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Integrated Bioinformatic Analysis of Plasma microRNA Sequencing Profiles Identifies a Potential Regulatory Network in Atopic Dermatitis

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ABSTRACT

Atopic dermatitis is a prevalent, chronic inflammatory skin disorder characterized by complex interactions between epidermal barrier dysfunction and immune system dysregulation. Although microRNAs have emerged as crucial post-transcriptional regulators of gene expression, their specific systemic profiles and overarching regulatory networks in human plasma remain insufficiently characterized. This study aims to provide a comprehensive, network-level understanding of microRNA-mediated regulation in atopic dermatitis to identify central molecular drivers and potential therapeutic targets. We conducted a systematic re-analysis of plasma microRNA sequencing data from patients with atopic dermatitis and healthy controls. The computational workflow utilized the Galaxy platform and the DESeq2 algorithm for differential expression analysis, incorporating rigorous statistical pre-filtering to ensure data quality. High-confidence target genes were predicted through a triple-consensus approach integrating multiple specialized databases. A comprehensive microRNA-target interaction network was then constructed, followed by topological analysis to identify influential regulatory hubs and biological pathway enrichment. Our analysis identified twenty-six differentially expressed miRNAs, comprising seventeen down-regulated and nine up-regulated molecules. Topological analysis revealed that hsa-miR-93-5p functions as the primary high-connectivity hub microRNA, interacting with one hundred and ninety-five high-confidence targets. Furthermore, the gene ATXN1 was identified as a central hub within the messenger RNA network. Functional enrichment analysis demonstrated that these targets are primarily involved in enzyme-linked receptor signaling pathways and, additionally, pathways related to metabolic stress, hypoxia-inducible factor-1 signaling, and adenosine monophosphate-activated protein kinase signaling were significantly enriched. This study highlights a novel, systematic regulatory axis involving hsa-miR-93-5p and ATXN1 in the pathogenesis of atopic dermatitis. By shifting the focus from single-pair interactions to a global network perspective, these findings provide a robust framework for identifying biomarkers and developing multi-target therapeutic strategies aimed at restoring skin barrier homeostasis and modulating cutaneous inflammation. While these computational insights offer high-confidence candidates, further experimental validation is essential to confirm their clinical utility.

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Introduction

Atopic dermatitis (AD), the most common inflammatory skin condition, affects about one-fifth of young children and 3% to 5% of adults, typically arising from environmental triggers in genetically predisposed individuals (Afshari *et al.,* 2024). AD develops from a genetic

predisposition influenced by environmental and lifestyle factors, with over 30 genomic regions linked to the disease, particularly those affecting epidermal structure and immune function. Key mechanisms include skin barrier defects-such as those caused by FLG gene mutations-and T-cell-mediated inflammation driven by type 2 cytokines (IL-4, IL-5, IL-13) (Wollenberg *et al.,* 2023). AD is characterized by recurrent eczematous lesions, severe pruritus, and dry, sensitive skin, which, over time, can lead to dull, red, and lichenified patches due to persistent inflammation and scratching, ultimately resulting in a significant decrease in the quality of life due to persistent itching that interferes with daily activities and causes insomnia and sleep disorders (Facheris *et al.,* 2023; Sroka *et al.,* 2021)

In AD, numerous potential biomarkers from genomic, transcriptomic, proteomic, and morphologic data, measurable in samples such as blood, saliva, urine, or skin, have been identified for disease risk, diagnosis, prognosis, treatment prediction, and monitoring, yet none have been adopted into routine clinical practice (Bakker *et al.,* 2023).

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression post-transcriptionally and contribute to various diseases, including skin inflammation, yet their expression profiles in the skin of atopic dermatitis patients have been scarcely investigated (Carreras-Badosa *et al.,* 2022). MicroRNAs have been proposed as a regulatory link between skin barrier dysfunction and immune dysregulation in atopic dermatitis. Multiple microRNAs, including miR-151a, miR-155, miR-10a-5p, miR-29b, miR-124, miR-143, miR-146a-5p, and miR-223, have been implicated in the pathogenesis, diagnosis, and potential treatment of atopic dermatitis through roles in immune regulation, skin barrier integrity, keratinocyte dynamics, and inflammatory pathways, offering promising avenues for biomarker development and targeted therapies (Khosrojerdi *et al.,* 2024). However, most studies have focused on individual miRNAs or limited pathways, leaving the broader systemic regulatory landscape of circulating miRNAs insufficiently characterized. In addition, differences in analytical approaches and filtering strategies may lead to inconsistent identification of key miRNAs, highlighting the need for complementary re-analysis.

Bioinformatics analysis of various data, including non-coding RNA and mRNA expression, enables the identification of key factors involved in disease pathogenesis and advances understanding of complex genetic disorders (Peng *et al.,* 2021; Sindhu *et al.,* 2025).

Despite prior analyses of this dataset focusing mainly on single miRNA-target axes, broader regulatory interactions may have been overlooked. In addition, different analytical frameworks and stricter filtering can reveal additional biologically relevant miRNAs and regulatory hubs. To address this, we applied an integrated network-based re-analysis with a triple-consensus and stringent pre-filtering strategy to improve robustness and reduce method-specific bias. This approach enhances the identification of reproducible regulatory hubs relevant to AD pathophysiology. Therefore, this study aims to identify novel hub microRNAs and key regulatory genes in Atopic Dermatitis using a systematic re-analysis of raw high-throughput data, hypothesizing that a complementary bioinformatic framework can uncover previously unrecognized regulatory interactions.

Materials and Methods

Data collection and study design

Plasma miRNA sequencing data were obtained from the NCBI BioProject database (Accession: PRJNA511723). The dataset includes raw sequence reads from 10 samples (5 atopic dermatitis patients and 5 healthy controls), generated by the Shanghai Skin Disease Hospital (submission date: December 25, 2018). The total data volume was 5 Gbases, processed as described below to identify differentially expressed miRNAs (DE-miRNAs) and explore their regulatory roles in AD pathogenesis.

miRNA-Seq data processing

Raw miRNA sequencing data (FASTQ format) from BioProject PRJNA511723 were uploaded to the Galaxy platform (usegalaxy.org). Initial quality control was performed using FastQC (v0.12.1) to evaluate read quality and adapter content. Reads were trimmed using Fastp (v0.23.4) to retain sequences with a length of 18–24 nucleotides, applying quality filtering (Phred

score≥ 20) and adapter removal. Trimming parameters were selected based on the typical length distribution of mature miRNAs and commonly used thresholds in small RNA-seq analyses. Post-trimming quality was assessed using MultiQC (v1.25.1) to ensure data integrity. For mapping, known mature miRNA sequences were retrieved from miRBase and imported into Galaxy. Reads were mapped to the human reference genome (hg38) using the miRDeep2 Mapper tool (v0.1.3) with default parameters. Default miRDeep2 settings were used as they have been previously validated for accurate miRNA identification in human small RNA-seq datasets. miRNA quantification was performed using the miRDeep2 Quantifier tool, generating a count matrix of miRNA expression levels for downstream analysis.

Differential expression analysis

Differential expression analysis (DEA) was performed using DESeq2 (v1.44.0) in R to compare AD patients (n= 5) with healthy controls (n= 5). DESeq2 remains one of the most robust and reproducible tools for differential expression analysis, particularly due to its empirical shrinkage of dispersion and fold-change estimates, which improves stability in small-sample RNA-seq datasets (Kalantari-Dehaghi *et al.,* 2025). To reduce noise and bias, a pre-filtering step was applied to remove miRNAs with either zero/low counts or disproportionately high counts (outliers). The remaining count matrix from miRDeep2 was normalized via the median-of-ratios method. Significantly DE-miRNAs were identified using thresholds of P-adj< 0.05 and |log2FC| > 1.

miRNA target prediction and multi-database integration

To enhance the reliability of the identified regulatory interactions, potential target genes for the significantly DE-miRNAs were predicted using the miRWalk v3.0 platform. A rigorous integration strategy was employed, where only targets consistently identified across three major databases, TargetScan, miRTarBase, and miRDB were retained for further analysis. This intersection-based approach was used to ensure high-confidence miRNA-target pairs by combining validated evidence with advanced predictive algorithms.

Network topology and hub identification

The miRNA-target interaction network was constructed and analyzed using custom R scripts. To identify key regulatory elements, we evaluated the network's topological properties by calculating node degrees. Given the directed bipartite nature of miRNA-target networks, out-degree and in-degree are appropriate and biologically interpretable measures of regulatory influence, and were therefore prioritized over more complex centrality metrics. Hub miRNAs were defined as those with the highest out-degree (maximum number of targets), while Hub genes were identified based on their in-degree (targeted by the highest number of miRNAs). These hub nodes represent the most influential components within the Atopic Dermatitis (AD) regulatory landscape.

Functional enrichment and pathway analysis

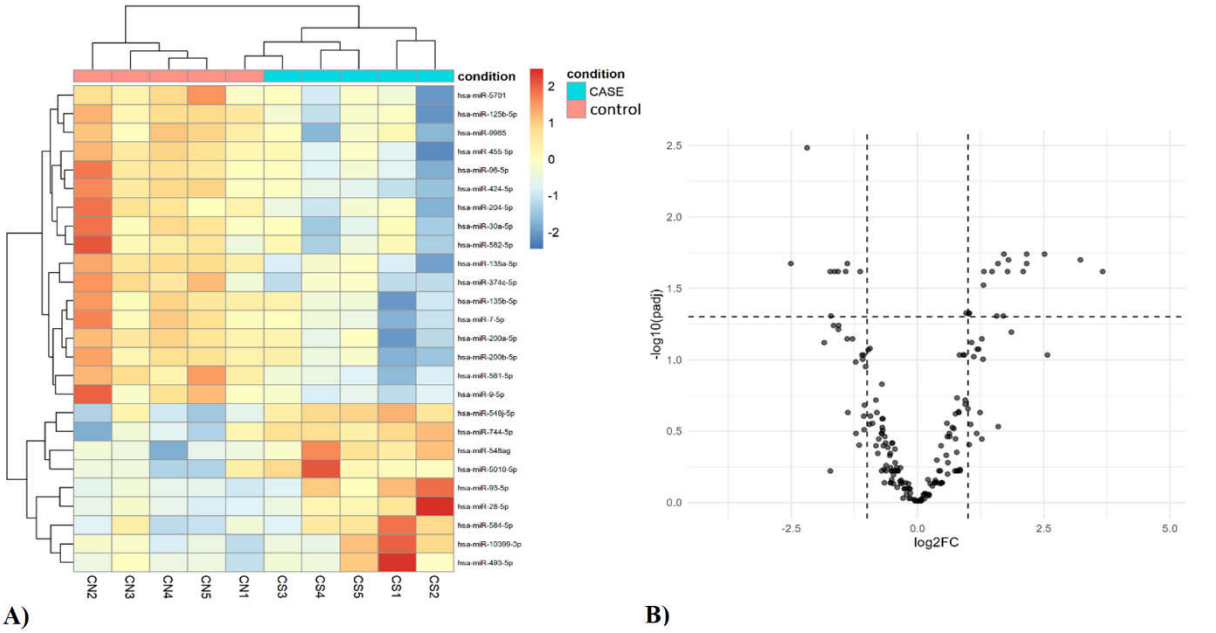
To elucidate the biological significance of the identified target genes, functional enrichment analysis was performed using the DAVID (Database for Annotation, Visualization, and Integrated Discovery) bioinformatics resource. The analysis encompassed Gene Ontology (GO) terms, including Biological Process (BP), Molecular Function (MF), and Cellular Component (CC), as well as KEGG pathway enrichment. To identify the most biologically relevant functions, results were ranked by their statistical significance. For each category, the top 10 terms with the highest -log10(P-value) were selected for further interpretation and visualization.

Results

Identification of DE-miRNAs

The differential expression analysis using DESeq2 identified 26 significant miRNAs in Atopic Dermatitis (AD) patients compared to healthy controls, based on thresholds of P-adj< 0.05 and |log_2 FC|> 1. The volcano plot illustrates the global distribution of these transcripts, showing a clear divergence into significantly up-regulated and down-regulated groups. Hierarchical clustering further confirmed these findings, as the heatmap showed a robust

separation between the CASE and CONTROL groups. This set of 26 DE-miRNAs serves as the primary regulatory candidates for subsequent functional analysis (Fig. 1).



A) B)

Fig. 1. Differential expression of miRNAs in Atopic Dermatitis: A) Hierarchical clustering heatmap of 26 DE-miRNAs, with red and blue representing up- and down-regulation, respectively, showing distinct separation between CASE (CS) and CONTROL (CN) groups; B) Volcano plot displaying the global miRNA distribution; vertical dashed lines denote |log2 FC| > 1 and the horizontal line indicates P-adj < 0.05.

miRNA-target network construction

Following the identification of the 26 DE-miRNAs, target prediction was performed using the miRWalk platform. By selecting only the targets common to TargetScan, miRTarBase, and miRDB, a total of 528 high-confidence target genes were identified. This consensus-based approach ensured a robust regulatory network, filtering out potential false positives and focusing the analysis on the most reliable miRNA-target interactions for further topological study.

Topological analysis and hub selection

Topological analysis of the miRNA-target network was performed to identify central regulatory hubs. Based on out-degree connectivity, hsa-miR-93-5p emerged as the most prominent hub miRNA, regulating 195 targets, followed by hsa-miR-204-5p and hsa-miR-125b-5p (Table 1). Regarding target genes, ATXN1) NM-000332)exhibited the highest in-degree; it is regulated by three distinct miRNAs. These high-connectivity nodes represent the core regulatory elements within the atopic dermatitis landscape.

Table 1. Top 10 Hub miRNAs ranked by out-degree centrality.

Rank	miRNA ID	Target Count (Out-degree)
1	hsa-miR-93-5p	195
2	hsa-miR-204-5p	73
3	hsa-miR-125b-5p	60
4	hsa-miR-424-5p	38
5	hsa-miR-7-5p	28
6	hsa-miR-9-5p	28
7	hsa-miR-96-5p	28
8	hsa-miR-30a-5p	12
9	hsa-miR-135b-5p	9
10	hsa-miR-455-5p	6

Gene ontology enrichment analysis

Functional enrichment analysis of the 528 high-confidence target genes was performed across three Gene Ontology (GO) categories: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). The results, ranked by -log10(P-value), reveal a significant involvement

of these targets in signaling and regulatory mechanisms associated with Atopic Dermatitis.

In the Biological Process category, the most significant enrichment was observed for "enzyme-linked receptor protein signaling pathway," which exhibited the highest statistical significance. Other prominent terms included the negative and positive regulation of cellular processes, regulation of developmental processes, and cell surface receptor signaling pathways. The Cellular Component analysis indicated that the target gene products are primarily localized within "intracellular anatomical structures," "cytoplasm," and "cytosol." Significant enrichment was also noted in the nucleoplasm and various organelle compartments, including intracellular membrane-bounded organelles and cell junctions. For Molecular Function, the targets were significantly associated with "transcription cis-regulatory region binding" and "transcription regulatory region nucleic acid binding." Other highly ranked functions included transcription factor binding, various forms of DNA binding (double-stranded and sequence-specific), and protein binding, with "SMAD binding" also appearing among the top enriched terms. Collectively, these GO findings suggest that the DE-miRNAs primarily influence Atopic Dermatitis by modulating signal transduction and transcriptional regulation (Fig. 2).

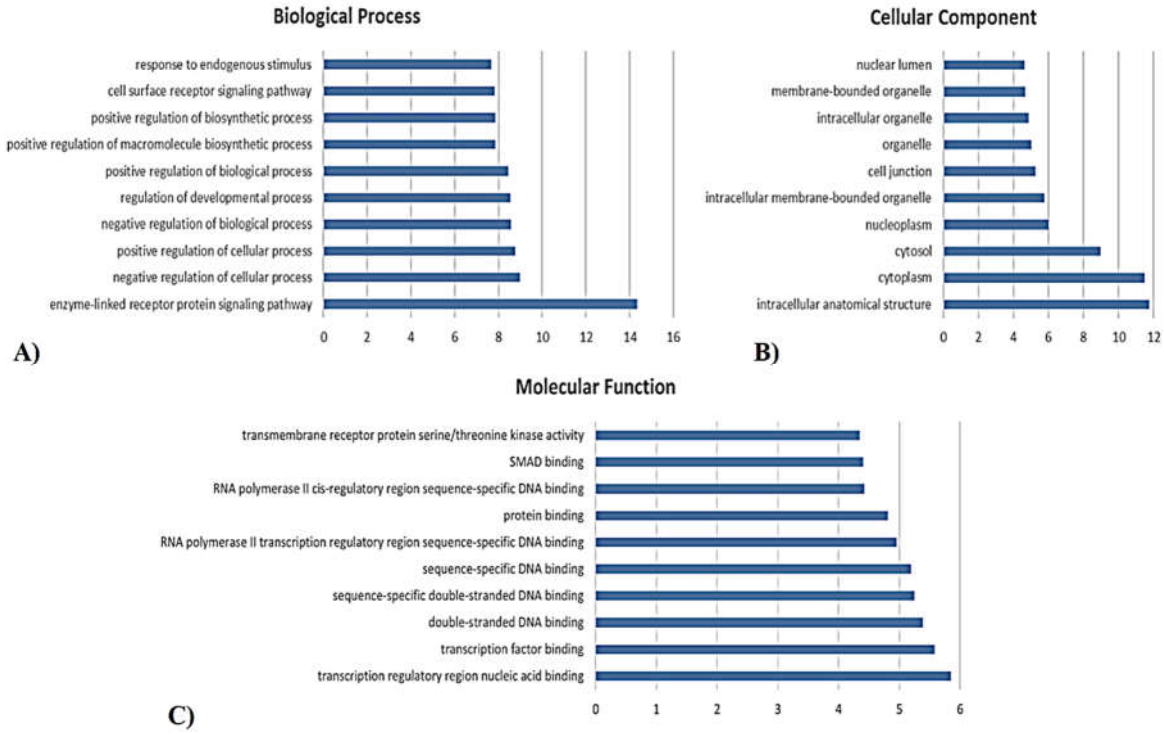


Fig. 2. Top 10 GO functional enrichment analysis of DE-miRNA targets: A) Biological process; B) Cellular component; C) Molecular function.

KEGG pathway analysis

KEGG enrichment analysis was performed to identify the signaling cascades modulated by the DE-miRNA targets. The most significant enrichment was observed for "MicroRNAs in cancer", followed by pathways regulating pluripotency and the HIF-1 signaling pathway. Additionally, targets were significantly associated with growth factor-related routes, including EGFR tyrosine kinase inhibitor resistance and Endocrine resistance. Other notable enriched pathways included AMPK signaling, Neurotrophin signaling, and Focal adhesion. These results suggest that the identified miRNA hubs may contribute to AD-associated molecular dysregulation by coordinating metabolic, stress-response, and cell-junction signaling networks (Fig. 3).

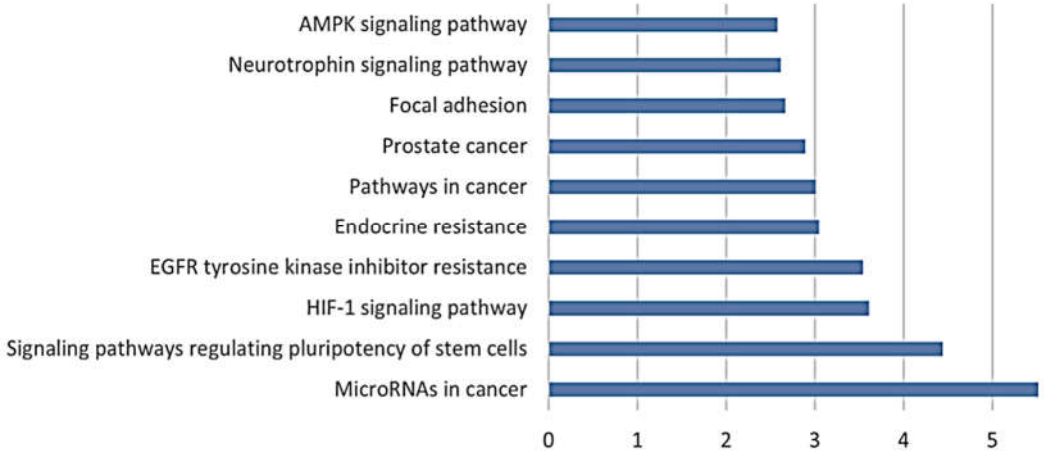


Fig. 3. KEGG pathway enrichment analysis of DE-miRNA targets. The bar chart illustrates the top 10 significantly enriched pathways. The x-axis represents the -log10 (P-value).

Discussion

In this study, differential expression analysis identified 26 significant miRNAs in Atopic Dermatitis patients, comprising 17 down-regulated and 9 up-regulated transcripts. Topological analysis revealed hsa-miR-93-5p as the primary hub miRNA, coordinating a regulatory network of 528 high-confidence target genes. The predominance of down-regulated miRNAs suggests a broad loss of post-transcriptional repression, potentially leading to the over-activation of inflammatory pathways characteristic of AD pathogenesis. Although the cohort size (n=10) is limited, this study was designed as an exploratory re-analysis, and the application of strict filtering and consensus-based network inference helps mitigate false positives and improve robustness; however, findings should be interpreted cautiously and validated in independent cohorts. In addition, the absence of detailed clinical metadata and the reliance on computational target prediction without experimental validation represent further limitations of this study.

In comparison with the previous study by Meng (Meng *et al.,* 2019), who analyzed a larger cohort and focused on validating a single regulatory axis (miR-194-5p/HS3ST2) using experimental assays, our study re-analyzes the same dataset using a stricter preprocessing and a consensus-based network approach. While Meng emphasizes a single mechanistic pathway, our work provides a broader systems-level view, identifying 26 DE-miRNAs and prioritizing hsa-miR-93-5p and ATXN1 as central network hubs based on connectivity. Both studies are consistent in using plasma miRNA profiles in AD, but they differ in scope and methodology: experimental validation versus network-level inference. A shared limitation is the small sample size and reliance on computational predictions, although Meng et al. include functional validation, whereas our findings remain in silico and hypothesis-generating.

Notably, most of the identified DE-miRNAs in this study have not been previously characterized in the context of Atopic Dermatitis (AD), highlighting the novelty of our findings. Among the few exceptions, miR-28-5p was previously reported to be upregulated in AD skin (Carreras-Badosa *et al.,* 2022), consistent with our results, suggesting its role as a potential immune-modulating biomarker. Our primary hub, hsa-miR-93-5p, although not yet directly linked to AD, has been implicated in inflammatory skin damage. Specifically, miR-93-5p is known to be sequestered by lncRNA Meg3, leading to the derepression of epiregulin (Ereg) signaling and the amplification of UVB-induced skin inflammation (Zhang *et al.,* 2019). Furthermore, miR-424-5p has been identified as a component of MSC-derived extracellular vesicles that regulate AD by suppressing mast cell activation and modulating Th2/Th17 responses (He *et al.,* 2024). Other significant miRNAs in our study, such as miR-135a and miR-96-5p, have

established roles in skin wound healing by modulating fibroblast migration and keratinocyte proliferation via LATS2 and BNIP3 targeting, respectively (Gao *et al.,* 2020; Wu *et al.,* 2019). The identification of these miRNAs in our AD dataset suggests they may be associated with processes involved in epidermal barrier integrity and cutaneous inflammation. However, as these findings are based on bioinformatic predictions, further experimental validation, including RT-qPCR for expression levels and dual-luciferase reporter assays for target interaction, is essential to confirm the functional involvement of each of these miRNAs in AD pathology.

In addition to the miRNA hubs, Ataxin-1 (ATXN1) emerged as a primary hub gene in our regulatory network. ATXN1 is a ubiquitous polyglutamine protein that functions as a transcriptional repressor by binding to chromatin and interacting with various transcriptional corepressors (Didonna *et al.,* 2020). While ATXN1 is well-characterized in the context of neurodegenerative disorders, specifically Spinocerebellar Ataxia Type-1 (SCA1), where its expansion leads to proteotoxic gain-of-function and protein aggregation, its role in cutaneous biology remains largely unexplored (Buijsen *et al.,* 2023; Vagiona *et al.,* 2020). To our knowledge, ATXN1 has not been previously investigated in the pathogenesis of Atopic Dermatitis or general skin physiology. Given its established role as a key regulator of gene expression, our findings suggest that the targeting of ATXN1 by DE-miRNAs may represent a novel regulatory axis in AD. The dysregulation of such a central transcriptional repressor could lead to downstream imbalances in epidermal gene expression, which may be associated with dysregulation observed in AD patients. Nevertheless, the precise role of ATXN1 within the skin's molecular framework remains speculative based on our current data; therefore, rigorous experimental validation, such as protein expression analysis in AD skin biopsies and gene knockdown studies, is required to substantiate its functional significance as a pathological driver in this condition.

The functional enrichment results suggest a high probability of overlap between our identified miRNA-target network and the established molecular architecture of Atopic Dermatitis (AD). Regarding Biological Process (BP), the high significance of the enzyme-linked receptor protein signaling pathway potentially correlates with the aberrant activation of protease-activated receptors (PAR-2) and tyrosine kinases observed in clinical AD. It is likely that the dysregulated miRNAs in our study may be linked to dysregulation of this signaling axis, where imbalanced protease activity and tyrosine kinase signaling (such as the Jak-Stat pathway) contribute to barrier dysfunction and inflammatory microenvironments (Lee *et al.,* 2010; Szilveszter *et al.,* 2019).

In the Cellular Component (CC) category, the enrichment of targets in the intracellular anatomical structure and cell junctions suggests these miRNAs may influence the skin's role as a primary immune barrier. Given that the epidermis functions as an "alarm sensor," these targets might be involved in the release of alarmins (TSLP, IL-25, and IL-33) that orchestrate Th2-mediated immunity. Specifically, the targeting of genes within these compartments may be associated with changes in filaggrin expression and the resulting "leaky" barrier characteristic of AD lesions (Criado *et al.,* 2024).

Finally, the Molecular Function (MF) enrichment in transcription cis-regulatory region binding probably reflects the broad genomic reprogramming required for AD pathogenesis. This is supported by GWAS evidence showing that *cis*-regulated genes linked to AD are primarily over-expressed in skin and immune-related tissues. The identification of these binding functions within our network indicates that the DE-miRNAs may act as central switches, modulating the expression of genes that GWAS has already highlighted as critical genetic risk factors for the disease (Song *et al.,* 2022).

The KEGG pathway analysis provided systemic insights into how the 26 DE-miRNAs and their 528 targets are associated with molecular processes relevant to AD. The enrichment of MicroRNAs and pathways in cancer reflects the complex epidemiological relationship between AD and skin malignancies, where chronic inflammation may predispose patients to basal or squamous cell carcinomas (Zhu *et al.,* 2022). Similarly, the identification of Prostate cancer signaling may relate to the documented heterogeneous associations between AD severity

and the risk of specific solid organ malignancies (Wan *et al.,* 2022; Wan *et al.,* 2023).

The involvement of the Signaling pathway regulating pluripotency of stem cells is particularly relevant given that human-induced pluripotent stem cell-derived keratinocytes (iKera) express functional PAR2, a protein central to AD-related inflammatory axes (Nishimoto *et al.,* 2023). Furthermore, the HIF-1 signaling pathway likely modulates the chronic hypoxia and oxidative stress observed in AD lesions, which exacerbates inflammatory responses and itching symptoms (Na *et al.,* 2026).

The identification of EGFR tyrosine kinase inhibitor (TKI) resistance correlates with the clinical observation that EGFR inhibition often triggers xerosis and eczematous rashes mimicking AD histology (Zhu *et al.,* 2025). Additionally, the enrichment of Endocrine resistance highlights the impact of sex hormones, such as estrogen and progesterone, on epidermal barrier integrity and filaggrin expression (Weare-Regales *et al.,* 2022).

Finally, pathways such as Focal adhesion, which regulates the production of barrier proteins like loricrin and involucrin, and the Neurotrophin signaling pathway, which facilitates neuroimmune interactions and pruritus via BDNF and NGF, underscore the structural and sensory disruptions in AD (Kim *et al.,* 2019; Weihrauch *et al.,* 2023). The presence of AMPK signaling further suggests a regulatory mechanism for autophagy and pro-inflammatory cytokine inhibition, potentially mediated by IL-37 (Hou *et al.,* 2020). Together, these pathways suggest that the identified miRNA-target network governs a multi-layered response involving barrier function, immune signaling, and metabolic homeostasis.

In conclusion, this study identified 26 differentially expressed plasma miRNAs in atopic dermatitis and constructed a high-confidence regulatory network of 528 target genes. hsa-miR-93-5p emerged as the main hub miRNA, while ATXN1 was identified as a novel hub gene, suggesting a potentially novel regulatory association in AD. Enrichment analyses indicated that these miRNAs primarily modulate signaling pathways related to inflammation, transcriptional regulation, barrier function, and neuroimmune interactions. Overall, our findings provide new candidate biomarkers and mechanistic insights into AD, although experimental validation in larger cohorts is required.

Declarations

The English language of this manuscript was refined and improved for clarity and grammatical accuracy using Grammarly (Grammarly Inc.). The scientific content and data analysis remain the sole work and responsibility of the author.

Conflict of interest

The authors declare that there are no conflicts of interest.

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