Construction of a lncRNA-miRNA-mRNA network to determine the regulatory roles of lncRNAs in psoriasis

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Abstract. Psoriasis is a chronic inflammatory skin disorder that impairs the quality of life of affected patients. Emerging studies indicate that certain long non-coding RNAs (lncRNAs) have important roles in psoriasis. However, the exact functions of lncRNAs and their regulatory mechanisms as competitive endogenous RNAs (ceRNAs) in psoriasis have remained to be fully elucidated. In the present study, differentially expressed lncRNAs, microRNAs (miRNAs) and mRNAs were identified by analyzing public datasets, and a psoriasis-associated lncRNA-miRNA-mRNA network was constructed based on the ceRNA theory. Furthermore, previously validated abnormally expressed miRNAs in psoriasis were identified by a systematic literature search in the PubMed and Web of Science databases, and a specific miRNA-associated lncRNA-miRNA-mRNA sub-network was extracted. Furthermore, Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses were performed using DAVID 6.8. A total of 253 lncRNAs, 106 miRNAs and 1,156 mRNAs were identified as being differentially expressed between psoriasis skin and healthy control skin. The present study identified two key lncRNAs that may potentially have a role in the pathogenesis of psoriasis: AL035425.3 and Prader Willi/Angelman region RNA 6. This integrative analysis enhances the understanding of the molecular mechanism of psoriasis and may provide novel therapeutic targets for the treatment of psoriasis.

Introduction

Psoriasis is a chronic, systemic, recurrent inflammatory disease, which is characterized by erythema, papules and scaling (1). This condition is caused by genetic and environmental factors, including gene mutations, infection and stress (2).

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The pathological manifestations of psoriasis include abnormal keratinocyte differentiation/proliferation and inflammatory cell infiltration (3). It is currently recognized that the pathogenesis of psoriasis is associated with the interleukin (IL)-23/type 17 T-helper cell immune axis, leading to abnormalities in immune cells and associated cytokines, which further induces excessive proliferation of keratinocytes (4). Although extensive research has been performed on the pathogenesis of psoriasis, the mechanisms of psoriasis have remained to be fully elucidated.

Long non-coding RNAs (lncRNAs) are a type of non-coding RNA with a length of >200 nt (5,6). It is speculated that lncRNAs are involved in numerous important biological processes, including cellular homeostasis, genomic imprinting, immunity and development (7). In addition, certain lncRNAs have a role in cardiovascular, neurological and developmental diseases, as well as cancers (5,8). Recently, lncRNAs were reported to have pivotal roles in psoriasis. For instance, the lncRNA psoriasis susceptibility-associated RNA gene induced by stress (PRINS) is the most frequent transcript detected in the non-defective epidermis of patients with psoriasis, and it is thought to contribute to the pathogenesis of psoriasis (9,10). Certain studies have reported that PRINS is capable of regulating G1P3, which is expressed at high levels in psoriatic lesions and has an anti-apoptotic role in keratinocytes (9,11). Furthermore, stressors including microbial components and ultraviolet-B radiation are capable of inducing high expression of PRINS in keratinocytes (9). Msh homeobox 2 pseudogene 1 (MSX2P1), which is another lncRNA, facilitates the proliferation of IL-22-stimulated keratinocytes by suppressing microRNA (miRNA/miR)-6731-5p and upregulating the expression of S100A7 (12). In addition, lncRNAs have been indicated to be an important type of competing endogenous RNA (ceRNA) (13). lncRNAs inhibit miRNA-mediated target repression by competing for miRNA-binding sites with mRNAs. However, the regulatory mechanisms involving ceRNAs in psoriasis have remained elusive. In the present study, psoriasis-associated RNA networks were reconstructed based on the ceRNA theory, and the biological functions of the networks were also investigated.

Materials and methods

Processing of raw data. High-throughput sequencing data for psoriasis-associated lncRNAs, mRNAs and miRNAs
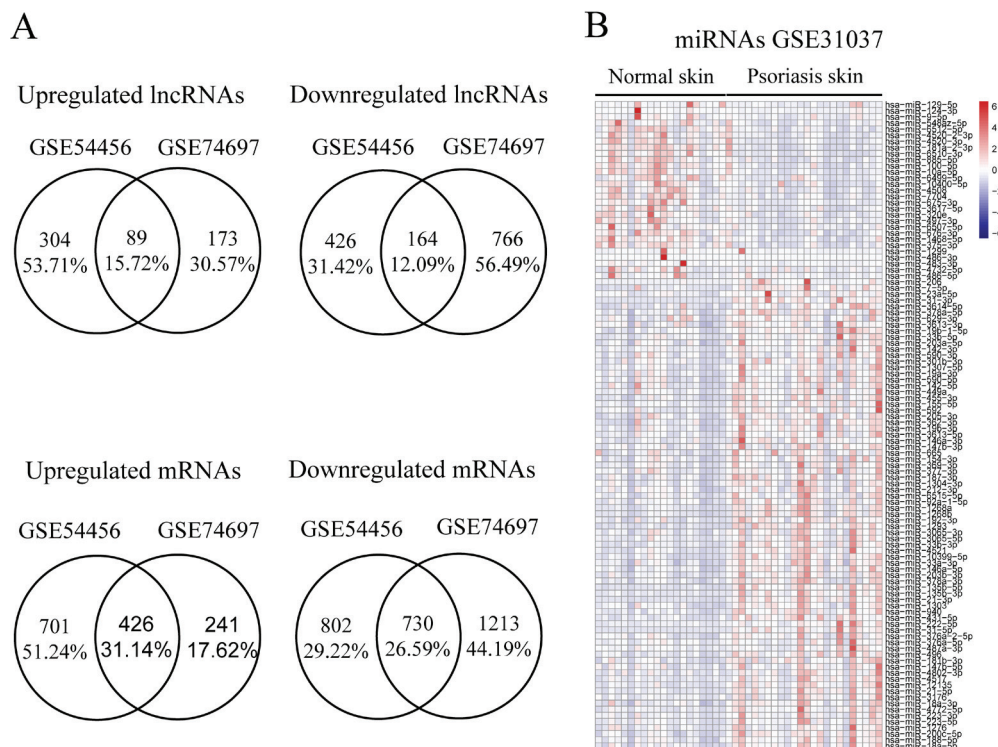
Figure 1. Identification of differentially expressed lncRNAs, mRNAs and miRNAs in psoriasis. (A) Integrated analysis of upregulated (top left) and downregulated (top right) lncRNAs. (B) Integrated analysis of upregulated (bottom left) and downregulated (bottom right) mRNAs. (B) Heat map displaying differential miRNA expression in psoriasis within the GSE31037 dataset. lncRNA, long non-coding RNA; miR/miRNA, microRNA; hsa, *Homo sapiens*.

were downloaded from the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/; lncRNA and mRNA expression profile accession numbers, GSE54456 and GSE74697; miRNA expression profile expression number, GSE31037). For the high-throughput raw sequencing data for lncRNAs and mRNAs, quality assessment was performed with FastQC (v0.11.7) (http://www.bioinformatics.babraham. ac.uk/projects/fastqc/); further, sequencing reads were trimmed by removing adapters and low-quality sequences were trimmed by using Trimmomatic (v0.38) (14). Hisat2 (v2.1.0) (15) was used to map the trimmed reads to the human GRCh38 reference genome (http://useast.ensembl. org/info/data/ftp/index.html), and the HTSeq-count (16) was then used to quantify the genes. Furthermore, microarray data (accession no. GSE13355) for comparing the difference in the expression of lncRNAs were also downloaded from the GEO database. After the probe was set, re-annotation was performed to identify specific lncRNAs. The method of the re-annotation method was performed as previously described by Shen *et al* (17). For the miRNA high-throughput raw sequencing data, miRDeep2 (18) was used to remove adapters, map the trimmed reads to the human GRCh38 reference genome and quantify the expression of miRNAs.

Screening for differentially expressed lncRNAs, miRNAs and mRNAs. The differentially expressed lncRNAs, mRNAs and miRNAs between psoriatic lesions involving the skin and healthy controls were identified with the DESeq2 package (19). The differentially expressed lncRNAs, mRNAs and miRNAs were selected according to the adjusted P-values (P<0.05 and |log2 fold change|>1).

Functional enrichment analysis. DAVID 6.8 (20) was used to perform the Gene Ontology (GO) functional enrichment analysis in the category Biological Processes (BP), and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway functional enrichment analysis of differentially expressed genes was also performed. P<0.05 was considered to indicate statistical significance.

Construction of the psoriasis-associated lncRNA-miRNA-mRNA network. miRNA-RNA interactions were downloaded from the experimentally verified databases DIANA-TarBase V8 (21) and miRTarBase (V7.0) (22), and miRNA-lncRNA interactions were downloaded from starBase v2.0 (23) and LncBase V2 (24). To construct the psoriasis-associated ceRNA network, the differentially expressed miRNAs, mRNAs and lncRNAs in psoriasis vs. normal samples were integrated with the miRNA-mRNA and miRNA-lncRNA pairs downloaded from the databases. Subsequently, miRNA-mRNA and miRNA-lncRNA pairs that shared common miRNAs were integrated into the psoriasis-associated ceRNA network. In the present study, to create the psoriasis-associated ceRNA network, only upregulated lncRNAs and downregulated miRNAs were integrated with upregulated mRNAs, while only downregulated lncRNAs and upregulated miRNAs were integrated with downregulated mRNAs (25). The degree of interaction - a topological property that indicates the number of edges that connect to a node-was also calculated. lncRNAs in the ceRNA network that interacted with >5 different miRNAs were identified as key lncRNAs in the present study. The networks were visualized using Cytoscape 3.6.1 (26).
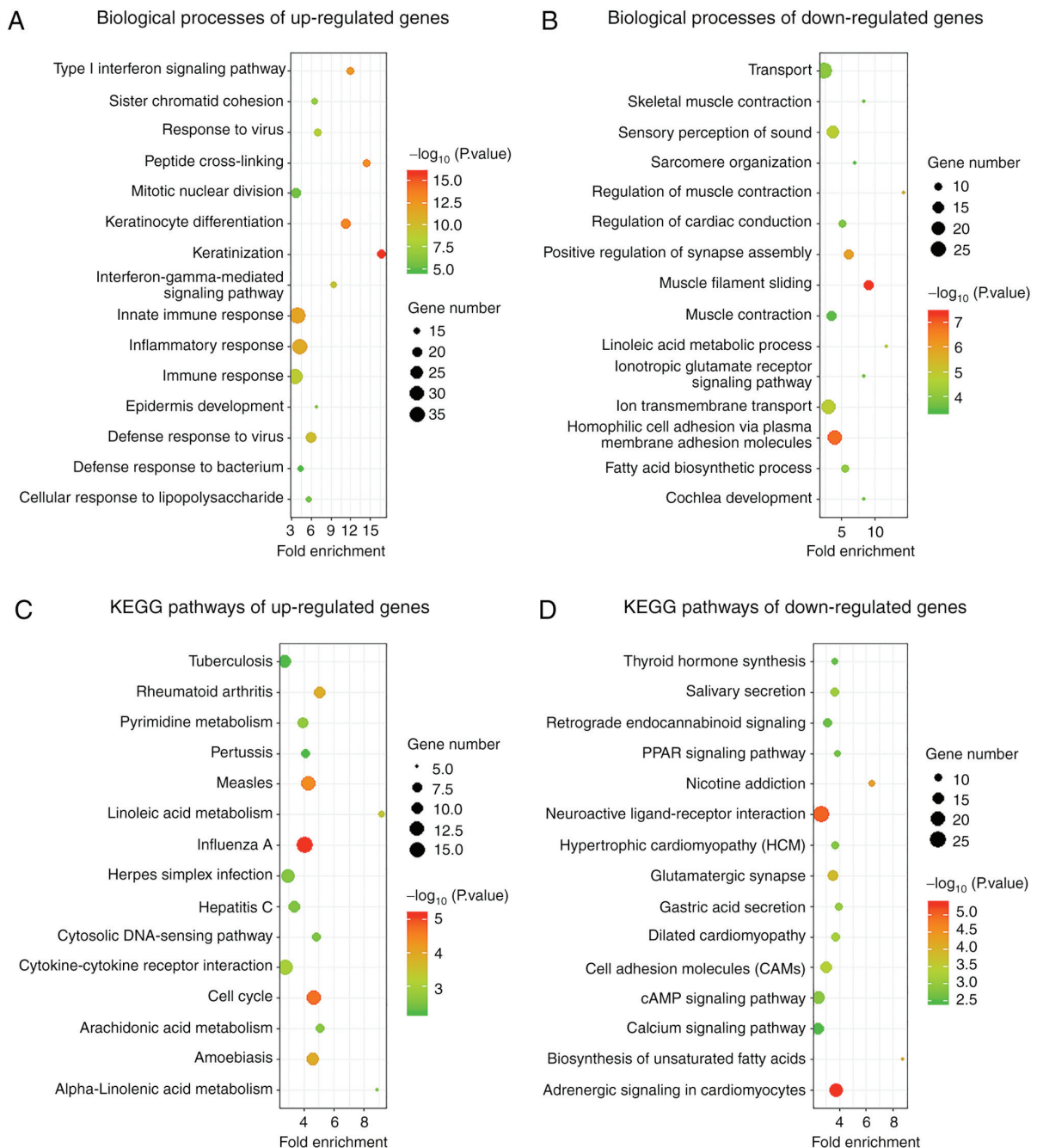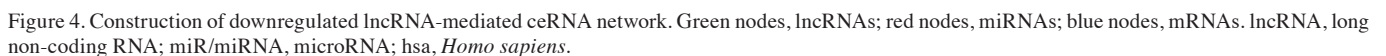
Figure 2. Biological function and pathway analysis of differentially expressed genes (top 15). (A) GO biological process enrichment analysis of upregulated mRNAs. (B) GO biological process enrichment analysis of downregulated mRNAs. (C) KEGG pathway analysis of upregulated mRNAs. (D) KEGG pathway analysis of downregulated mRNAs. KEGG, Kyoto Encyclopedia of Genes and Genomes; GO, gene ontology.

Results

Identification of differentially expressed lncRNAs, mRNAs and miRNAs. Analysis of the high-throughput data deposited under accession numbers GSE54456 and GSE74697 revealed that a total of 89 upregulated lncRNAs and 164 downregulated lncRNAs were shared between the datasets for psoriatic lesions involving the skin and healthy controls, 426 upregulated mRNAs and 730 downregulated mRNAs were shared between the two datasets (Fig. 1A). The sRNA sequencing data (GSE31037) were obtained from biopsy samples of 24 psoriasis lesions from skin biopsies and 20 normal skin biopsies from healthy controls. The expression profiles of

miRNAs between psoriasis-affected skin and healthy control skin were compared with the R Deseq2 package, and 77 upregulated miRNAs and 29 downregulated miRNAs were identified (Fig. 1B).

Functional enrichment analysis of differentially expressed mRNAs in psoriasis. To investigate the biological mechanisms of lncRNAs in the development of psoriasis, GO functional and KEGG pathway enrichment analyses were performed for differentially expressed genes (DEGs) in psoriasis. The results indicated that the upregulated mRNAs were enriched for the following GO terms: Keratinization, keratinocyte differentiation, peptide cross-linking, type I interferon

Figure 3. Construction of upregulated lncRNA-mediated ceRNA network. Green nodes, lncRNAs; red nodes, miRNAs; blue nodes, mRNAs. lncRNA, long non-coding RNA; miR/miRNA, microRNA; hsa, *Homo sapiens*.

Figure 4. Construction of downregulated lncRNA-mediated ceRNA network. Green nodes, lncRNAs; red nodes, miRNAs; blue nodes, mRNAs. lncRNA, long non-coding RNA; miR/miRNA, microRNA; hsa, *Homo sapiens*.

signaling pathway, innate immune response, inflammatory response, defence response to virus, interferon-γ-mediated response, immune response, response to virus, sister chromatid cohesion, epidermis development, cellular response to lipopolysaccharide, mitotic nuclear division and defence response to bacterium (Fig. 2A). By contrast, the downregulated genes were enriched in the following GO terms: Muscle filament sliding, homophilic cell adhesion via
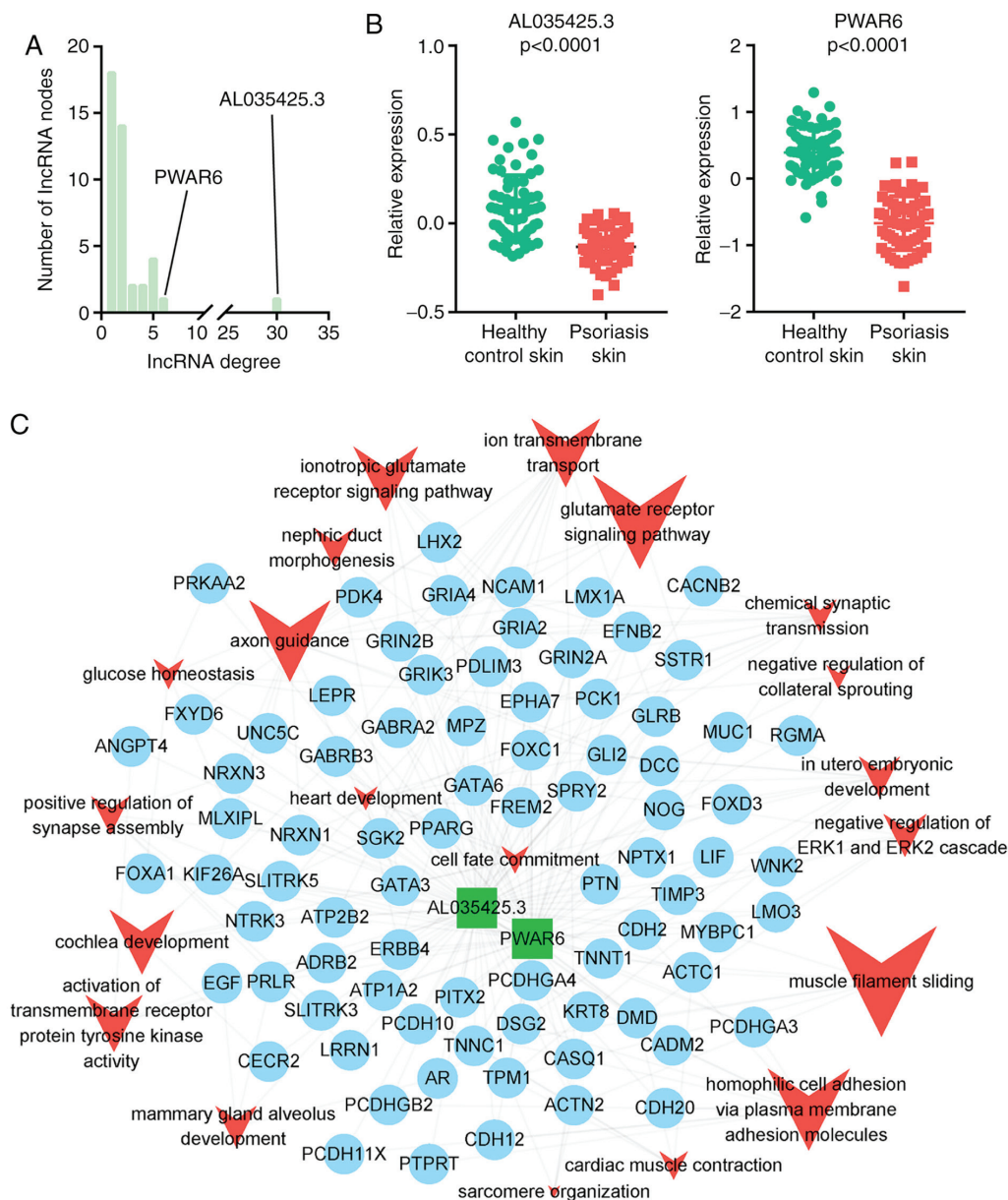
Figure 5. Identification of key lncRNA analysis. (A) The degree distribution of lncRNAs in the downregulated lncRNA-mediated ceRNA network are presented. (B) Expression level of two key lncRNAs in psoriasis skin and healthy control skin. (C) Key downregulated lncRNA-mediated biological processes analysis. lncRNA, long non-coding RNA; ceRNA, competing endogenous RNA; PWAR6, Prader Willi/Angelman region RNA 6.

plasma membrane adhesion molecules, positive regulation of synapse assembly, regulation of muscle contraction, ion transmembrane transport, linoleic acid metabolic process, sensory perception of sound, fatty acid biosynthesis process, transport, regulation of cardiac conduction, cochlear development, ionotropic glutamate receptor signaling pathway, skeletal muscle contraction, muscle contraction and sarcomere organization (Fig. 2B).

The most significant KEGG pathway terms for the upregulated mRNAs are provided in Fig. 2C: Influenza A, cell cycle, measles, amoebiasis, rheumatoid arthritis, linoleic acid metabolism, cytokine-cytokine receptor interaction, pyrimidine metabolism, α-linolenic acid metabolism, arachidonic acid metabolism, herpes simplex infection, hepatitis C, cytosolic DNA-sensing pathway, tuberculosis and pertussis. The downregulated genes were mainly involved in adrenergic signaling in cardiomyocytes, neuroactive ligand-receptor interaction, nicotine addiction, biosynthesis of unsaturated fatty acids, glutamatergic synapse, cell adhesion, dilated cardiomyopathy, salivary secretion, gastric acid secretion, cAMP signaling pathway, hypertrophic cardiomyopathy, peroxisome proliferator activated receptor-α signaling pathway, retrograde endocannabinoid signaling, thyroid hormone synthesis and calcium signaling pathway (Fig. 2D).

Construction of the psoriasis-associated ceRNA network. As presented in Figs. 3 and 4, the upregulated lncRNA-mediated ceRNA network contained 4 lncRNA nodes, 3 miRNA nodes and 139 mRNA nodes, and the downregulated lncRNA-mediated ceRNA network contained 42 lncRNA nodes, 43 miRNA nodes and 382 mRNA nodes.

Identification of key lncRNAs. lncRNA nodes that interacted with >5 different miRNAs were identified as key lncRNAs, which may have critical roles in biological networks. Of note, in the downregulated lncRNA-mediated ceRNA network, only two lncRNAs, AL035425.3 and Prader Willi/Angelman region RNA 6 (PWAR6), interacted with >5 different miRNAs (Fig. 5A), while in the upregulated lncRNA-mediated ceRNA network, none of the lncRNAs interacted with >5 different miRNAs. To further validate the differentially expressed key lncRNAs, a t-test was used to compare their expression between psoriasis lesions involving the skin and healthy controls. As presented in Fig. 5B, the key lncRNAs were downregulated in psoriasis-affected skin. To better understand the mechanism of those key lncRNAs in psoriasis, sub-ceRNA networks were extracted and GO functional enrichment analysis for the DEGs associated with those key lncRNAs was performed (Fig. 5C). In the GO enrichment analysis, the DEGs associated with lncRNA AL035425.3 and PWAR6 were involved in the biological processes of muscle filament sliding, glutamate receptor signaling pathway, homophilic cell adhesion via plasma membrane adhesion molecules, axon guidance, ion transmembrane transport, cochlear development and ionotropic glutamate receptor signaling pathway.

Construction of a specific validated miRNA-associated lncRNA-miRNA-mRNA sub-network. A systematic literature search in the PubMed and Web of Science databases was performed to identify real-time PCR-validated differentially expressed microRNAs, using the following key words: 'MicroRNA', 'microRNAs', 'miRNA', 'miRs' and 'Psoriasis'. A total of 37 miRNAs were identified, including 20 downregulated miRNAs and 17 upregulated miRNAs (Table I) (27-48). Of the identified miRNAs, 7 validated upregulated miRNAs were also present in the downregulated lncRNA-mediated ceRNA network, but none of the validated downregulated miRNAs were present in the upregulated lncRNA-mediated ceRNA network (Fig. 6A). The validated differentially expressed miRNA-associated lncRNA-miRNA-mRNA sub-networks were extracted (Fig. 6B). Finally, DEGs were identified from the literature. The miRNAs associated with the lncRNA-miRNA-mRNA sub-network were subsequently extracted and functional enrichment analysis was performed (Tables II and III). These genes were mainly enriched in the following GO terms: Muscle filament sliding, regulation of muscle contraction, in utero embryonic development, and enriched in the following KEGG pathways: AMPK signalling pathway, neuroactive ligand-receptor interaction, hypertrophic cardiomyopathy, calcium signalling pathway, insulin signalling pathway, adipocytokine signalling pathway, dilated cardiomyopathy, adrenergic signalling in cardiomyocytes and insulin resistance.

Discussion

Psoriasis is a chronic immune-mediated inflammatory disease that affects 3.2% of the adult population in the US (49). Over the past decades, the role of different cytokines in psoriasis has been studied widely (50), and therefore, cytokine-targeting drugs have been developed, including adalimumab (which targets tumor necrosis factor-α), secukinumab (which targets IL-17A) and ustekinumab (which targets IL-12 and IL-23

Table I. Differentially expressed miRNAs in psoriasis skin identified by the literature search.

A, Downregulated miRNAs

| miRNA name | miRNA fold-change in GSE31037 | | (Refs.) |
	log2 fold-change	P-value	
miR-10b-5p	-0.84	2.27×10^{-5}	(27)
miR-125b	-0.91	1.12×10^{-15}	(28)
miR-138	-0.22	2.98×10^{-2}	(29)
miR-143-3p	-0.33	4.32×10^{-2}	(27)
miR-145-5p	-0.05	7.84×10^{-1}	(27)
miR-181b-5p	-0.58	9.74×10^{-3}	(30)
miR-194	-0.28	1.17×10^{-1}	(31)
miR-196b-5p	-0.62	4.00×10^{-5}	(27)
miR-197	-0.28	2.11×10^{-2}	(32)
miR-20a-3p	0.61	1.26×10^{-4}	(33)
miR-217	0.17	5.51×10^{-1}	(34)
miR-320b	-0.54	5.42×10^{-4}	(35)
miR-338-3p	-0.48	5.24×10^{-3}	(27)
miR-423	0.05	8.52×10^{-1}	(32)
miR-424	0.83	1.99×10^{-6}	(36)
miR-4516	-0.90	1.03×10^{-2}	(37)
miR-486-3p	-1.09	4.17×10^{-3}	(38)
miR-876-5p	0.06	9.37×10^{-1}	(39)
miR-99a	-0.99	2.47×10^{-11}	(32)
miR-675-3p	-2.05	2.56×10^{-11}	(40)

B, Upregulated miRNAs

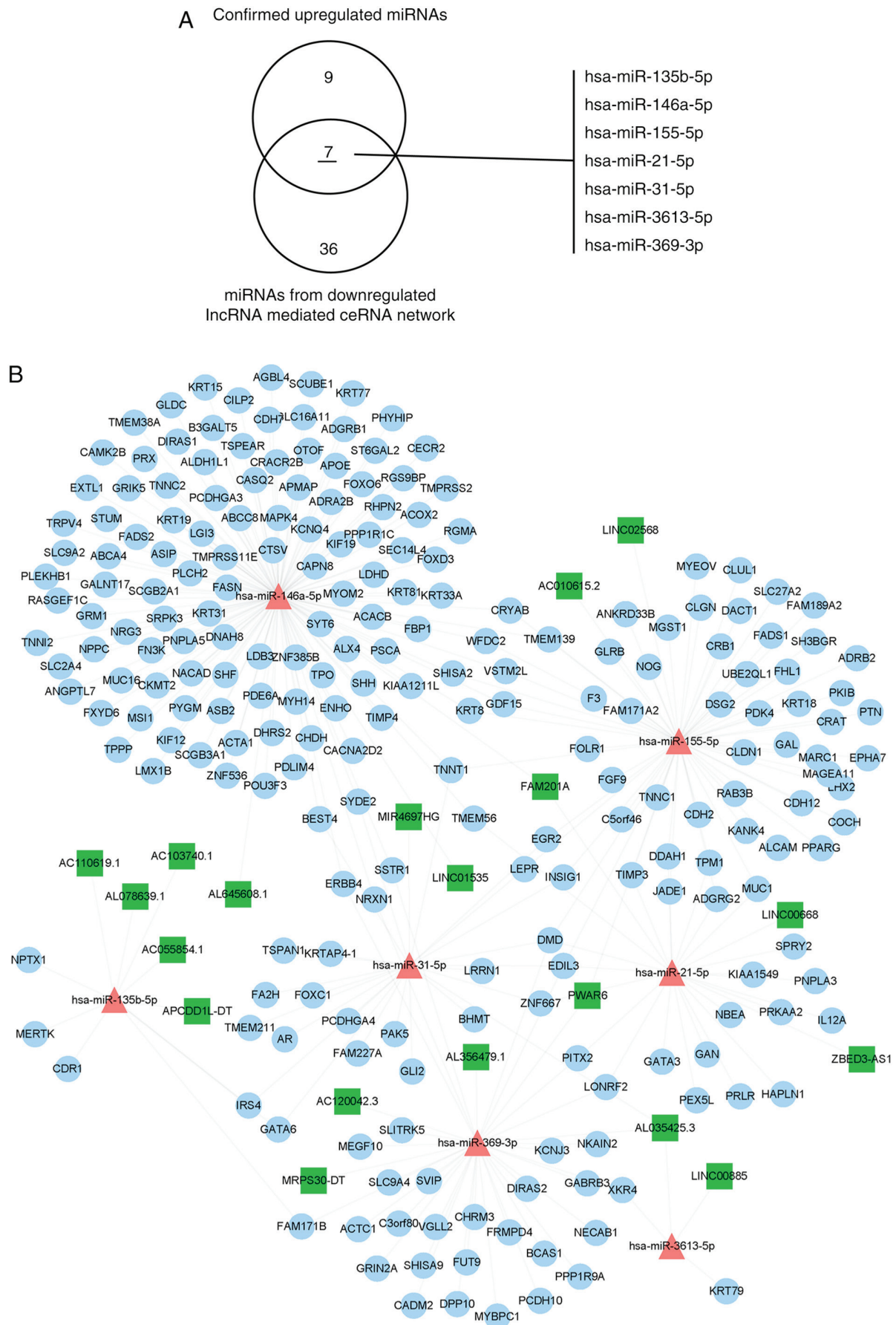| miRNA name | miRNA fold-change in GSE31037 | | (Refs.) |
	log2 fold-change	P-value	
miR-122-5p	-0.48	6.17×10^{-1}	(41)
miR-130a-3p	0.01	9.55×10^{-1}	(42)
miR-135b-5p	2.56	2.46×10^{-33}	(40)
miR-146a-5p	1.28	1.67×10^{-12}	(27)
miR-146b	0.36	9.03×10^{-2}	(43)
miR-155-5p	1.53	1.60×10^{-12}	(44)
miR-203	-0.12	5.77×10^{-1}	(28)
miR-205	0.56	8.04×10^{-5}	(45)
miR-21-5p	2.07	2.40×10^{-26}	(27)
miR-210	-0.54	2.03×10^{-2}	(46)
miR-221	-0.07	6.02×10^{-1}	(45)
miR-222-3p	0.11	4.26×10^{-1}	(45)
miR-31-5p	5.46	7.08×10^{-49}	(27)
miR-3613-5p	1.68	2.16×10^{-11}	(40)
miR-369-3p	1.30	3.78×10^{-11}	(47)
miR-431	2.20	1.67×10^{-7}	(40)
miR-744-3p	0.38	2.78×10^{-2}	(40)

miRNA/miR, microRNA.

Figure 6. Construction of a specific literature confirmed miRNA-associated lncRNA-miRNA-mRNA sub-network. (A) Intersection of confirmed upregulated miRNAs and miRNAs from downregulated lncRNA-mediated ceRNA network. (B) Confirmed differentially expressed miRNA-associated lncRNA-miRNA-mRNA sub-network. Green nodes, lncRNAs; red nodes, miRNAs; blue nodes, mRNAs. lncRNA, long non-coding RNA; miR/miRNA, microRNA; hsa, *Homo sapiens*.

Table II. Gene Ontology enrichment analysis of differentially expressed mRNAs from the specific miRNA-associated long non-coding RNA-miRNA-mRNA sub-networks (top 20).

Term	n (%)	P-value	Genes
GO:0030049~muscle filament sliding	9 (3.93)	1.17×10^{-8}	ACTC1, TNNT1, TNNC2, ACTA1, TNNC1, MYBPC1, DMD, TPM1, TNNI2
GO:0006937~regulation of muscle contraction	5 (2.18)	1.71×10^{-5}	TNNT1, TNNC2, TNNC1, TPM1, TNNI2
GO:0001701~in utero embryonic development	11 (4.80)	7.68×10^{-5}	MUC1, AR, NOG, LMX1B, GATA6, GATA3, FOXC1, GLI2, TPM1, PITX2, FOXD3
GO:0003009~skeletal muscle contraction	5 (2.18)	1.66×10^{-4}	TNNT1, TNNC2, TNNC1, MYH14, TNNI2
GO:0060048~cardiac muscle contraction	6 (2.62)	1.81×10^{-4}	ACTC1, TNNC1, DMD, TPM1, CASQ2, TNNI2
GO:0045214~sarcomere organization	5 (2.18)	3.54×10^{-4}	KRT19, KRT8, LDB3, TPM1, CASQ2
GO:0007267~cell-cell signaling	11 (4.80)	8.84×10^{-4}	AR, ADRB2, CRB1, SSTR1, FGF9, FADS1, ADRA2B, GDF15, MERTK, ASIP, SHH
GO:0042493~response to drug	12 (5.24)	9.89×10^{-4}	ACTC1, GATA6, GATA3, PPARG, NPPC, GRIN2A, PTN, TIMP4, ACACB, GAL, ABCC8, MGST1
GO:0048645~organ formation	3 (1.31)	1.35×10^{-3}	AR, GATA6, SHH
GO:0045165~cell fate commitment	5 (2.18)	2.08×10^{-3}	SPRY2, ERBB4, GATA6, GATA3, PPARG
GO:0007156~homophilic cell adhesion via plasma membrane adhesion molecules	8 (3.49)	2.72×10^{-3}	CDH12, CDH7, DSG2, CADM2, PCDH10, CDH2, PCDHGA4, PCDHGA3
GO:0007010~cytoskeleton organization	8 (3.49)	3.03×10^{-3}	APOE, DMD, KRT15, PAK5, KRT31, CECR2, GAN, TPM1
GO:0042472~inner ear morphogenesis	5 (2.18)	3.26×10^{-3}	SPRY2, KCNQ4, FGF9, GATA3, INSIG1
GO:0007605~sensory perception of sound	7 (3.06)	4.96×10^{-3}	COCH, SPRY2, KCNQ4, TSPEAR, GABRB3, OTOF, MYH14
GO:0009953~dorsal/ventral pattern formation	4 (1.75)	6.22×10^{-3}	NOG, LMX1B, LHX2, SHH
GO:0042593~glucose homeostasis	6 (2.62)	6.89×10^{-3}	SLC2A4, LEPR, PDK4, PPARG, TRPV4, PRKAA2
GO:0043627~response to estrogen	5 (2.18)	7.25×10^{-3}	KRT19, GATA6, GATA3, PPARG, GAL
GO:0032868~response to insulin	5 (2.18)	8.06×10^{-3}	EGR2, FADS1, TRPV4, GAL, ABCC8
GO:0007171~activation of transmembrane receptor protein tyrosine kinase activity	3 (1.31)	8.45×10^{-3}	ADRB2, NRG3, PRLR
GO:0034332~adherens junction organization	4 (1.75)	9.35×10^{-3}	CDH12, CDH7, CADM2, CDH2

GO, Gene Ontology; miRNA, microRNA.

p40) (51). However, the roles of lncRNAs in psoriasis have remained largely elusive.

lncRNAs have important roles in immune and inflammatory pathways by regulating gene expression through multiple mechanisms (52). Among these mechanisms, the ceRNA theory is commonly studied. According to this theory, lncRNAs act as 'sponges' for miRNAs and decrease the effects of miRNAs on their target genes, thus promoting the expression of target genes (53). For instance, Qiao *et al* (12) reported that lncRNA-MSX2P1 activates S100A71 and facilitates the growth of IL-22-stimulated keratinocytes by inhibiting miR-6731-5p. Furthermore, Li *et al* (54) demonstrated that lncRNA H19 regulates the differentiation of keratinocytes by increasing desmoglein 1 expression through sponging miR-130b-3p.

In the present study, psoriasis-associated lncRNA-miRNA-mRNA networks were constructed based on the ceRNA theory, and the DEGs were also subjected to GO BP enrichment analysis and KEGG pathway enrichment analysis.

GO BP enrichment analysis of the upregulated mRNAs indicated that the significantly enriched GO BP terms were psoriasis-associated biological processes, including keratinization (55), keratinocyte differentiation (3), inflammatory response (56) and immune response (56). Furthermore, the downregulated mRNAs were mainly enriched in the BP terms muscle filament sliding, homophilic cell adhesion via plasma membrane adhesion molecules, positive regulation of synapse assembly and regulation of muscle contraction.

In the present study, the downregulated lncRNAs AL035425.3 and PWAR6 were identified as key lncRNAs. GO BP analysis of the key lncRNAs revealed that AL035425.3 and PWAR6 were involved in muscle filament sliding, the glutamate receptor signaling pathway, homophilic cell adhesion via plasma membrane adhesion molecules, axon guidance, ion transmembrane transport, cochlear development and ionotropic glutamate receptor signaling pathway. Of the two key lncRNAs, PWAR6 was previously reported

Table III. Kyoto Encyclopedia of Genes and Genomes signaling pathway enrichment analysis of differentially expressed mRNAs from the specific miRNAs-associated long non-coding RNA-miRNA-mRNA sub-network.

Term	n (%)	P-value	Genes
hsa04152:AMPK signaling pathway	8 (3.49)	8.22×10^{-4}	IRS4, SLC2A4, LEPR, PPARG, FASN, FBP1, PRKAA2, ACACB
hsa04080:Neuroactive ligand-receptor interaction	11 (4.80)	2.25×10^{-3}	GLRB, ADRB2, PRLR, GABRB3, CHRM3, SSTR1, LEPR, GRIK5, GRIN2A, ADRA2B, GRM1
hsa05410:Hypertrophic cardiomyopathy	6 (2.62)	2.80×10^{-3}	ACTC1, TNNC1, DMD, PRKAA2, CACNA2D2, TPM1
hsa04020:Calcium signaling pathway	8 (3.49)	6.85×10^{-3}	ADRB2, TNNC2, CHRM3, ERBB4, TNNC1, GRIN2A, CAMK2B, GRM1
hsa04910:Insulin signaling pathway	7 (3.06)	7.39×10^{-3}	IRS4, PYGM, SLC2A4, FASN, FBP1, PRKAA2, ACACB
hsa04920:Adipocytokine signaling pathway	5 (2.18)	1.12×10^{-2}	IRS4, SLC2A4, LEPR, PRKAA2, ACACB
hsa05414:Dilated cardiomyopathy	5 (2.18)	2.06×10^{-2}	ACTC1, TNNC1, DMD, CACNA2D2, TPM1
hsa04261:Adrenergic signaling in cardiomyocytes	6 (2.62)	2.88×10^{-2}	ACTC1, ADRB2, TNNC1, CAMK2B, CACNA2D2, TPM1
hsa04931:Insulin resistance	5 (2.18)	4.58×10^{-2}	PYGM, SLC2A4, PRKAA2, ACACB, SLC27A2

miRNA, microRNA; hsa, *Homo sapiens*.

to be a tumor suppressor lncRNA in glioma, and high expression of PWAR6 was reported to be an indicator of better survival in glioma patients (57). In addition, PWAR6 is functionally important in Prader-Willi syndrome, and the disruption of its expression is associated with the pathogenesis of the disease (58). Two potential target miRNAs of PWAR6 were identified from the validated miRNA-associated lncRNA-miRNA-mRNA sub-network: miR-155-5p and miR-369-3p. Previous studies have demonstrated that knockdown of miR-155-5p suppresses psoriasis-associated inflammatory responses through regulation of the NLR family pyrin domain containing 3 inflammasome (44); furthermore, the expression levels of miR-369-3p in skin had a positive correlation with the Psoriasis Area and Severity Index, which is used to assess disease severity (47). Taken together, these results indicate that PWAR6 may be involved in the progress of psoriasis via regulation of the expression of miR-155-5p and miR-369-3p.

The present study has certain limitations that should be considered: First, although the expression profiles of lncRNA and mRNA were determined from the same specimens, the miRNA expression profile is from an independent dataset. Thus, combining these profiles into a network may introduce selection bias, and further experiments using the same specimens are required. In addition, further validation of key lncRNA expression levels in psoriasis samples is required. Finally, additional functional investigations of these lncRNAs in the context of psoriasis progression are required.

In summary, the present study presented a novel and important psoriasis-associated ceRNA network based on the ceRNA theory. The results indicate that certain lncRNAs have key roles in the development of psoriasis. In addition, the present study identified two lncRNAs, AL035425.3 and PWAR6, that were indicated to have a central role in psoriasis. The present study provides insight into the molecular mechanisms of psoriasis, and this may help to identify novel therapeutic targets for the treatment of psoriasis in the future.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

QZ and YS designed the current study, performed data analysis and wrote the manuscript. QY and YG performed the literature review regarding microRNAs in psoriasis. ZL, HX and YW analyzed the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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