS**

YZ, XC, and YZ carried out the experiments. JW, QW, YZ, XC, and YZ designed the study and edited the manuscript. All authors read and approved the final manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcell.2021.636477/full#supplementary-material
REFERENCES

Albert, M. L., Pearce, S. F., Francisco, L. M., Sauter, B., Roy, P., Silverstein, R. L., et al. (1998). Immature dendritic cells phagocytose apoptotic cells via alaphavbeta5 and CD36, and cross-present antigens to cytotoxic T lymphocytes. J Exp Med. 188, 1359–1368. doi: 10.1084/jem.188.7.1359

Andrea, R. N., Luis, F. C. E., Anselmo, L. B., Leite, K. R. M., Buzaid, A. C., Cámara-Lopes, L. H., et al. (2005). Dendritic cells derived from metastatic cancer patients vaccinated with allogeneic dendritic cell–autologous tumor cell hybrids express more CD86 and induce higher levels of interferon-gamma in mixed lymphocyte reactions. Cancer Immunol. Immunother. 54, 61–66. doi: 10.1007/s00262-004-0550-8

Banchereau, J., and Steinman, R. M. (1998). Dendritic cells and the control of immunity. Nature 392, 245–252. doi: 10.1038/32588

Bousquet, J., Khaltaev, N., Cruzà, A., Denburg, J., Fokkens, W. J., Togias, A., et al. (2008). Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA (2) LEN and Aller Gen). Allergy 63, 8–160.

Cao, M.-D., Chen, Z.-D., and Xing, Y. (2004). Gamma irradiation of human dendritic cells influences proliferation and cytokine profile of T cells in autologous mixed lymphocyte reaction. Cell Biol. Int. 28, 223–228. doi: 10.1016/j.cellbi.2003.12.006

Chang, C. C., Lin, C. C., Hsieh, W. L., Lai, H. W., Tsai, C. H., and Cheng, Y. W. (2014). MicroRNA expression profiling in PBMCs: a potential diagnostic biomarker of chronic hepatitis C. Dis. Markers 2014:157.

Delves, P. J. (2016). Roi's essential immunology, 11th edn. Lambrecht, B. N. (2001). Allergen uptake and presentation by dendritic cells. Kopp, F., and Mendell, J. T. (2018). Functional classification and experimental mechanisms.

Duperrier, K., Eljaafari, A., Dezutter-Dambuyant, C., Bardin, C., Jacquet, C., Monceau, K., et al. (2000). Distinct subsets of dendritic cells resembling dermal DCs can be generated in vitro from monocytes, in the presence of different serum supplements. J. Immunol. Methods 238, 119–131. doi: 10.1016/s0022-1759(00)00147-2

Ebner, S., Ratzinger, G., Krosbacher, B., Schmuth, M., Weiss, A., Reider, D., et al. (2004). Acute hyperglycemia causes intracellular formation of CML and activation of ras,p42/44 MAPK, and nuclear factor kappaB in PBMCs. Diabetes 52, 621–633. doi: 10.2337/diabetes.52.5.621

Froidure, A., Shen, C., and Pilette, C. (2016). Dendritic cells revisited in human replies in dendritic cells. Cell Biol. Int. 1759(00)00147-2

Ghosh, S., Nechama, M., Kobzik, L., and Arredouani, Majid, P. K., Rakhshi, N., Aleagha, M. S. E., Abdari, M., Alikhah, A., Safarian, G., et al. (2010). Differential expression of STAT3 gene and its regulatory long non-coding RNAs, namely Inc-DC and THRIL, in two eastern Iranian ethnicities with multiple sclerosis. Neurol. Sci. 41, 561–568. doi: 10.1007/s10072-019-04092-y

Haydn, T. K., Dunn, L. K., Ghosh, S., Nechama, M., Kobzik, L., and Arredouani, Majid, P. K., Rakhshi, N., Aleagha, M. S. E., Abdari, M., Alikhah, A., Safarian, G., et al. (2010). The scavenger receptor MARCO modulates TLR- induced responses in dendritic cells. J. Immunol. Methods 344, 310–313. doi: 10.1016/j.jim.2010.06.020

Krois, A., Shen, C., and Pilette, C. (2016). Dendritic cells revisited in human and experimental allergic inflamma- tion. Cell 172, 393–407. doi: 10.1016/j.cell.2018.01.011

Lambrecht, B. N. (2001). Allergen uptake and presentation by dendritic cells. J. Allergy Clin. Immunol. 109; 51–59. doi: 10.1007/978-0-387-57414-7

Le Maire, B., Neukirch, C., Kony, S., Guenewou, A., Bousquet, J., Aubier, M., et al. (2004). Association between asthma and rhinitis according to atopic reproduction is permitted which does not comply with these terms.

Majid, P. K., Rakhshi, N., Aleagha, M. S. E., Abdari, M., Alikhah, A., Safarian, G., et al. (2010). Differential expression of STAT3 gene and its regulatory long non-coding RNAs, namely Inc-DC and THRIL, in two eastern Iranian ethnicities with multiple sclerosis. Neurol. Sci. 41, 561–568. doi: 10.1007/s10072-019-04092-y

Ouyang, Y., Miyata, M., Hattusaka, K., Ohnuma, Y., Katoh, R., Ogawa, H., et al. (2010). TGF-beta signaling may play a role in the development of goblet cell hyperplasia in a mouse model of allergic rhinitis. Allergol. Int. 59, 313–319. doi: 10.2332/allergoint.10-sc-0172

Pin, W., Xue, Y., Han, Y., Lin, L., Wu, C., Xu, S., et al. (2014). The STAT3-binding long noncoding RNA Inc-DC controls human dendritic cell differentiation. Science 344, 310–313. doi: 10.1126/science.1251446

Poggi, A., Canevalli, P., Contatore, M., and Ciriprandi, G. (2012). Higher frequencies of CD161+ circulating T lymphocytes in allergic rhinitis patients compared to healthy donors. Int. Arch. Allergy Immunol. 158, 151–156. doi: 10.1159/000330903

Qiao, J., Yao, H., Xia, Y., Chu, P., Li, M., Wu, Y., et al. (2016). Long non-coding RNAs expression profiles in hepatocytes of mice after hematopoietic stem cell transplantation. J. Immunol. 190, 254–262. doi: 10.1016/j.expeu.2004.07.009

Schierwer, K., Eljaafari, A., Dezutter-Dambuyant, C., Bardin, C., Jacquet, C., Monceau, K., et al. (2000). Distinct subsets of dendritic cells resembling dermal DCs can be generated in vitro from monocytes, in the presence of different serum supplements. J. Immunol. Methods 238, 119–131. doi: 10.1016/s0022-1759(00)00147-2

Shen, C., and Pilette, C. (2016). Dendritic cells revisited in human long noncoding RNA lnc-DC controls human dendritic cell differentiation. Science 344, 310–313.

Thurner, B., Roder, C., Ciechmann, D., Heuer, M., Kruse, M., Glaser, A., et al. (1998). Immature dendritic cells phagocytose apoptotic cells via CD86 and induce higher levels of interferon-gamma in mixed lymphocyte reactions. Cancer Immunol. Immunother. 46, 633–641. doi: 10.1007/s00262-004-0550-8

Ulitsky, I., and Bartel, D. P. (2013). lincRNAs: genomics, evolution, and mechanism. Cell 154, 26–46. doi: 10.1016/j.cell.2013.06.020

Wahlstedt, C. (2013). Targeting long non-coding RNA to therapeutically upregulate gene expression. Nat. Rev. Drug Discov. 12, 433–446. doi: 10.1038/nrd4018

Wang, X. D., Zheng, M., Lou, H. F., Wang, C. S., Zhang, Y., Bo, M. Y., et al. (2016). MicroRNA expression profiling in PBMCs: a potential diagnostic biomarker of chronic hepatitis C. Dis. Markers 2014:157.

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