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Differential expression analysis of serum exosome miRNAs in acral melanocytic tumor

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Abstract: **Background**: Acral melanocytic tumors are a common cutaneous neoplasm with malignant potential. Early and non-invasive biomarkers for identifying malignant transformation remain lacking. Exosomal microRNAs (miRNAs) have shown great potential as stable diagnostic indicators in various cancers. **Objectives**: To explore the differential expression and clinical significance of serum exosomal miRNAs in patients with acral melanocytic tumors. **Methods**: Exosomes were identified by transmission electron microscopy, nanoparticle tracking analysis, and Western blot. MiRNA sequencing was used to screen differentially expressed miRNAs. Target genes were predicted and analyzed using Gene Ontology and Kyoto Encyclopedia of Genes and Genomes. **Results**: A total of 69 differentially expressed miRNAs were identified, of which 14 were up-regulated and 55 down-regulated. Bioinformatics analysis showed that target genes were mainly enriched in cancer-related pathways and the MAPK signaling pathway. **Conclusion**: Acral melanocytic tumor-related miRNAs are stably present in serum exosomes and may serve as potential non-invasive biomarkers for the early detection and auxiliary diagnosis of acral melanoma.

Keywords: Acral melanoma; Exosome; miRNAs; Nevus; Signal pathways

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INTRODUCTION

Melanocytic tumors encompass both benign and malignant melanocytic neoplasms. The most common benign melanocytic tumor is the pigmented nevus, while the malignant counterpart is malignant melanoma (Melanoma). Malignant melanoma ranks among the most aggressive skin tumors, characterized by high invasiveness and lethality, accounting for approximately 90% of all skin cancer deaths (Swetter *et al*., 2019). A pigmented nevus is a benign neoplasm composed of nevus cells, representing the most common benign skin tumor in humans. Pigmented nevi can occur on the skin and mucous membranes of any body part. Data analysis and observations of numerous cases indicate that pigmented nevi possess a certain probability of malignant transformation under chronic stimuli such as long-term irritation or trauma (Jaroonwanichkul *et al*., 2023). Acral lentiginous melanoma, also known as acral lentiginous nevus melanoma, represents a distinct histological subtype of melanoma. It is the most common malignant melanoma in Asians and individuals with darker skin tones, accounting for up to 50% of cases in China. This subtype particularly favors the soles of the feet, exhibiting greater invasiveness and poorer prognosis compared to typical cutaneous malignant melanomas. Early-stage acral lentiginous melanoma can be cured through surgical excision of the lesion. However, due to its hidden nature and atypical presentation, it is often overlooked, potentially leading to fatal consequences. Therefore, early diagnosis of acral lentiginous melanoma is critically important. Exosomes are extracellular vesicles secreted by various cell types that mediate intercellular communication by transferring their contents (e.g., miRNAs) from secreting cells to recipient cells via carrier functions (Tan *et al*., 2022). miRNA is a short RNA molecule approximately 18–25 nucleotides in length. Research indicates that exosomes carry a significant amount of miRNA involved in tumor progression, metastasis, cellular immunity and other processes, playing a crucial role in tumor diagnosis, treatment and prognosis (Li *et al*., 2021). We hypothesize that extracellular miRNA may also hold clinical significance in the pathogenesis, diagnosis and treatment of acral melanoma.

MATERIALS AND METHODS

Data and methods

Clinical data

Five cases of acral melanoma and five cases of plantar nevus (pathologically diagnosed as junctional nevus) were collected from patients who visited the Civil Aviation General Hospital between October 1, 2022 and October 1, 2023 and were confirmed by histopathology and immunohistochemistry. Patient ages ranged from 53 to 76 years, with a median age of 63.5 (63, 64) years and a mean age of 62.5 years. *Inclusion criteria*: confirmed patients (selected based on the ABCDE rule for atypical nevi: irregular shape, asymmetry, irregular borders, uneven color, diameter >6 mm, or elevation; meeting one or more criteria), with acral lentiginous melanoma diagnosed clinically in conjunction with histopathology and immunohistochemistry. Each patient signed an informed consent form prior to surgery. *Exclusion criteria*: unclear diagnosis or absence of histopathological or immunohistochemical results; history of neurological disorders, immune-related skin diseases, or relevant neoplastic conditions. This study was approved by the Ethics Committee.

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Methods

Serum sample processing

Collected patient serum samples and promptly stored them at -80°C.

Exosome extraction

Thawed serum samples on ice. Centrifuged using an Optima XPN-100 ultracentrifuge (Beckman Coulter, USA) to remove supernatant. Resuspended pellet in sterile phosphate-buffered saline and collected resuspension.

Exosome characterization

Characterized exosomes using three mutually corroborating methods:

Observed and photographed exosomes under transmission electron microscopy (JEOL JEM-1400, JEOL Ltd., Japan); Nanosight tracking analysis (NTA) was performed using a Malvern Panalytical NanoSight NS300 system (Malvern Panalytical, UK) for real-time individual imaging and observation of specific exosomes and microvesicles within the 50–1000 nm diameter range in suspension was performed to determine hydrodynamic particle size; Western blot (WB) was used to detect exosomal marker proteins.

Exosome RNA extraction, quality control and miRNA sequencing

Following exosome lysis, total RNA containing miRNAs was extracted using the miRNeasy Micro Kit (QIAGEN, Germany). The extracted total RNA underwent quality control via Agilent 2100 (Agilent Technologies, USA). Upon passing quality control, cDNA libraries were prepared using the NEXTflex small RNA-Seq Kit (Bioo Scientific, USA). Enriched miRNAs were sequenced using the Illumina NovaSeq 6000 platform (Illumina, USA). Raw sequencing data were filtered to remove contamination and adapter sequences. miRNA sequence diversity, abundance, length distribution, read counts and data yield were quantified. All miRNAs were aligned and annotated against reference RNA sequences. After standardizing raw miRNA sequence data, results were filtered based on significance criteria (≥2-fold change in miRNA expression and a False Discovery Rate (FDR) adjusted P-value ≤ 0.05) to identify significantly differentially expressed miRNAs. The FDR correction was performed using the Benjamini-Hochberg procedure to account for multiple testing. The fold-change threshold of ≥2 was selected as it represents a common standard in the field of miRNA differential expression analysis and has been reliably validated in melanoma-related miRNA studies (Gencia *et al*., 2020; Prodan *et al*., 2024). This threshold aims to prioritize miRNAs with substantial expression changes, ensuring that the observed differences are of both statistical and biological significance, thereby reducing the likelihood of false positives arising from minor fluctuations in miRNA expression (Prodan *et al*., 2024).

miRNA bioinformatics analysis

Sequences obtained from sequencing were aligned against known miRNAs in the miRBase database (release 22.1) to annotate known miRNAs. Sequences were also aligned against the human reference genome GRCh38 (hg38) to predict novel miRNAs using folding models. Differential miRNA expression was analyzed between samples from patients with acral melanoma and pigmented nevi. Using miRanda software, we predicted potential target sites for miRNA sequences (including known and novel miRNAs) and corresponding genomic cDNA sequences of the species. We performed GO enrichment analysis, KEGG enrichment analysis and functional prediction for the target genes of differentially expressed miRNAs.

Validation of miRNA expression by quantitative real-time PCR (qRT-PCR)

To validate the sequencing results, the top five most significantly differentially expressed miRNAs (NovelmiRNA-1212, NovelmiRNA-49, NovelmiRNA-728, NovelmiRNA-181, NovelmiRNA-225) were selected for qRT-PCR analysis. Total RNA extracted from serum exosomes was reverse transcribed using the miRcute Plus miRNA First-Strand cDNA Kit (Tiangen, China). qRT-PCR was then performed using the miRcute Plus miRNA qPCR Kit (Tiangen, China) on a QuantStudio 5 Real-Time PCR System (Applied Biosystems, USA). U6 small nuclear RNA was used as an endogenous control for normalization. The relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method.

RESULTS

Isolation and identification of exosomes

Serum samples revealed flat spherical or disc-shaped microvesicles under electron microscopy, characteristic of exosomal structures (Fig. 1A). Serum NTA results showed particles predominantly within the 60–200 nm diameter range, particularly those between 106–162 nm. Exosomes are named for their morphology, being the smallest extracellular vesicles with diameters ranging from 40–200 nm (Krylova and Feng, 2023). This indicates a high proportion of exosomes present (Fig. 1B). WB analysis of target bands demonstrated positive expression of exosome markers CD9 and TSG101 (Fig. 1C). Combined results from transmission electron microscopy, NTA and WB experiments conclude that substantial exosome populations are present in serum samples from both acral lentiginous melanoma and pigmented nevus patients.

Analysis of differentially expressed miRNAs

Experimental results revealed 69 differentially expressed miRNAs screened from serum samples of pigmented nevi and acral melanoma, including 14 upregulated and 55 downregulated miRNAs (Fig. 2). Table 1 lists the top ten significantly differentially expressed miRNAs.

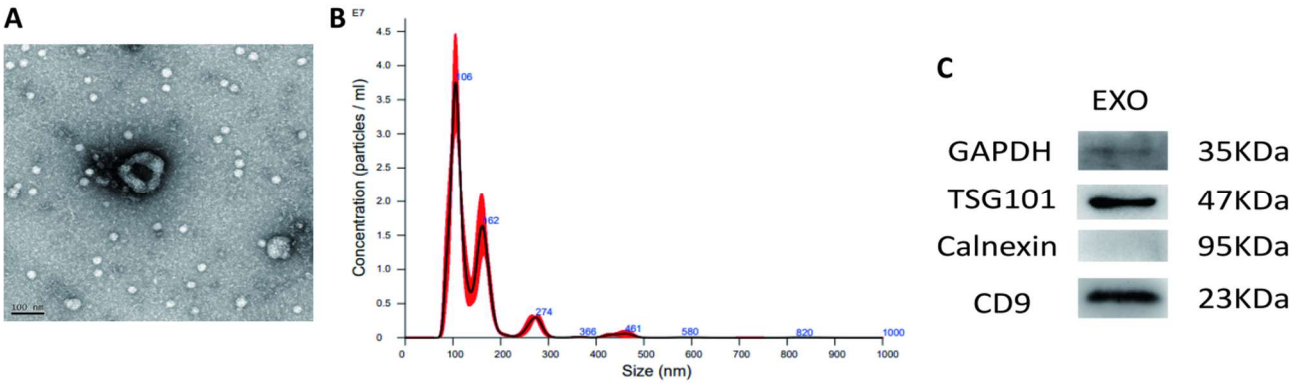

Fig.1: Characterization of serum-derived exosomes from acral melanocytic tumors
(A) Transmission electron microscopy (TEM) image revealing the classic cup-shaped morphology of isolated vesicles (scale bar: 100 nm). (B) Nanoparticle tracking analysis (NTA) profile showing the size distribution of isolated particles. (C) Western blot (WB) analysis confirming positive expression of exosomal markers CD9 and TSG101, with calnexin as negative control.

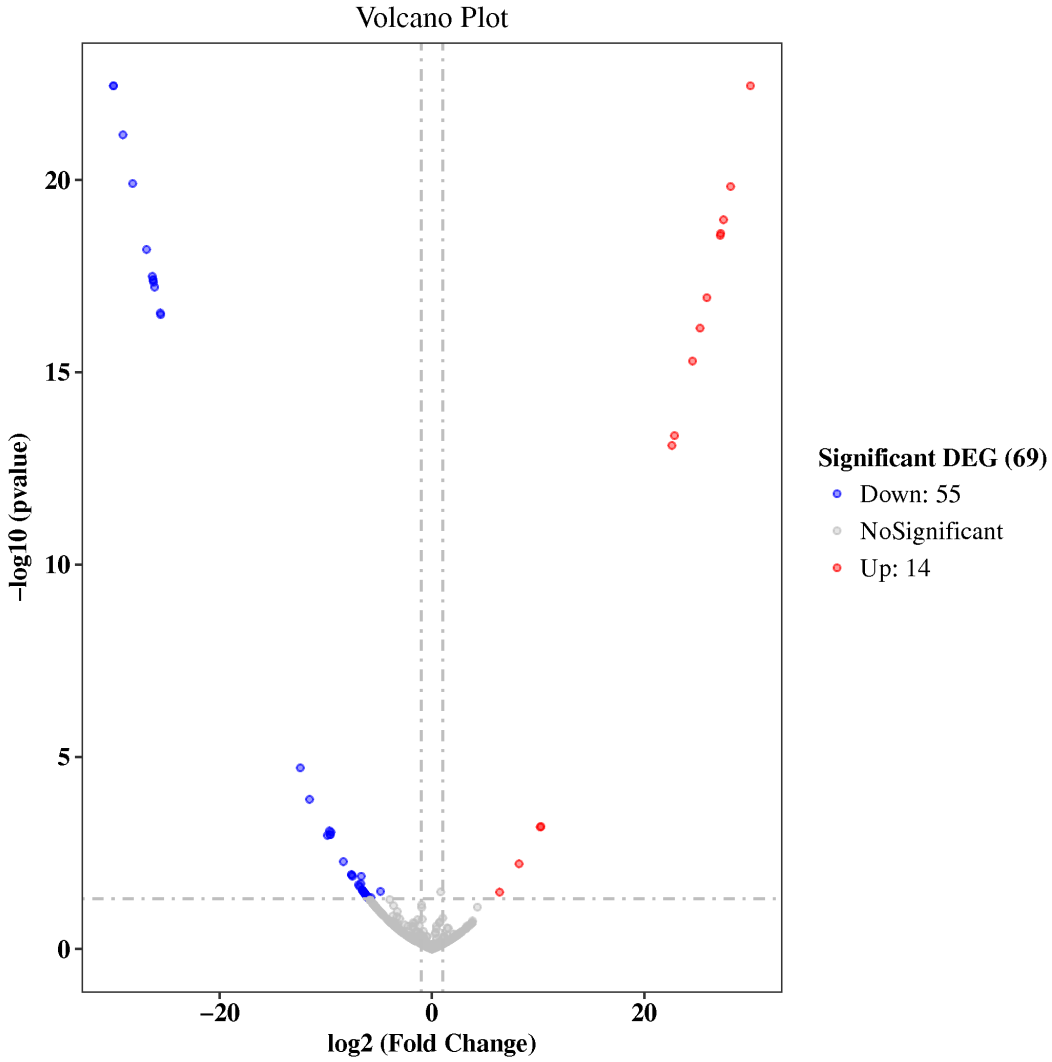

Fig. 2: Volcano map of differentially expressed miRNA
Each point represents a single miRNA. Red points denote significantly up-regulated miRNAs, blue points denote significantly down-regulated miRNAs, and gray points represent non-significantly changed miRNAs. The horizontal axis shows the log2-transformed fold change, and the vertical axis shows the -log10 (P-value). A total of 69 differentially expressed miRNAs were

Validation of differentially expressed miRNAs by qRT-PCR

To independently confirm the reliability of the miRNA sequences data, we performed qRT-PCR validation on the top five most significant miRNAs (NovelmiRNA-1212, NovelmiRNA-49, NovelmiRNA-728, NovelmiRNA-181 and NovelmiRNA-225). The qRT-PCR validation results are detailed in table 2. As shown, the qRT-PCR results were consistent with the sequencing data, confirming the significant up-regulation of NovelmiRNA-1212 and the significant down-regulation of NovelmiRNA-49, NovelmiRNA-728, NovelmiRNA-181 and NovelmiRNA-225 in the acral melanoma group compared to the pigmented nevus group.

Identification of key miRNA-target gene interactions in oncogenic pathways

To elucidate the potential functional impact of the differentially expressed miRNAs, we focused on the top five most significantly dysregulated miRNAs (NovelmiRNA-1212, NovelmiRNA-728, NovelmiRNA-181, NovelmiRNA-225 and hsa-miR-4732-3p). Using miRanda software, we predicted their target genes and further identified key cancer-related targets based on existing literature. These included GSTT4 (implicated in MAPK pathway and drug resistance), GSTT2 and DRG1 (involved in tumor microenvironment modulation and cell proliferation), ZNF367 and MMP9 (associated with tumor invasion and metastasis), FOXJ3 (regulating proliferation and apoptosis) and APP (promoting cancer cell proliferation and invasion). The detailed roles of these key target genes in cancer are summarized in table 3.

Functional and signaling pathway enrichment analysis of differentially expressed miRNA target genes

GO functional enrichment analysis results for differentially expressed miRNA target genes

GO enrichment analysis was performed on differentially expressed miRNA target genes between the acral melanoma group and the nevus group. Results after significance thresholding ($P < 0.05$) are shown in fig. 3. Differentially expressed miRNA target genes were primarily enriched in GO terms across three categories: Molecular Function, Cellular Component and Biological Process. The most significantly enriched biological processes included: 10,161 target genes enriched in “Cytosol” under “Cellular Component”; 3,770 involved in “ATP binding” under “Molecular Function”; and 1,830 involved in “positive regulation of transcription from RNA polymerase II promoter” under “Biological Process.” These primarily encompass biological processes such as cell differentiation, cell adhesion, ATP binding, receptor signaling protein serine kinase activity, transcriptional regulation and protein autophosphorylation.

KEGG enrichment analysis of differentially expressed miRNA target genes

KEGG metabolic pathway enrichment analysis revealed that common differentially expressed genes participated in signaling pathways targeting cancer therapy, the mitogen-activated protein kinase (MAPK) signaling pathway, the Ras signaling pathway, the Wnt signaling pathway and processes involving the initiation and progression of multiple tumors (Figs. 4 and 5). Differential miRNA target genes showed the most significant enrichment in cancer therapy signaling pathways (921 target genes) and the MAPK signaling pathway (906 target genes).

DISCUSSION

Cutaneous melanoma is the most lethal form of skin cancer. Once metastatic melanoma develops, effective treatment options remain limited. Although targeted therapies and immunotherapy have improved patient survival rates to some extent, drug resistance and severe treatment side effects persist. Therefore, early detection and diagnosis of melanoma are critically important. Recent research indicates that exosomes participate in critical biological processes of melanoma, including cell proliferation, differentiation and apoptosis. As carriers of microRNAs, exosomes may offer potential as tools for early melanoma diagnosis and effective treatment. However, it is important to emphasize that the clinical translation of these findings requires validation in larger cohorts and the development of standardized detection protocols.

The progression from a pigmented nevus to melanoma typically involves transformation from a normal nevus cell nevus to an atypical nevus, followed by the development of melanoma and ultimately advancing to metastatic invasive malignant melanoma (Zia *et al*., 2023). The most prevalent melanoma in the Chinese population is acral lentiginous melanoma, which exhibits high malignancy and may arise from the malignant transformation of junctional nevi on the feet due to prolonged friction. Blindly performing skin biopsies on multiple lesions is impractical for individual examination and may carry risks of metastasis or recurrence. Therefore, we compared serum-derived extracellular miRNA profiles between pigmented nevus and acral melanoma patients, identifying 69 differentially expressed miRNAs: 14 upregulated and 55 downregulated. The most significantly upregulated miRNAs included NovelmiRNA-1212, NovelmiRNA-218, hsa-miR-4732-3p, NovelmiRNA-447 and NovelmiRNA-632. The most significantly downregulated miRNAs included NovelmiRNA-49, NovelmiRNA-728, NovelmiRNA-181, NovelmiRNA-225 and hsa-miR-145-5p. Several of these significantly dysregulated miRNAs have been implicated in melanomagenesis.

Table 1: The top ten miRNAs significantly differentially expressed in exosomes

Term	Length	P value	Up/Down
NovelmiRNA-1212	18	3.64E-23	Up
NovelmiRNA-49	18	3.64E-23	Down
NovelmiRNA-728	18	3.64E-23	Down
NovelmiRNA-181	21	6.75E-22	Down
NovelmiRNA-225	18	1.23E-20	Down
NovelmiRNA-218	19	1.47E-20	Up
hsa-miR-4732-3p	23	1.13E-19	Up
NovelmiRNA-447	20	2.55E-19	Up
NovelmiRNA-632	18	2.88E-19	Up
hsa-miR-145-5p	21	6.63E-19	Down

Table 2: qRT-PCR validation results of top 5 differentially expressed miRNAs

miRNA	Group	Relative expression (2^–ΔΔCt, Mean ± SD)	Fold change
NovelmiRNA-1212	Pigmented nevus	1.00 ± 0.15	4.50
	Acral melanoma	4.50 ± 0.32	
NovelmiRNA-49	Pigmented nevus	1.00 ± 0.09	0.18
	Acral melanoma	0.18 ± 0.04	
NovelmiRNA-728	Pigmented nevus	1.00 ± 0.11	0.22
	Acral melanoma	0.22 ± 0.05	
NovelmiRNA-181	Pigmented nevus	1.00 ± 0.08	0.25
	Acral melanoma	0.25 ± 0.05	
NovelmiRNA-225	Pigmented nevus	1.00 ± 0.10	0.31
	Acral melanoma	0.31 ± 0.06	

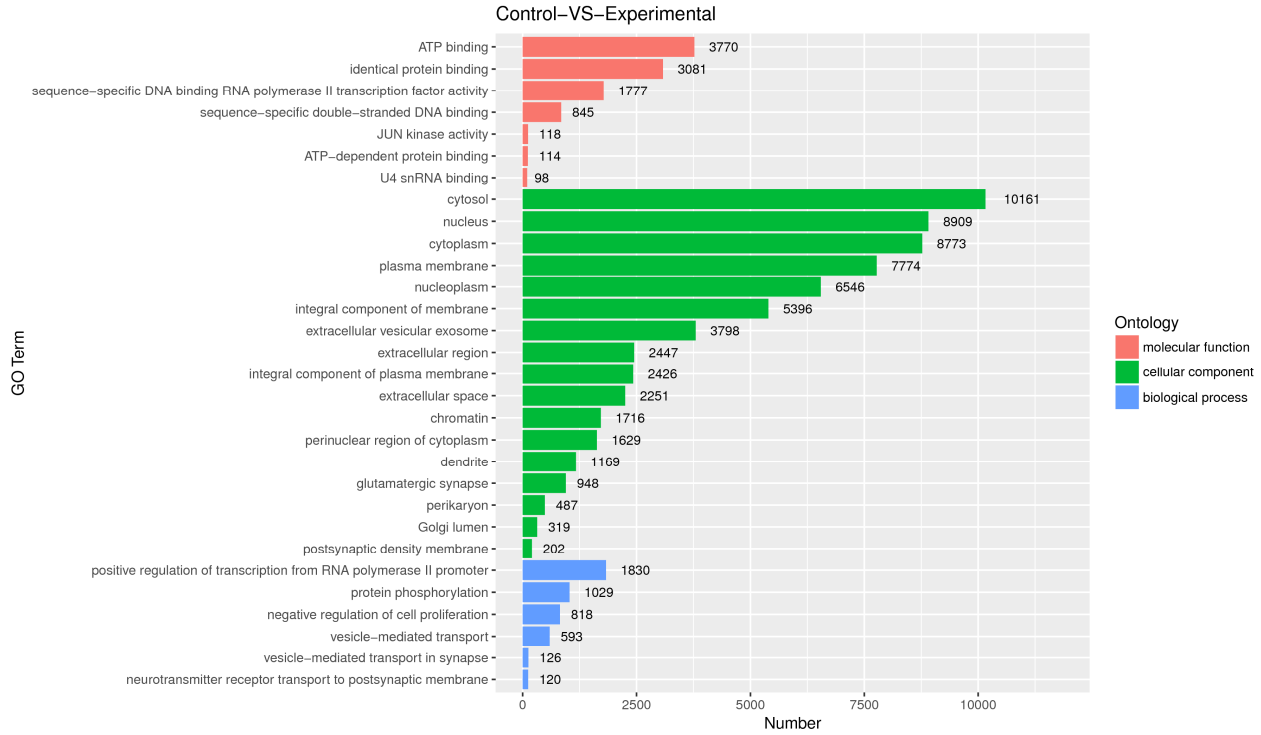

Fig. 3: Bar graph of GO enrichment analysis of target genes of differential miRNAs
The *x*-axis represents the number of target genes enriched in each GO term, and the y-axis lists the significantly enriched GO terms. Different colors indicate three GO categories: red for molecular function (MF), green for cellular component (CC), and blue for biological process (BP).

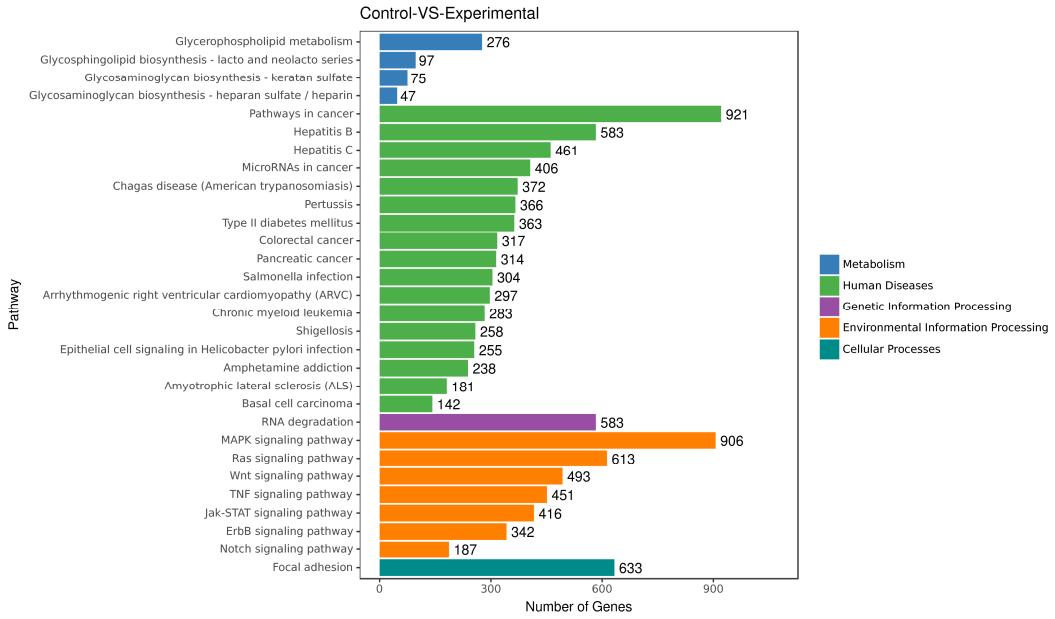

Fig. 4: Bar graph of KEGG pathway enrichment analysis of target genes of differential expressed miRNAs
The x-axis represents the number of target genes enriched in each pathway, and the y-axis lists the significantly enriched pathways. Different colors represent pathway categories: blue for metabolism, green for human diseases, purple for genetic information processing, orange for environmental information processing, and teal for cellular processes.

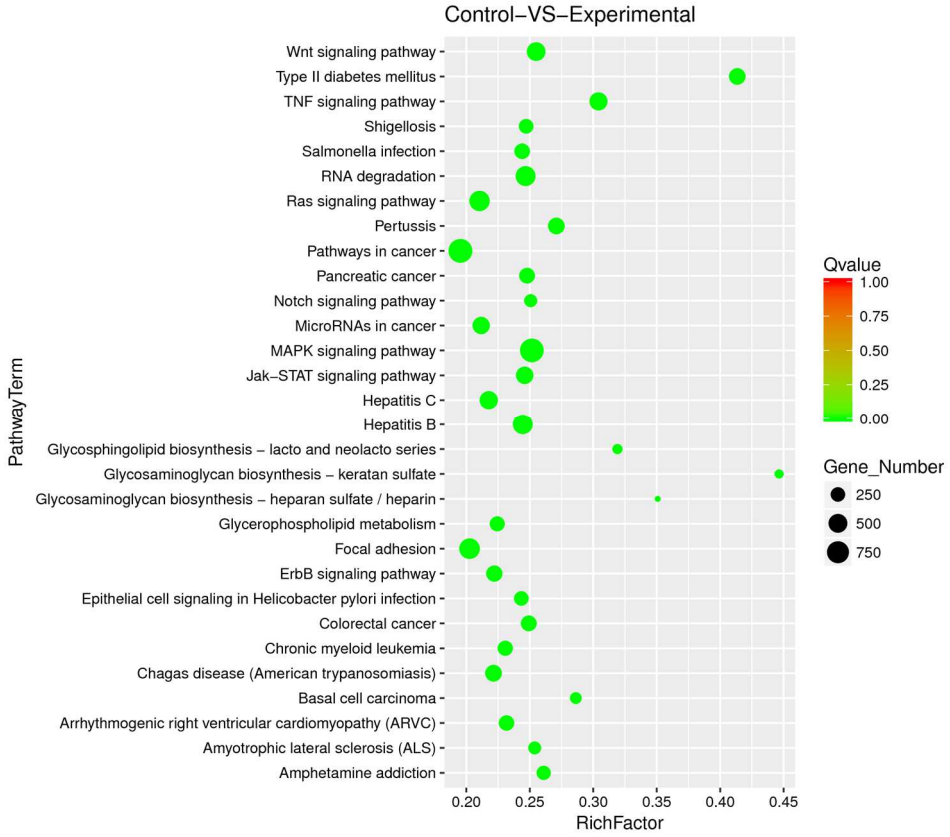

Fig. 5: Scatter plot of KEGG pathway enrichment analysis of target genes of differential expressed miRNAs
The *x-axis* represents the enrichment factor. The y-axis lists the significantly enriched pathways. The size of each point indicates the number of differentially expressed miRNA target genes within that pathway, and the color of each point denotes different Q-value thresholds. A higher enrichment factor indicates greater enrichment, while a lower Q-value indicates more significant enrichment.

Table 3: Predicted target genes of differentially expressed miRNAs

miRNA	Predicted target genes	Key target gene and potential functional relevance in cancer
NovelmiRNA-1212	G6PC2, GSTT4, TMEM50B, DEAF1, TMEM179, LY6G5C, EEF1D, B2M	GSTT4: Enriched in MAPK pathway; associated with drug resistance (Townsend and Tew, 2003).
NovelmiRNA-728	GP6, LST1, GSTT2, DRG1, MYLIP, ZNF516, null, GSTT2B	GSTT2: Modulates tumor microenvironment (Patwardhan *et al*., 2024); DRG1: Influences tumor cell proliferation (Lu *et al*., 2016).
NovelmiRNA-181	UPK3B, PRAMEF2, ALG12, SLC19A1, ZNF367, MMP9, PLCB2, EFR3B	ZNF367: Affects cell proliferation and invasion (Jain *et al*., 2014). MMP9: Promotes tumor invasion and metastasis (Tang *et al*., 2013);
NovelmiRNA-225	USP17L4, FOXJ3, CLIC6, ZZEF1, CYP11A1, SNTG2, CYP11A1, ZNF696, TOMM70	FOXJ3: Regulates tumor cell proliferation and apoptosis (Huang *et al*., 2020; Rajakumar *et al*., 2014).
hsa-miR-4732-3p	OR5P3, OR11A1, SLC43A2, CACNA1I, APP, SLC2A10, CDH22, GAD2	APP: Promotes cancer cell proliferation and invasion (Lee *et al*., 2021).

For instance, miRNA-145-5p, which was significantly down-regulated in our dataset, is a recognized tumor suppressor in melanoma. Its diminished expression is known to promote melanoma cell proliferation and invasion by targeting key oncogenic pathways such as N-RAS and MYC (Chen *et al*., 2020; Noguchi *et al*., 2012).

Another significantly down-regulated miRNA, miRNA-218, has been previously shown to directly target DKK3, thereby inhibiting the proliferation and invasion of melanoma cells (Yang *et al*., 2021). Of particular interest is the significant downregulation of miRNA-181 identified in our acral melanoma samples. Our target prediction and pathway analysis suggest that this novel miRNA may target MMP9—a well-established promoter of melanoma invasion, angiogenesis and metastasis (Tang *et al*., 2013). Furthermore, integrative genomic studies have confirmed that the miR-181/TFAM pathway is a key driver of drug resistance in melanoma (Barbato *et al*., 2021). This collective evidence suggests that the downregulation of NovelmiRNA-181 may contribute to the invasive phenotype and treatment resistance observed in acral melanoma through a potentially novel biological function.

The significant enrichment of MAPK and Ras signaling pathways among the target genes of differentially expressed miRNAs further underscores their pivotal role in acral melanoma pathogenesis. The MAPK pathway, particularly the Ras-Raf-MEK-ERK cascade, is a well-established driver of melanoma progression, frequently activated by mutations in genes such as BRAF and NRAS. This pathway regulates critical cellular processes, including proliferation, survival and invasion, all of which are hallmarks of melanoma malignancy (Calipel *et al*., 2003; Leung *et al*., 2019; Wang and Qi, 2013). Similarly, the Ras signaling pathway serves as a central regulator of oncogenic processes (Healey *et al*., 2013; Khan *et al*., 2019). The enrichment observed in our study suggests that the identified exosomal miRNAs may contribute to acral melanomagenesis by modulating these key pathways. For example, the downregulation of miR-145-5p, a known regulator of Ras-related signaling, alongside novel miRNAs targeting MAPK pathway components, could collectively promote pathway activation and facilitate malignant transformation (Chen *et al*., 2020; Rezaei *et al*., 2020). This mechanistic link between miRNA dysregulation and pathway enrichment provides a plausible explanation for the aggressive behavior of acral melanoma and highlights potential targets for future therapeutic intervention.

However, this study has several limitations that should be acknowledged. First, the functional roles and mechanistic insights of these differentially expressed miRNAs, particularly the novel miRNAs and their regulatory networks in acral melanoma, as proposed by our bioinformatic analyses, remain predictive and require further experimental validation. The associations between miRNA dysregulation, target genes and signaling pathways, while strongly suggested by our data, need to be confirmed through *in-vitro* and *in-vivo* functional studies. For instance, gain- and loss-of-function experiments are necessary to definitively establish the impact of candidates like NovelmiRNA-181 on MMP9 expression and the consequent phenotypic effects on melanoma cells. Additionally, the relatively small sample size may limit the generalizability of our findings and future validation in larger, multi-center cohorts is warranted. Therefore, our findings should be viewed as generating valuable hypotheses that pave the way for subsequent rigorous functional investigations into the molecular pathogenesis of acral melanoma.

The precise mechanism by which pigmented nevi

progress to melanoma remains incompletely understood. It may involve the positive or negative regulation of multiple known or unknown miRNAs, leading to mutations in target genes within melanocytes. Through the combined effects of signaling pathways targeted for cancer therapy, such as the MAPK signaling pathway, pigmented nevi may evolve into melanoma. The transformation of pigmented nevi into melanoma may be associated with the activation and inactivation of the MAPK pathway. Mutations in oncogenes or tumor suppressor genes are predominantly mediated through MAPK pathway activation (Safa *et al*., 2020). Studies have confirmed sustained high-level activation of the MAPK pathway in melanoma (Li *et al*., 2024). Additional reports indicate that dysregulation of the RAS signaling pathway also contributes to melanoma development (Al Mahi and Ablain, 2022). Several molecules within the RAS pathway have been identified and their regulatory mechanisms elucidated. Ongoing research seeks to identify molecules that can directly target these signaling pathways. This represents a significant step toward effective clinical diagnosis and treatment for melanoma patients driven by pathways such as MAPK, Ras and Wnt signaling. In recent years, researchers have progressively enhanced their understanding of melanoma exosomes (Benito-Martín *et al*., 2022; Tengda *et al*., 2018; Wróblewska *et al*., 2022). While studies on the genetics, environmental factors, gene mutations and rearrangements associated with malignant melanoma have proliferated, investigations into the mechanisms underlying the progression of pigmented nevi to melanoma remain scarce. Future research should focus on validating these findings in larger patient cohorts and establishing standardized protocols for exosomal miRNA analysis. Functional studies are essential to elucidate the precise mechanisms through which these miRNAs regulate oncogenic pathways. The clinical translation will require extensive validation before considering diagnostic applications.

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Authors' contributions
TZ, YW and JLW: Contributed to the study conception, design, analysis and interpretation of the data; CMW, YH, YJW and YHH: Drafted the manuscript and revised it critically for intellectual content; TZ and YJW: Gave final approval for the version to be published. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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

Ethical approval
All research is in strict accordance with and adheres to the Declaration of Helsinki. The study was approved by the Ethics Committee of Civil Aviation General Hospital (Approval No: 202222). This study was performed in adherence with the STROBE guidelines. See Supplementary file for the STROBE checklist.

Conflict of interest
All authors declare no conflicts of interest.

Consent to participate
All patients have signed written informed consent.

Supplementary data
https://www.pjps.pk/uploads/2026/04/SUP1775374048.pdf

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