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Extracellular Vesicles from miR-146a Overexpressing Mesenchymal Stem Cells Attenuate Imiquimod-Induced Psoriasis by Regulating Cytokine Expression

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ABSTRACT

Background: Psoriasis is a chronic inflammatory skin disorder characterized by elevated levels of proinflammatory cytokines. Mesenchymal stem cells (MSCs) have demonstrated therapeutic potential, yet the specific mechanisms involved are not fully understood. In this study, we investigated the effectiveness of extracellular vesicles (EVs) derived from MSCs that were genetically modified to overexpress miR-146a, in a mouse model of psoriasis.

Methods: To enhance miR-146a expression, MSCs were transfected, and their EVs were subsequently purified. Thirty mice were randomly assigned to three groups and induced with imiquimod cream to develop psoriasis-like skin lesions. The treatment groups included: (1) a control group administered PBS, (2) a group treated with EVs containing a control miRNA (miR-control EVs), and (3) a group receiving EVs enriched with miR-146a (miR-146a-EVs). EVs were administered intravenously and lesions were evaluated. Following intravenous administration of EVs, the severity of skin lesions was assessed. Concentrations of key cytokines, including IFN-γ, IL-17, TNF-α, IL-23, IL-6, IL-1β, TGF-β, IL-10, and IL-4, were quantified in both spleen and skin tissue lysates using ELISA and qRT-PCR techniques.

Results: The experimental findings demonstrated that the administration of miR-146a-enriched EVs led to a significant improvement in clinical symptoms. There were substantial reductions observed in combined erythema, scaling, and skin thickness measurements compared to untreated controls. Additionally, levels of proinflammatory cytokines IFN-γ, IL-17, TNF-α, IL-23, IL-6, and IL-1β were significantly downregulated in the miR-146a-EV group, while anti-inflammatory TGF-β, IL-10 and IL-4 were upregulated. The same results were obtained in the spleens of mice.

Conclusion: EVs derived from miR-146a-modified MSCs effectively reduced psoriasis-like inflammation by modulating cytokine expression. This novel cell-free therapy holds promise for the treatment of psoriasis.

Keywords: Cytokine, Exosome, Extracellular vesicle, Mesenchymal stem cell, Psoriasis

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INTRODUCTION

Psoriasis is a chronic, immune-mediated dermatological disorder of non-infectious origin, characterized by chronic inflammation, uncontrolled keratinocyte proliferation and aberrant cellular maturation (1). It is estimated to affect approximately 2-3% of the global population, with the potential to develop at any age and in both genders (2). Females and individuals with a family history of the condition may experience an earlier onset. The emergence of psoriasis is a result of the interplay between genetic factors and the surrounding environment (3, 4). Although the precise mechanism behind psoriasis remains elusive, it is hypothesized to be a T-cell-driven disorder due to the involvement of T helper cells during the psoriatic state. In addition to adaptive immunity, innate immunity also contributes to the etiopathogenesis of psoriasis through the activation of dendritic cells and macrophages upon exposure to external stimuli (5). The available treatments for psoriasis include topical medications, phototherapy, and systemic therapy (6). Current treatment options for psoriasis, including steroids and biologics, offer varying degrees of effectiveness but also come with significant limitations. Steroids, although effective for short-term relief from symptom, are linked to side effects like skin atrophy, systemic immunosuppression, and tachyphylaxis, which restrict their long-term use (7, 8). On the other hand, biologics, which target specific immune pathways, have revolutionized the management of psoriasis. However, they are costly, and carry the risk of immunogenicity (9).

Mesenchymal stem cells (MSCs), as postnatal stem cells, exhibit diverse characteristics, including self-renewal capability and the ability to differentiate into multiple lineages (10). Over the past three decades, researchers have explored the intriguing cell biology and promising clinical applications of MSCs. Their unique abilities, such as secreting bioactive molecules, make them ideal candidates for promoting tissue repair and restoration (11). Due to these attributes, it is evident that MSCs will play a significant therapeutic role in clinical trials. Previous investigations have demonstrated that MSCs can ameliorate psoriasis-like dermatitis, decrease pro-inflammatory cytokine levels, and accelerate healing processes by regulating immune responses (12, 13). Moreover, MSCs can impact biological systems through the release of exosomes/extracellular vesicles (EVs) containing regulatory molecules such as microRNAs (miRNAs) (14, 15). One particularly notable miRNA, miR-146a, displays robust anti-inflammatory properties and has proven effective in mitigating symptoms in several disease models (16, 17). Overexpression of miR-146a in MSCs enhances their immunomodulatory capacity and therapeutic efficacy (18). MiR-146a achieves these feats by inhibiting signaling cascades triggered by pro-inflammatory cytokines, such as TNF-α and IL-1β, through targeting TNF receptor-associated factor 6 (TRAF6) and IL-1 receptor-associated kinase 1 (IRAK1) (19). We hypothesize that bone marrow MSCs (BMSCs) overexpressing miR-146a may offer an advanced therapeutic strategy for psoriasis due to their enhanced anti-inflammatory properties. As MSCs can exert their effects through released EVs, our current research aims to assess the therapeutic potential of EVs derived from miR-146a-overexpressing BMSCs (miR-146a BMSC-EVs) in treating psoriasis.

MATERIALS AND METHODS

BMSC Culture and Characterization

Human bone marrow-derived mesenchymal stem cells (BMSCs) were isolated from donor samples after obtaining ethical approval and informed consent in accordance with the Declaration of Helsinki. mononuclear cells were isolated through Ficoll gradient centrifugation, and plated at a concentration of 2×10^6 cells per well in

tissue culture dishes. Cells were maintained in MSC growth medium containing 10% human platelet lysate, 1% L-glutamine, and 1% antibiotic-antimycotic solution. After an initial 24-hour incubation period, non-adherent cells were eliminated through medium replacement. Once cells reached 80-90% confluency, they were routinely passaged for subsequent experimental use (20).

Before conducting experiments, the multipotency of BMSC was confirmed through directed differentiation protocols. Third-passage cells were treated with lineage-specific induction media to stimulate osteogenic and adipogenic differentiation. After 21 days of culture, differentiated cells were processed for histological evaluation. Mineralized matrix deposition was detected by Alizarin Red staining (5-minute incubation), while lipid accumulation was visualized using Oil Red O (30-minute staining). Phenotypic characterization was performed via flow cytometric analysis, confirming the expression of CD73 and CD90 surface markers and the absence of CD34 and CD45 hematopoietic markers.

Preparation of BMSC-miR-146a

For transfection, BMSCs at approximately 80% confluency were transfected with miR-146a mimics or negative control sequences using Lipofectamine 3000 transfection reagent according to the manufacturer's instructions. The transfection process included incubating the cells in Opti-MEM reduced-serum medium containing the Lipofectamine 3000 reagent complexed with either miR-146a mimics or control oligonucleotides for a 72-hour period.

Collection and Characterization of BMSC-EVs

After two days of cultivation in the full medium, BMSCs underwent a 48-hour incubation period in medium containing 10% exosome-free fetal bovine serum (FBS). Exosome-free FBS was obtained through serial centrifugations conducted at 4°C with speeds of 200 ×g for 10 minutes, 2000 ×g for 20 minutes, 10,000 ×g for 30 minutes, and finally, 110,000 ×g for 7 hours, followed by filtration using a 0.22 μm filter. Similarly, BMSC-EVs were extracted from culture supernatants using a sequential centrifugation process, yet with the final stage being 110,000 ×g for 2 hours. The resulting pellet was then suspended in PBS, rinsed twice, and filtered again using a 0.22-micron filter (21).

The process of identifying individual proteins in BMSC-EVs involved lysing the EVs in modified radioimmunoprecipitation assay (RIPA) buffer, determining the protein content using a bicinchoninic acid (BCA) protein assay kit, loading 100 μg of EV protein onto 10% sodium dodecyl-sulfate (SDS) gels, running the gels, transferring the proteins onto polyvinylidene fluoride (PVDF) membranes, incubating the membranes with primary antibodies against CD9 and CD63 and horseradish peroxidase-conjugated anti-rabbit IgG secondary antibody.

Induction of Psoriasis-like Skin and Treatment Protocol

The study involved thirty 7-week-old female BALB/cByJNarl mice, which were kept under standardized vivarium conditions with a controlled temperature of 24±1°C and a 12-hour light/dark cycle. The animals were provided with autoclaved feed and sterile water ad libitum to ensure specific pathogen-free conditions were maintained. All experimental procedures were carried out in strict compliance with the ARRIVE guidelines for animal research. Stringent measures were taken to minimize any potential discomfort or suffering experienced by the animals during the study. The same protocol as reported by van der Fits et al. (22), which involves the induction of psoriasis-like lesions in mice, was applied in this study. To induce psoriasis-like lesions, the dorsal skin of each mouse was shaved, and a daily topical application of 62.5 mg of imiquimod cream was administered for six consecutive days. The cream was applied to the back of the mouse.

A quantitative scoring metric was developed to assess the severity of cutaneous inflammation in murine subjects. This metric adapted principles from the clinical Psoriasis Area and Severity Index (PASI) but excluded surface area measurements. Three key clinical parameters - erythema, desquamation, and dermal thickening - were independently graded using a 5-point ordinal scale (0: absent; 1: mild; 2: moderate; 3: severe; 4: very severe). Erythema intensity was objectively quantified through comparative analysis with standardized color references. The cumulative score, obtained by adding the scores for erythema, scaling, and thickening, provided a comprehensive measure of inflammation severity on a scale from 0 to 12 (23).

After successfuly inducing of psoriasiform lesions, the experimental cohort (n=30) was randomly divided into three treatment arms (n=10/group): (1) vehicle control (PBS administration), (2) negative control (EVs containing scrambled miRNA sequences), and (3) experimental intervention (EVs loaded with miR-146a). All groups received a single intravenous bolus of their respective treatments (100 μg EV dose for miRNA-containing groups).

Gene Expression Analysis

Total RNA extraction was performed from BMSC-EVs using TRIzol, following the manufacturer's guidelines. To assess the expression of miR-146a, 1 μg of RNA was converted into complementary DNA (cDNA) using the MiRcute miRNA First-Strand cDNA Synthesis Kit from Tiangen Biotech. Relative quantification of miR-146a expression levels was determined through the $2^{-\Delta\Delta CT}$ method on an ABI 7500 Real-Time PCR System from Applied Biosystems, utilizing the MiRcute miRNA qPCR Detection Kit from Tiangen Biotech.

Thirty days after induction, skin lesion samples were collected from all experimental groups to assess the expression of multiple cytokines. Total RNA was isolated from the tissue specimens, and the RNA concentrations were measured using a NanoDrop spectrophotometer. 1 μg of total RNA was then used for cDNA synthesis with a cDNA Reverse Transcription kit. The quality of the resulting cDNA was confirmed with another NanoDrop measurement. Nine genes, including interferon-gamma (IFN)-γ, interleukin (IL)-17, tumor necrosis factor (TNF)-α, IL-23, IL-6, IL-1β, transforming growth factor (TGF)-β, IL-10 and IL-4, were analyzed using real-time RT-PCR in triplicate. β-actin was selected as the internal reference, for normalization. The $2^{-\Delta\Delta CT}$ method was used to calculate threshold values for gene expression, and mRNA expression folds relative to the control were then analyzed.

Cytokine Measurement

After splenectomy, a cell suspension was created in Roswell Park Memorial Institute (RPMI)-1640 medium by homogenizing tissue fragments through a 70-micron cell strainer. The suspension was then treated with an ammonium chloride buffer at 4°C for ten minutes to eliminatered blood cells (RBCs) . The resulting cell pellet was obtained by centrifugation at 300 ×g for five minutes at 4°C . The pellet was washed twice with RPMI-1640 medium. Finally, the splenocytes were resuspended in a complete RPMI-1640 medium containing 10% FBS from Shellmax, and 100 μg/ml penicillin-streptomycin as antibiotics from Gibco (UK).

Splenic lymphocytes were separated and plated in 24-well culture plates at a concentration of 2×10^6 cells/well. Following stimulation with phytohemagglutinin (PHA, 10 μg/mL; Gibco) for 48 hours, conditioned media containing cellular secretions were collected for subsequent analysis. The levels of cytokines including IFN-γ, IL-17, TNF-α, IL-6, IL-1β, IL-23, TGF-β, IL-10, and IL-4 in the supernatants were quantified using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, USA). The ELISA assays were performed following the manufacturer's instructions. To ensure precision, all samples underwent testing in triplicate measurements.

Statistical Analysis

The statistical analysis included comparing groups with a normal distribution using one-way ANOVA followed by Tukey's post hoc test. For groups with a non-normal distribution, the Kruskal-Wallis test was applied. Quantitative data is presented as mean±standard deviation (SD). A probability threshold of $p<0.05$ was forest to determine statistical significance. Data visualization was done with GraphPad Prism 8 (GraphPad Software, San Diego, CA), and all statistical calculations were performed using IBM SPSS Statistics (Version 25, IBM Corp., Armonk, NY).

RESULTS

Characterization of BMSCs

Phase-contrast microscopy revealed that BMSCs exhibited a characteristic fibroblast-like morphology with typical adherent growth properties. Following 21 days of adipogenic differentiation, intracellular lipid accumulation was confirmed through Oil Red O staining, which specifically highlights neutral lipids. Parallel osteogenic differentiation assays, evaluated after 21 days using Alizarin Red S staining, demonstrated extensive mineralization as evidenced by calcium-rich nodule formation. Additionally, flow cytometric analysis identified BMSCs as expressing specific cell surface antigens. The results revealed that these cells possessed CD73 and CD90, while lacking expression of CD34 and CD45 (depicted in Fig. 1).

Characterization of BMSC-EVs

BMSCs were transfected with a miR-146a mimic and a negative control, and then evaluated for EV markers. Western blot analysis of BMSC-EVs showed the presence of two canonical EV marker proteins, CD9 and CD63, confirming the successful isolation of EVs from transfected BMSCs (as shown in Fig. 2A).

BMSCs Encapsulated miR-146 Within Released EVs

The qRT-PCR results showed a significant increase in miR-146a expression levels in EVs derived from miR-146a-transfected BMSCs

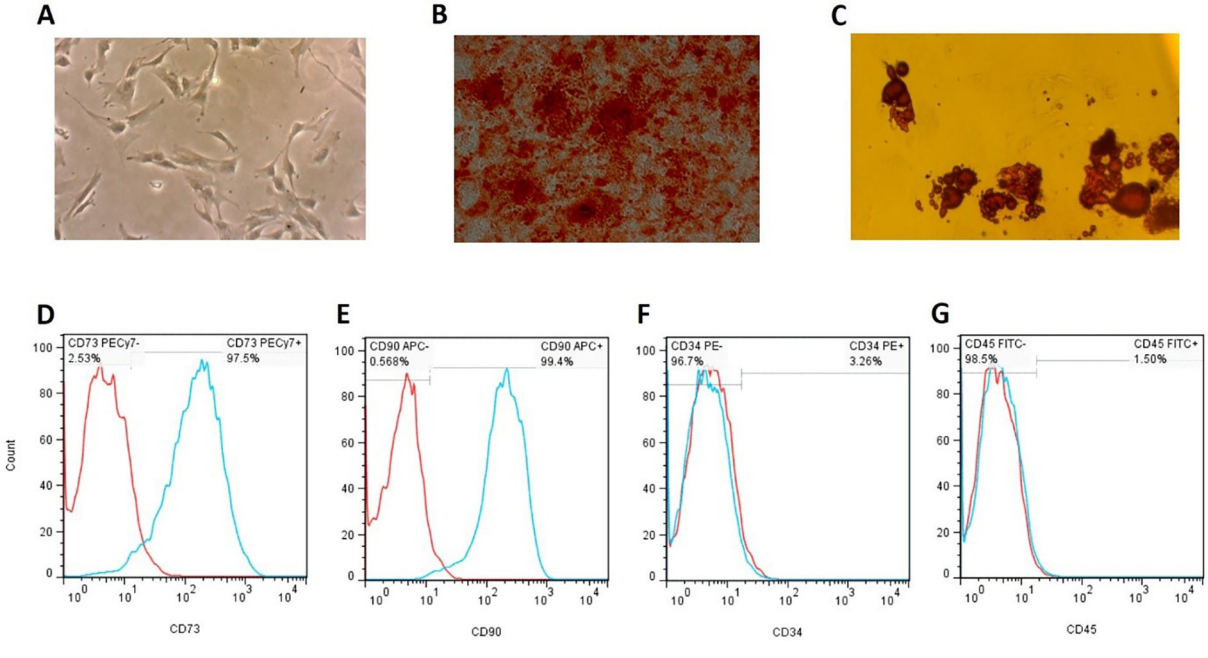

Fig. 1. Characterization of BMSCs. Morphological examination of BMSCs indicated a fibroblastic appearance with an adherence characteristic (A). Osteogenesis was assessed via Alizarin Red staining, which demonstrated the presence of calcium deposits (B). Upon adipogenic induction, Oil Red O staining revealed the formation of lipid droplets (C). Flow cytometric analysis of BMSCs showed that these cells expressed CD73 (D) and CD90 (E), while they lacked expression of CD34 (F) and CD45 (G). BMSC: bone-marrow mesenchymal stem cell.

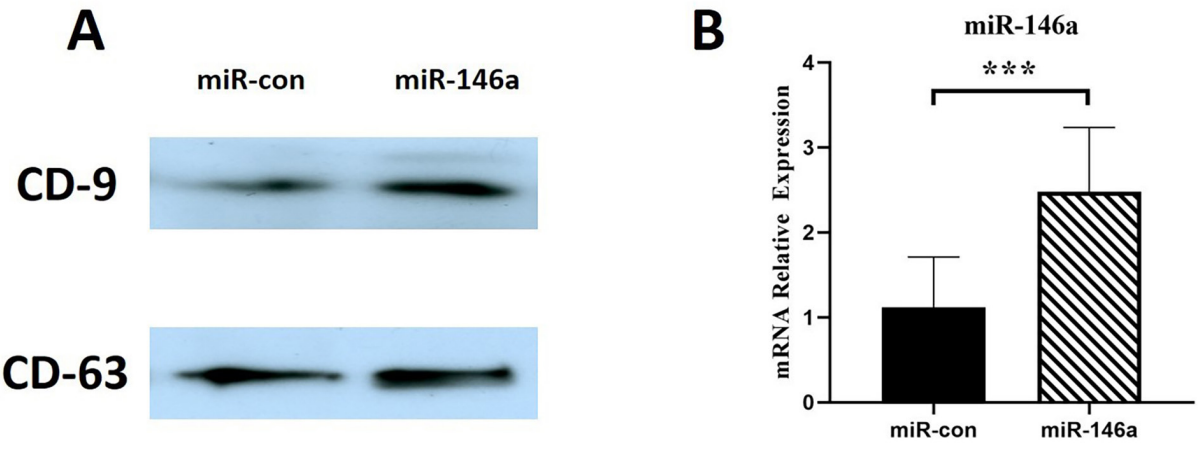

Fig. 2. miR-146a packaging efficiency in BMSC-derived EVs. (A) Western blot analysis of canonical EV markers (CD9 and CD63) in vesicles isolated from BMSCs transfected with miR-146a or control miRNA (miR-con). (B) Quantitative RT-PCR analysis demonstrates significant enrichment of miR-146a in EVs derived from miR-146a-transfected BMSCs compared to controls. Data represent mean±SD (***p<0.001). BMSC: bone marrow-derived mesenchymal stem cell; EV: extracellular vesicle; qRT-PCR: quantitative reverse transcription polymerase chain reaction.

compared to those from BMSCs transfected with miR-con, as demonstrated in Fig. 2B. These results highlight the successful packaging of miR-146a into EVs secreted by BMSCs (Fig. 2B).

EVs from BMSCs Overexpressing miR-146a Attenuate Imiquimod-induced Psoriasis

The study observed the first clinical signs of erythema, scaling, and thickening 2 to 3 days after the start of imiquimod application. The results indicated that EVs containing miR-146a significantly reduced the cumulative score (erythema, scaling, and thickening) compared to the untreated control mice. No significant results were observed when comparing miR-con mice to untreated control mice or miR-146a EVs mice (Fig. 3).

Impact of EVs Containing miR-146a on Splenocyte Cytokine Secretion

To investigate the effect of EVs carrying miR-146a on the functional abilities of immune cells, spleen samples were collected from mice with imiquimod-induced psoriasis. After a 48-hour co-culture period, ELISA

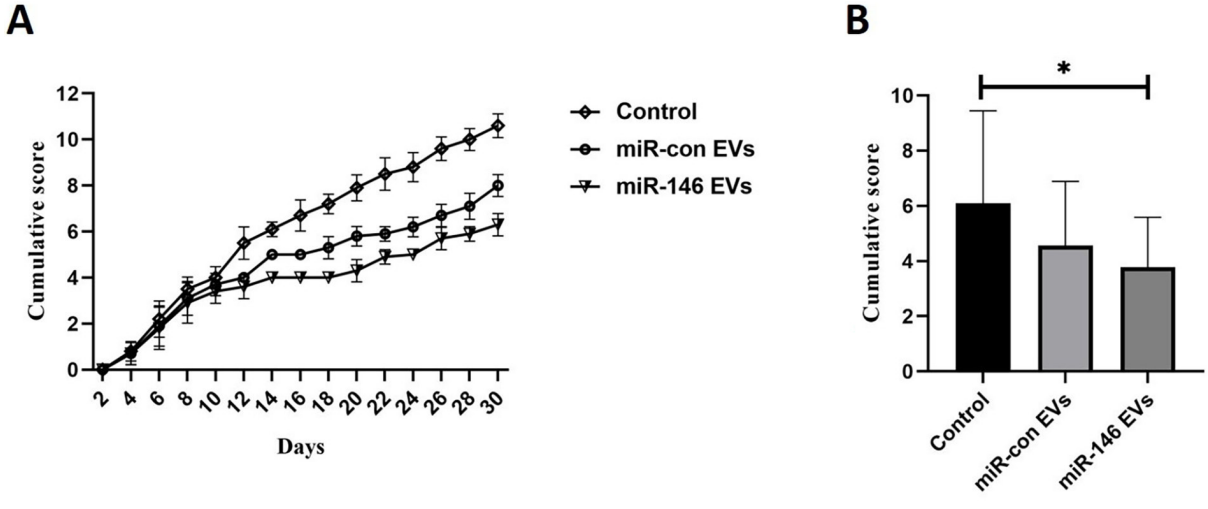

Fig. 3. Comparison of the cumulative scores between untreated control mice, miR-con EVs mice, and miR-146a EVs mice. The EVs containing miR-146a significantly reduced the cumulative score (erythema, scaling, and thickening) compared to the untreated control mice. The data is presented as mean±SD (*p<0.05). EV: extracellular vesicle.

measurements revealed that miR-146-EVs significantly decreased the secretion of pro-inflammatory cytokines, such as IFN-γ, IL-17, TNF-α, IL-23, IL-6, and IL-1β, compared to the untreated control group (shown in Fig. 4). In contrast, miR-146-EVs significantly increased the release of anti-inflammatory cytokines, including TGF-β, IL-10, and IL-4, compared to the untreated control group (Fig. 5).

Our findings further highlight that EVs containing miR-146a significantly reduced the release of pro-inflammatory cytokines, such as IFN-γ, IL-17, TNF-α, IL-6, and IL-1β, while simultaneously decreasing the levels of anti-inflammatory cytokines, like TGF-β and IL-10, compared to EVs without miR-146a (referred to as miR-con) shown in Figs. 4 and 5). This evidence suggests that miR-146a- containing EVs have the ability to influence the behavior of splenocytes, shifting their cytokine profiles towards an anti-inflammatory phenotype.

EVs Enriched with miR-146a Exhibit Dual Regulatory Effects on Cytokine Networks

Influenced by EVs containing miR-146a, the expression of pro-inflammatory cytokines IFN-γ, IL-17, TNF-α, IL-23, IL-6, and IL-1β within the skin tissues displayed significant reductions when compared to the untreated control group (Fig. 6).

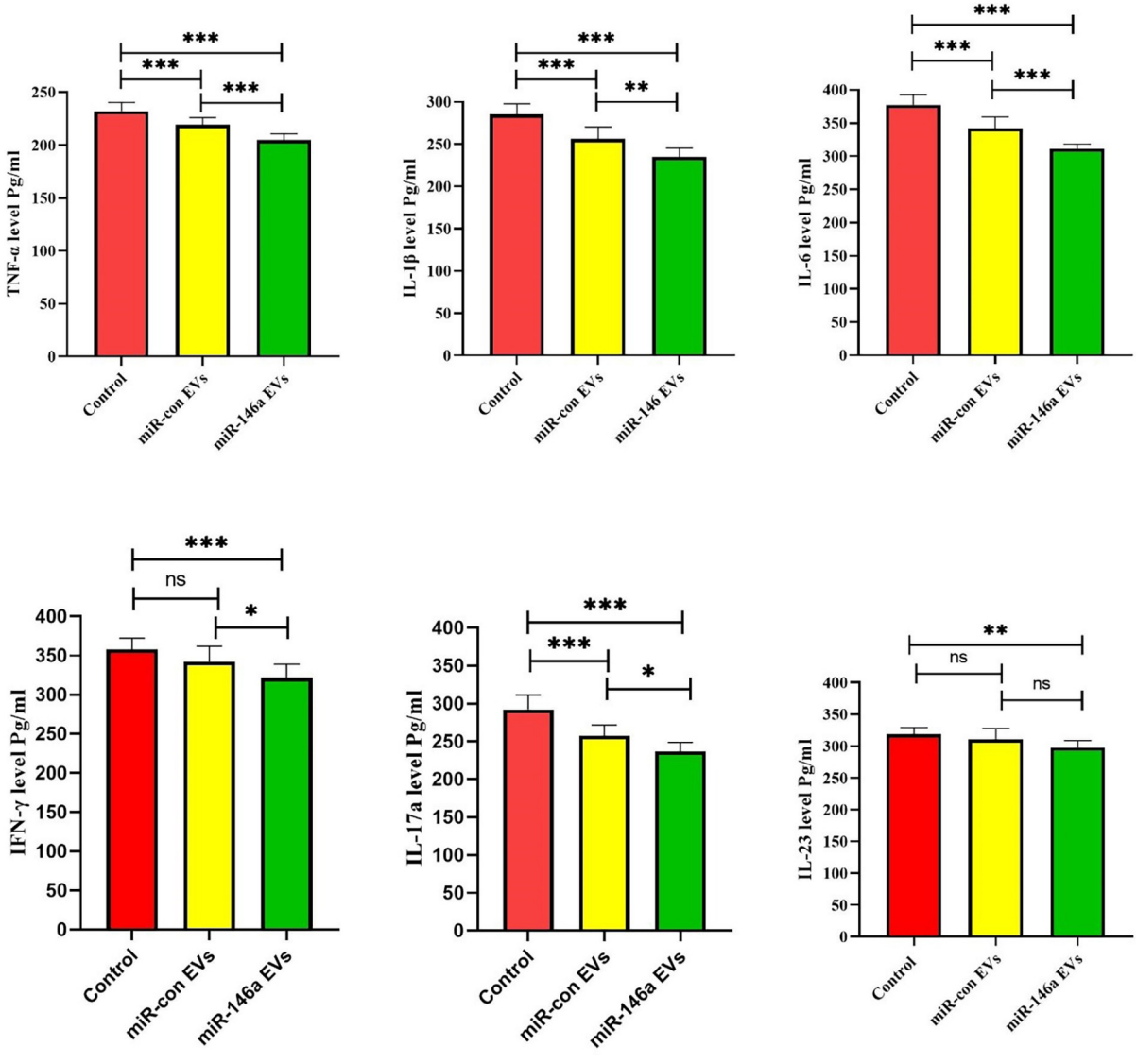

Fig. 4. The results of the inquiry, which involved assessing the secretion of pro-inflammatory cytokines by splenocytes within the experimental groups. The data is presented as mean±SD (***p<0.001, ** p<0.01, and * p<0.05). EV: extracellular vesicle; IFN: interferon; TNF: tumor necrosis factor; IL: interleukin.

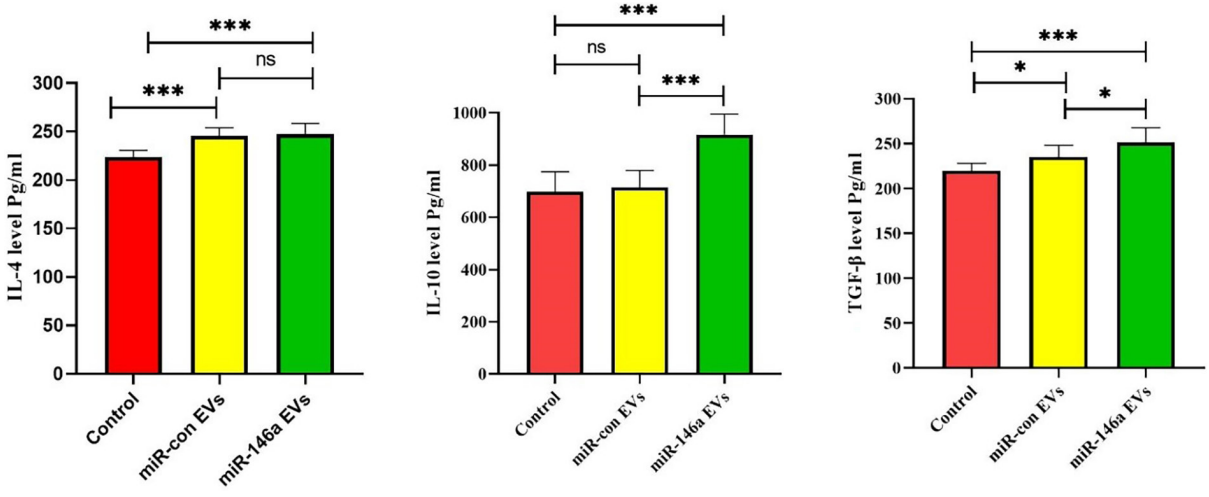

Fig. 5. The inquiry involved in assessing the release of anti-inflammatory cytokines by splenocytes in the experimental groups. The data represent mean±SD (***p<0.001, **p<0.01, and *p<0.05). EV: extracellular vesicle; IL: interleukin; TGF: Transforming growth factor.

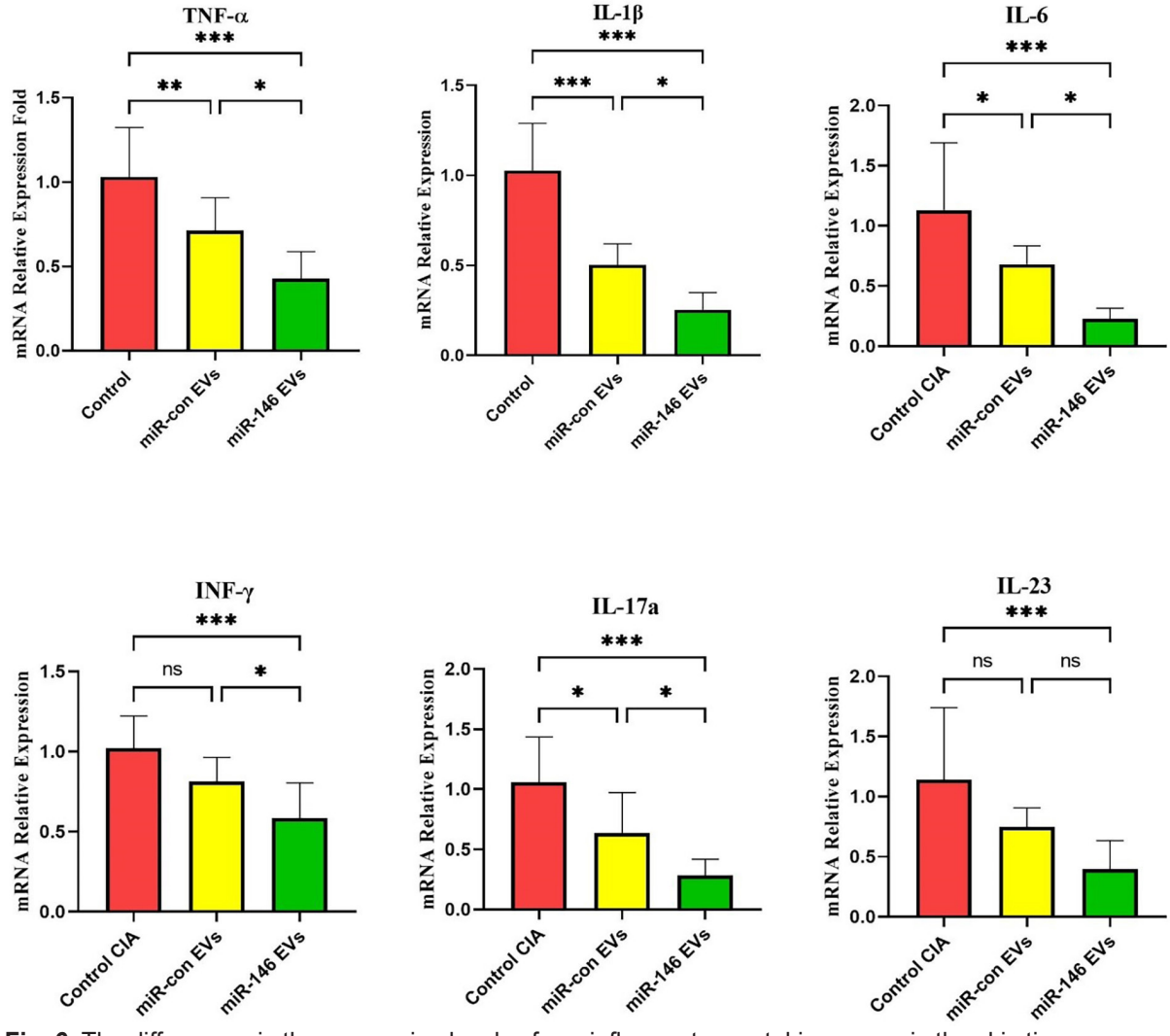

Fig. 6. The differences in the expression levels of pro-inflammatory cytokine genes in the skin tissue among the experimental groups, each consisting of 10 mice. The presence of EVs containing miR-146a significantly reduced the expression levels of pro-inflammatory cytokines (IFN-γ, IL-17, TNF-α, IL-23, IL-6, IL-1β) in skin tissues compared to the untreated control group. Statistical significance is denoted as ***p<0.001, **p<0.01, and *p<0.05. TNF: tumor necrosis factor; EV: extracellular vesicle; IL: interleukin; IFN: interferon.

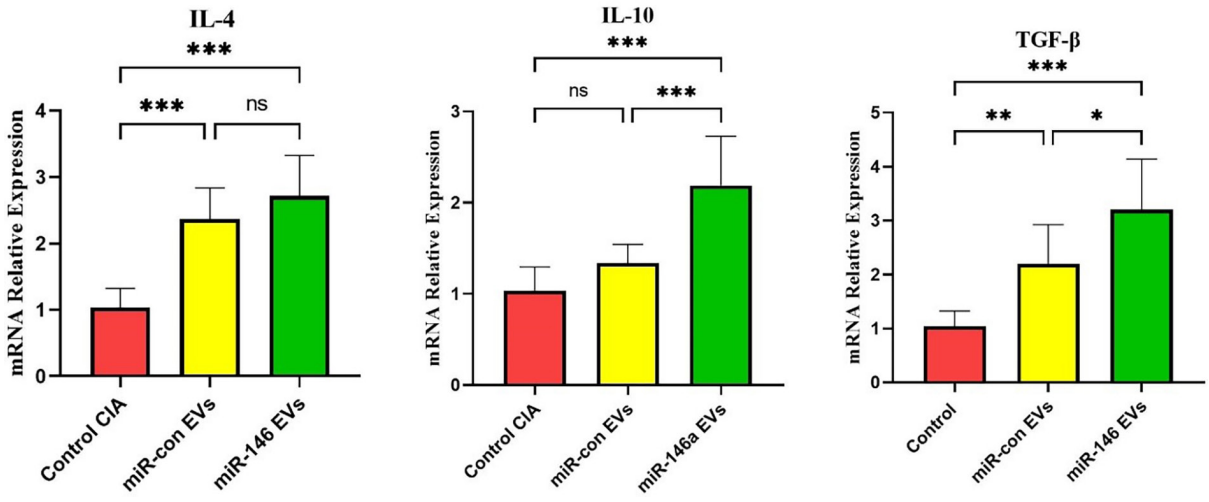

Fig. 7. The differences in the expression levels of anti-inflammatory cytokine genes in the skin tissue among the experimental groups, each consisting of 10 mice. EVs containing miR-146a significantly increased the expression levels of anti-inflammatory cytokines TGF-β, IL-10, and IL-4. Statistical significance is indicated as ***p<0.001, **p<0.01, and *p<0.05. EV: extracellular vesicle; IL: interleukin, TGF: Transforming growth factor.

On the other hand, EVs containing miR-146a robustly augmented the expression of anti-inflammatory cytokines TGF-β, IL-10, and IL-4 (Fig. 7). An evaluation of EVs containing miR-146a compared to EVs lacking miR-146a (miR-con) revealed that EVs containing miR-146a led to significant reductions in the expression of pro-inflammatory cytokines, such as IFN-γ, IL-17, TNF-α, IL-6, and IL-1β, while also showing an increase in the expression of anti-inflammatory cytokines, specifically TGF-β and IL-10 (Figs. 6 and 7). These findings collectively suggest that miR-146a within EVs is plays a crucial role in shaping the cytokine environment towards an anti-inflammatory state by influencing the expression of both pro- and anti-inflammatory cytokine gene.

DISCUSSION

In this study, it was found that EVs obtained from BMSCs modified with miR-146a were successful in reducing symptoms of imiquimod-induced psoriasis by modulating cytokine expression. Key findings supporting this conclusion include: 1. EVs obtained from BMSCs that overexpressed miR-146a reduced the expression of pro-inflammatory cytokines IFN-γ, IL-17, TNF-α, IL-23, IL-6, and IL-1β both systemically in spleen samples and locally in skin lesions. This indicates that miR-146a-EVs can inhibit the inflammatory response that drives the development of psoriasis through various mechanisms. MiR-146a is known for its ability to inhibit pro-inflammatory signaling by targeting NF-kβ, IRAK1, and TRAF6, which are essential adaptor proteins involved in the signaling of IL-1β and TNF-α (24, 25). The decrease in these pathways likely contributed to the lower levels of various downstream pro-inflammatory cytokines that were observed. Moreover, miR-146a might inhibit cytokine production indirectly by regulating the activation of antigen-presenting cells and the differentiation of T helper cell subsets such as Th1 and Th17, which are responsible for producing inflammatory cytokines (26, 27). 2. Additionally, miR-146a-EVs increased the expression of anti-inflammatory cytokines TGF-β, IL-10, and IL-4 in both systemic and local contexts. This shift towards an anti-inflammatory cytokine environment provides further evidence that miR-146a-EVs can modify the inflammatory response associated with psoriasis. Anti-inflammatory cytokines like TGF-β and IL-10 have been shown to negatively regulate T cell activation

and differentiation, thereby decreasing the pathological inflammatory processes associated with psoriasis (28, 29). The increased production of these cytokines as a result of miR-146a likely contributed to the resolution of skin inflammation in the disease model (18, 30). 3. Assessments showed that treatment using miR-146a-EVs significantly reduced the typical manifestations of psoriasis induced by imiquimod, including erythema, scaling, and skin thickening. This positive result aligns with the change in cytokine expression regulated by miR-146a-EVs, highlightingtheir therapeutic potential.

The study has some limitations, such as its focus on a mouse model of psoriasis instead of clinical disease. Although imiquimod can simulate some pathogenic characteristics of psoriasis, it may not entirely reflect the complexity of human psoriasis. Furthermore, the exact mechanisms through which miR-146a-EVs interact with immune cells to regulate their functions were not fully clarified and require further exploration. Collectively, the data offer persuasive evidence that miR-146a-modified BMSC-derived EVs hold great promise as a groundbreaking cell-free therapeutic method for treating psoriasis by rectifying the dysregulated cytokine signaling networks underlying persistent skin inflammation. Further development could lead to improved treatment options with fewer side effects compared to current biologic therapies. Additional preclinical work is still needed, but these findings support continued exploration of exosome-mediated microRNA delivery facilitated by stem cells. A potential limitation of this study is the reliance on commercial ELISA kits for cytokine quantification. While these kits offer high specificity and sensitivity, there is a possibility that cytokine isoforms or low-abundance targets may not be fully captured, which could impact the reliability of certain measurements. Another limitation of the current study is the lack of a control group treated with mesenchymal stem cells (MSCs) without vesicles. Including this additional control group in future studies would allow for a clearer comparison of the therapeutic effects mediated by MSCs versus their extracellular vesicles. This would help determine whether the observed therapeutic outcomes are primarily due to the vesicle cargo or other MSC-derived factors.

CONCLUSION

In summary, this research demonstrated that EVs secreted from miR-146a-overexpressing BMSCs have beneficial effects in alleviating psoriasis induced by imiquimod in mice. Treatment with miR-146a-EVs resulted in significant reductions in clinical symptoms and pro-inflammatory cytokine levels, while also increasing anti-inflammatory mediators in both systemic and localized skin lesions. These findings provide a proof-of-concept demonstration that engineered EVs derived from MSCs can serve as a cell-free therapeutic tool for delivering anti-inflammatory miRNAs to address imbalanced inflammatory networks in psoriasis. Whike further research in human disease is needed, miR-146a-EVs show promise as an innovative treatment option for psoriasis. Further study to characterize exosomal cargo, understand mechanisms of immune modulation, conduct toxicology testing, and perform clinical evaluation will aid in translating these findings into new regenerative medicine applications.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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