

# Exosomes in Psoriasis: From Pathogenic Mechanisms to Therapeutic Innovations

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**Abstract:** Psoriasis is a chronic recurrent inflammatory disease driven by keratinocytes and immune cells. Exosomes, as key mediators of intercellular communication, play multidimensional roles in this disease. In terms of pathogenic mechanisms, exosomes released from psoriatic lesions carry non-coding RNAs and proteins that program T-cell polarization, drive M1 macrophage activation, and amplify keratinocyte inflammation, thereby sustaining the IL-23/Th17 immune axis. Translational breakthroughs have repurposed these same vesicles into diagnostic and therapeutic tools. Circulating exosomal fingerprints offer non-invasive biomarkers for disease activity and psoriatic arthritis differentiation. Leveraging their biocompatibility and low immunogenicity, exosomes from mesenchymal stem cells, plants, and microbes serve as cell-free platforms achieving immune regulation, antioxidant effects, and microecological repair. Engineering strategies—including cargo loading, membrane surface modification and intelligent microneedle delivery systems—further enhance targeting and efficacy. Despite these advances, clinical translation faces fundamental challenges: lack of production standardization, undefined core active components and insufficient high-level clinical evidence. Future efforts should prioritize international standards, rational design, and rigorous trials to accelerate exosome-based precision medicine for psoriasis.

**Keywords:** psoriasis, exosomes, biomarkers, cell-free therapy, immunomodulation

## Introduction

Psoriasis is a chronic recurrent inflammatory disease characterized by skin erythema, scales, and immune infiltration.<sup>1,2</sup> Its pathological essence is far from simple skin barrier dysfunction but rather an imbalance in a complex network formed by keratinocytes, T cells, dendritic cells, and other immune cells, along with the cytokines they secrete, triggered by environmental factors in genetically susceptible individuals.<sup>3,4</sup> This persistent inflammatory microenvironment not only drives the stubbornness of skin lesions but also forms the basis for systemic comorbidities such as psoriatic arthritis, leading to the chronic and relapse-prone nature of the disease. Currently, the core pathological mechanism of this disease has been clearly focused on the abnormal activation of the interleukin-23 (IL-23)/T helper 17 (Th17) axis.<sup>5,6</sup> With the innovation of treatment concepts, some perspectives further propose that early precise intervention combined with advanced therapies to reshape immune homeostasis holds promise for achieving a clinical cure, and this has now become a groundbreaking research direction.<sup>7</sup>

Exosomes, a class of extracellular vesicles actively secreted by cells with a diameter of approximately 30–150 nanometers and abundant bioactive molecules, have garnered unprecedented attention because of their central role in intercellular communication.<sup>8</sup> The discovery of exosomes as intercellular messengers dates back to the 1980s, but their potential as disease biomarkers and therapeutic tools accelerated notably after the 2013 Nobel Prize in Physiology or Medicine, and since 2021, research on exosomes in psoriasis therapy has witnessed explosive growth.<sup>9,10</sup> In the complex pathological environment of psoriasis, exosomes play multiple and seemingly contradictory dual roles: on the one hand,



exosomes derived from lesional keratinocytes or activated immune cells can act as precise messengers of inflammatory signals, delivering specific inflammatory instructions accurately to neighboring and distal target cells and participating in and amplifying the disease-specific immune imbalance network; on the other hand, this natural delivery system, owing to its excellent biocompatibility, low immunogenicity, and efficient targeting capabilities, is regarded as a highly promising “cell-free therapy” carrier and a diagnostic tool for liquid biopsy.<sup>11</sup> Exosomes also carry cytokines, as evidenced by elevated circulating exosomal IL-23 and TNF- $\alpha$  mRNAs<sup>12</sup> and increased IL-17A exosome levels<sup>13</sup> in psoriasis, directly implicating the IL-23/Th17 axis.

Moreover, the translational potential of exosomes in the fields of diagnosis and treatment is increasingly evident. At the diagnostic level, the specific “molecular fingerprints” carried by exosomes in patient circulation, such as specific phospholipid profiles, differentially expressed miRNAs, and disease-associated protein cargo, demonstrate the potential to assess disease activity, subtypes, and treatment responses. This facilitates noninvasive monitoring.<sup>14,15</sup> At the therapeutic level, exosomes derived from mesenchymal stem cells, plants, and even probiotics, which leverage their natural immunomodulatory and tissue-repairing properties, are considered promising cell-free therapeutic agents. They can regulate the Th17/Treg balance by delivering microRNA molecules while intervening in the IL-23/Th17 axis.<sup>16,17</sup> Furthermore, through engineered modifications to equip exosomes with targeting ligands or therapeutic payloads, their precision therapeutic efficacy can be significantly enhanced, highlighting their immense potential for development into intelligent delivery systems.<sup>17</sup>

Currently, research in this field has progressed from phenomenological descriptions to functional molecular analysis and animal model validation, with preliminary clinical exploration initiated, positioning it at a critical juncture transitioning toward clinical translation and application. A recent review<sup>18</sup> covered exosome roles in psoriasis pathogenesis, drug delivery, and therapy, but several gaps remain: the diagnostic potential of exosomal cargoes as liquid biopsy biomarkers is underexplored, engineering strategies for targeted therapy lack systematic comparison, and an integrated framework connecting pathogenic mediators to therapeutic vectors is missing. Therefore, systematically organizing the multidimensional roles and translational logic of exosomes in psoriasis is crucial. This review focuses on interconnected areas: (1) pathogenic mechanisms (exosomal cytokines and non-coding RNAs driving T-cell polarization, innate immune amplification, and tissue remodeling); (2) non-invasive biomarkers (exosomal cargoes for severity assessment, treatment monitoring, and psoriatic arthritis differentiation); and (3) therapeutic applications (diverse natural sources and engineering/delivery strategies). By bridging pathogenesis, diagnosis, and therapy, this review provides a framework for exosome-based precision medicine in psoriasis.

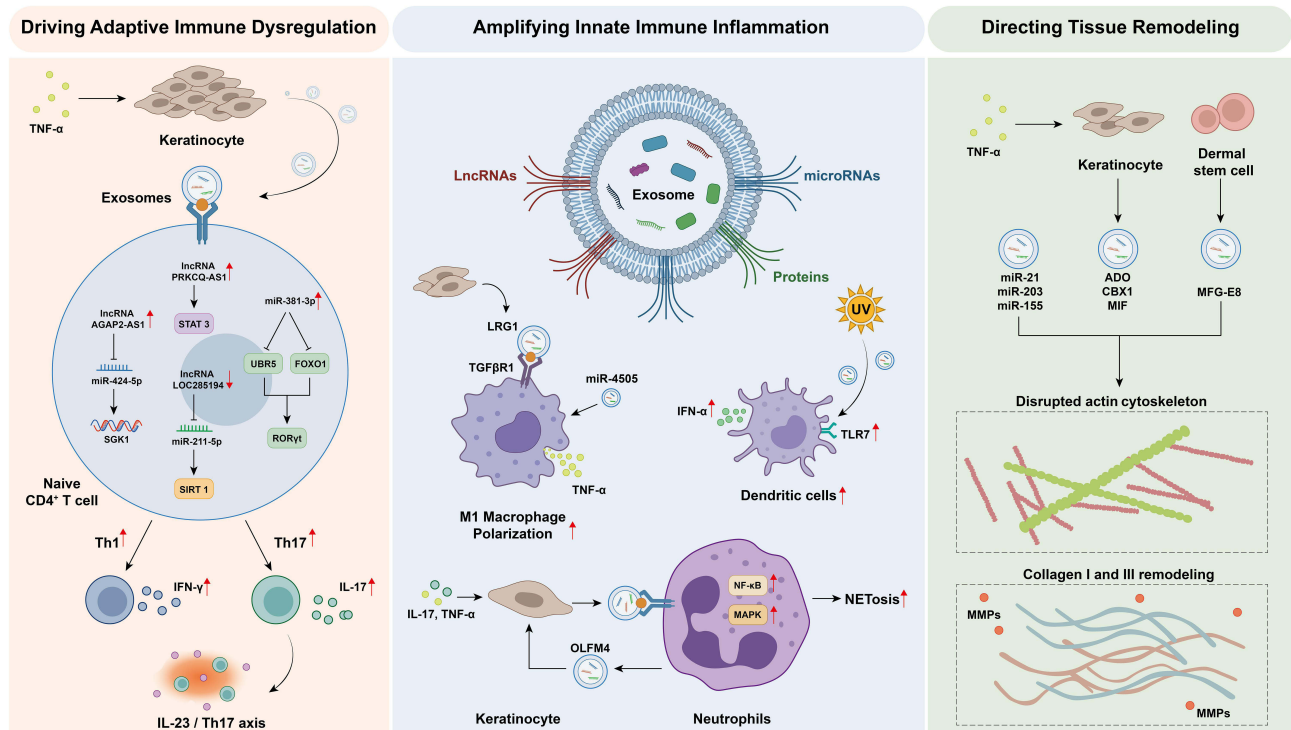
## Pathogenic Mechanisms of Exosomes in Psoriasis

Psoriatic skin lesions represent a pathological ecosystem with highly active intercellular communication. Exosomes serve as core signaling vehicles, delivering bioactive molecules (proteins, nucleic acids) that precisely regulate immune responses and tissue structure. The pathogenic role of these exosomes is characterized by multidimensionality and cascade amplification (Figure 1). Among the various pathways, three interconnected themes emerge as dominant: T-cell polarization (core adaptive event), the keratinocyte–neutrophil amplification loop (key innate amplifier), and tissue remodeling (downstream effector).

## Exosomes Participate in Regulating Adaptive Immune Responses

The abnormal differentiation of CD4<sup>+</sup> T cells into Th1 and Th17 cells is a primary driver of psoriasis. Among the numerous exosomal cargoes identified, non-coding RNAs delivered by keratinocyte (KC)-derived exosomes have been most consistently shown to reprogram CD4<sup>+</sup> T cells in vitro and in animal models. This process begins with the establishment of an inflammatory microenvironment: key cytokines such as IL-17A can significantly alter the release kinetics and cargo composition of KC-derived extracellular vesicles, preparing the carrier for subsequent communication.<sup>19</sup>

When these exosomes are taken up by CD4<sup>+</sup> T cells, the specific lncRNA they carry initiates precise posttranscriptional regulation. For example, under TNF- $\alpha$  stimulation, the lncRNA AGAP2-AS1 enriched in KC exosomes can act as a “molecular sponge” to adsorb miR-424-5p, thereby relieving its inhibition of the downstream target gene SGK1,



**Figure 1** Exosome-mediated pathogenic mechanisms in psoriasis. Activated keratinocytes and immune cells release exosomes carrying diverse bioactive molecules, driving pathogenesis through three core pathways: 1) Adaptive immune dysregulation: Keratinocyte-derived exosomes deliver regulatory non-coding RNAs to CD4<sup>+</sup> T cells, programming their differentiation into pro-inflammatory Th1/Th17 subsets. 2) Innate immune amplification: Exosome-mediated crosstalk between keratinocytes and neutrophils establishes a positive inflammatory feedback loop, promoting macrophage M1 polarization, neutrophil extracellular trap formation, and sustained keratinocyte hyperactivation. 3) Tissue remodeling: Exosomal cargo disrupts cytoskeletal dynamics and extracellular matrix homeostasis in resident skin cells, driving epidermal hyperplasia and dermal disorganization. Red arrows pointing upward indicate upregulation, while red arrows pointing downward indicate downregulation. In this figure, red upward arrows (↑) indicate upregulation or activation, red downward arrows (↓) indicate downregulation or inhibition, and black arrows (→) denote the direction of processes or interactions without implying quantitative change.

driving the differentiation of naive CD4<sup>+</sup> T cells into Th1/Th17 cells.<sup>20</sup> Another lncRNA, PRKCQ-AS1, directly activates the STAT3 signaling pathway in T cells, promoting Th17 differentiation and IL-17 secretion.<sup>21</sup> Moreover, miR-381-3p in KC exosomes simultaneously targets and inhibits UBR5 and FOXO1, synergistically stabilizing RORγt and increasing the suppression of the Th1/Th17 transcriptional program, thereby promoting the production of IFN-γ and IL-17A/F.<sup>22</sup> All three mechanisms converge on the IL-23/Th17 axis – the central hub of psoriasis – but operate through distinct molecular routes: lncRNA sponging, direct STAT3 activation, and miRNA-mediated stabilization of RORγt. Among them, direct STAT3 activation by PRKCQ-AS1 likely represents the most efficient route, though all contribute to Th17 skewing. Additionally, environmental factors influence this programming process. After stimulating cells, environmental pollutants such as benzo[a]pyrene release exosomes that activate the aryl hydrocarbon receptor signaling pathway, inducing Th1/Th17 differentiation in immune cells and mediating the long-term programming effects of environmental exposure on the immune system.<sup>23</sup>

The loss of protective regulatory mechanisms also exacerbates immune imbalance. In psoriatic patients, the downregulation of lncRNA LOC285194 expression in KC exosomes leads to the loss of its protective function in suppressing Th17 differentiation by adsorbing miR-211-5p to maintain the expression of the deacetylase SIRT1, which is equivalent to removing an intrinsic “immune checkpoint”.<sup>24</sup> Furthermore, bioinformatics analysis revealed a regulatory network formed by exosome-related genes, supporting the central role of exosomes in adaptive immune dysregulation at the systemic level. For example, the exosome-related gene *CD274* (encoding PD-L1) regulates T-cell activation through the PD-1/PD-L1 axis, *CXCL13* mediates inflammatory cell recruitment, and *BIRC5* participates in pathological hyperplasia by inhibiting keratinocyte apoptosis.<sup>25</sup> Taken together, the evidence strongly supports that KC-derived exosomal

non-coding RNAs are dominant upstream regulators of Th17 polarization – arguably the most critical pathogenic axis in psoriasis.

## Exosomes Participate in Regulating Innate Immune Responses

Abnormal activation and sustained amplification of the innate immune system constitute the cornerstone of psoriasis inflammation. Exosomes act as key messengers for intercellular inflammatory signal transmission and form a vicious positive feedback loop. Among the various innate pathways, the bidirectional crosstalk between KCs and neutrophils stands out as the most powerful amplifier, while macrophage and dendritic cell modulation play secondary supporting roles.

First, KC exosomes directly regulate the functional state of innate immune cells, primarily by reprogramming macrophages and activating dendritic cells. For example, under inflammatory stimulation, KCs release extracellular vesicles rich in leucine-rich alpha-2-glycoprotein 1 (LRG1), which drive macrophages toward the proinflammatory M1 phenotype by binding to TGF $\beta$ R1 on their surface.<sup>26</sup> Vitamin D receptor-deficient KC-derived exosomes promote M1 polarization of macrophages by delivering miR-4505.<sup>27</sup> Ultraviolet irradiation systematically modifies the miRNA cargo of KC exosomes, which, after being taken up by plasmacytoid dendritic cells, activate Toll-like receptor 7 and strongly induce type I interferon production, thereby initiating inflammatory responses.<sup>28</sup> While these pathways contribute to the inflammatory milieu, they are likely secondary amplifiers rather than primary initiators, as their blockade does not completely abrogate psoriatic inflammation in animal models.

Second, a robust positive inflammatory feedback loop is formed between KCs and neutrophils through exosomes, which is a crucial mechanism for the acute exacerbation of skin lesions. On the one hand, exosomes released by KCs stimulated by IL-17A and TNF- $\alpha$  can activate the NF- $\kappa$ B/p38 MAPK signaling pathway within neutrophils, inducing the formation of neutrophil extracellular traps (NETs) and the release of inflammatory factors, directly leading to tissue damage.<sup>29</sup> On the other hand, activated neutrophils (especially in generalized pustular psoriasis) release exosomes rich in olfactomedin-4 (OLFM4), which can “counterattack” KCs and activate their NF- $\kappa$ B, p38 MAPK, and ERK1/2 pathways, leading to the overexpression of IL-36 $\gamma$ , TNF- $\alpha$ , and other factors in KCs. This recruits more neutrophils, forming a self-amplifying inflammatory vortex.<sup>30</sup> This KC–neutrophil loop is self-sustaining and directly linked to acute exacerbations; therefore, it is prioritized as the most critical innate amplifier. This dysregulation also has systemic effects: elevated levels of platelet- and erythrocyte-derived microvesicles in the patient’s circulation can induce endothelial inflammation and activate the coagulation system, collectively shaping a systemic prothrombotic and proinflammatory state.<sup>31</sup>

## Exosomes Participating in the Cytoskeleton and Matrix Remodeling

In addition to immune regulation, exosomes are also deeply involved in the pathological destruction and abnormal reconstruction of local tissue structures in psoriatic skin lesions, synergistically mediating abnormal epidermal hyperplasia and dermal connective tissue disorganization. Unlike immune-driven pathways, these tissue remodeling events are largely downstream consequences of inflammation, although they feed back into disease chronicity and clinical severity.

Exosomes directly influence the cytoskeletal dynamics and extracellular matrix metabolic balance of cells by delivering specific regulatory molecules. For example, specific miRNAs (such as miR-21, miR-203, and miR-155) are transferred across cells via exosomes. After entering target cells, they precisely regulate downstream target genes, affecting processes such as actin polymerization during cytoskeletal reorganization, collagen synthesis, degradation, and the expression of matrix metalloproteinases.<sup>32</sup> Environmental factors such as TNF- $\alpha$  disrupt KC homeostasis and trigger the secretion of exosomes carrying specific proteins (eg, ADO, which is involved in angiogenesis; the epigenetic regulator CBX1; and the proinflammatory factor MIF). These vesicles act as signaling carriers that drive early tissue alterations.<sup>33</sup>

Moreover, the dysfunction of other cells in the local microenvironment of skin lesions also contributes to tissue remodeling through exosomes. For example, the function of dermal mesenchymal stem cells may be altered, and the expression of proteins related to skin barrier function (such as milk fat globule epidermal growth factor 8) in the exosomes they secrete is downregulated, thereby disrupting the microenvironment that maintains skin homeostasis.<sup>34</sup> Mesenchymal stem cells and the vesicles they secrete can also directly affect the expression of proliferation-related

markers in KCs by delivering bioactive molecules, contributing to the disruption of tissue homeostasis.<sup>35</sup> Overall, as multifunctional signaling platforms, exosomes carry diverse cargoes that collectively form a complex regulatory network. While exacerbating immune inflammation, they also directly instruct structural lesions in local tissues, reflecting their multidimensional role throughout the pathogenesis of psoriasis.<sup>36</sup> In the pathogenic hierarchy, this tissue remodeling layer is positioned as an effector consequence – essential for clinical manifestations (hyperplasia, scaling) but not a primary driver; thus, therapeutic strategies may prioritize upstream immune targets.

## Circulating Exosomes as Biomarkers for the Diagnosis and Subtyping of Psoriasis

Protected by their lipid bilayer, circulating exosomes can stably carry molecular fingerprints, such as proteins and nucleic acids derived from parent cells, providing an ideal “liquid biopsy” window for the dynamic monitoring of psoriasis. Their noninvasive and repeatable acquisition characteristics make it possible to assess disease activity in real time, monitor treatment response, and achieve precise clinical subtype differentiation. Routine clinical assessment of psoriasis still depends on the Psoriasis Area and Severity Index (PASI) and body surface area (BSA) – scores that vary considerably between observers. Skin biopsy, although definitive, is invasive and unsuitable for frequent monitoring. Serum markers such as C-reactive protein (CRP) lack disease specificity. Exosome-based miRNA profiling offers a quantitative, easily repeatable, and patient-friendly strategy that addresses many of these gaps. Currently, research focuses primarily on the analysis of specific miRNA profiles within exosomes. These molecules are not only closely associated with disease states but also reveal underlying pathological mechanisms through their regulatory pathways.

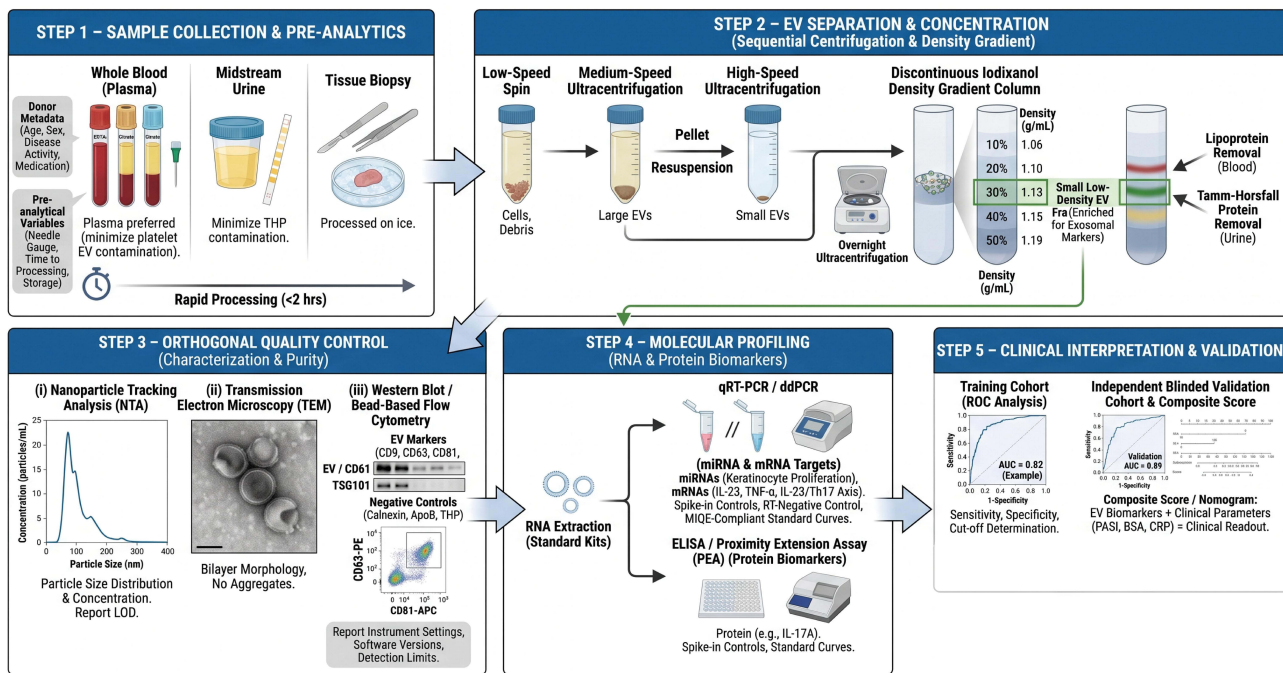
## Practical Workflow for Exosome-based Clinical Diagnostics

A clinically reliable exosome-based diagnostic workflow must integrate robust isolation, standardized characterization, and clear criteria for result interpretation. For tissue-derived EVs, a validated protocol<sup>37</sup> involves gentle mincing of tissues into 2×2×2 mm pieces, followed by enzymatic digestion with collagenase D and DNase I to release EVs trapped in the extracellular space. Subsequent differential ultracentrifugation separates large and small EVs, which are then resolved by iodixanol density gradient into six subpopulations: large/small low-density (LD) and high-density (HD) EVs. For liquid biopsies (eg, blood, urine), size-exclusion chromatography or ultracentrifugation combined with density gradients is recommended to remove highly abundant lipoproteins and protein aggregates. Following MISEV2023 guidelines,<sup>38</sup> each preparation should be characterized by orthogonal methods: particle concentration (nanoparticle tracking analysis), EV marker proteins including transmembrane (eg, CD9, CD63, CD81) and cytosolic markers (eg, ALIX, TSG101), and exclusion of non-vesicular contaminants (lipoproteins, Tamm-Horsfall protein). The ten-year evolution of MISEV<sup>39</sup> emphasizes transparent reporting of pre-analytical variables, separation yields and detection limits – all essential for clinical translation.

To implement exosomes as a routine diagnostic tool, we envisage a stepwise pipeline (Figure 2): (1) sample collection (blood, urine or tissue) under standardized pre-analytical conditions; (2) EV separation using a clinically compatible method (eg, automated SEC or density gradient); (3) quality control (particle count, protein/RNA yield, marker identification); (4) molecular profiling (eg, qPCR for IL-23/TNF- $\alpha$  mRNA or proteomics); and (5) algorithm-based scoring (eg, machine-learning) to discriminate patients from healthy controls. Despite current challenges – such as the 22-h processing time for tissue EVs, limited applicability to frozen samples, and potential surface protein alteration by enzymatic treatment – adherence to MISEV recommendations and further technological automation will pave the way for exosome-based liquid biopsy in psoriasis management.

## Disease Severity Assessment and Treatment Efficacy Monitoring

The correlation between circulating exosomal miRNA profiles and the clinical severity of psoriasis has been confirmed by multiple studies, with some molecules demonstrating exceptional diagnostic efficacy and dynamic monitoring potential. A study involving 63 patients revealed that the level of miR-625-3p in keratinocyte-derived extracellular vesicles was strongly positively correlated with the PASI and BSA scores, with an area under the curve (AUC) as high as



**Figure 2** Proposed workflow for exosome-based clinical diagnostics in psoriasis. The workflow follows MISEV2023 guidelines and includes (1) sample collection (plasma, urine or tissue, processed on ice within 1 h); (2) EV separation (differential ultracentrifugation plus iodixanol density gradient); (3) orthogonal quality control (NTA, TEM, EV markers CD9/CD63/CD81/ALIX/TSG101, and exclusion of non-EV contaminants such as calnexin); (4) molecular profiling (qRT-PCR or ddPCR for exosomal miRNAs or mRNAs); and (5) clinical interpretation (ROC-derived cut-offs, composite scores with PASI/CRP, independent validation). No exosome-based psoriasis test has yet received regulatory clearance.

0.9515 for distinguishing mild, moderate, and severe patients. Mechanistically, this miRNA activates the IGF-1/Akt proliferative pathway in keratinocytes by targeting and inhibiting insulin-like growth factor-binding protein 3 (IGFBP3). Notably, its levels are significantly decreased in treatment responders, suggesting its potential as a sensitive biomarker for monitoring therapeutic efficacy.<sup>40</sup> Another case-control study of 40 psoriasis patients and 43 healthy controls revealed that the expression of miR-16-5p, miR-21-5p, and miR-155-5p in total circulating vesicles of patients was generally downregulated. Among these, miR-21-5p exhibited the best diagnostic performance (AUC=0.7059), while the level of miR-16-5p and its ratio to miR-21-5p were positively correlated with the PASI score. The target genes coregulated by these differentially expressed miRNAs were enriched in key pathways, such as the TNF and PI3K-Akt pathways.<sup>41</sup> Importantly, some exosomal miRNAs may exert protective feedback effects. For example, a clinical study of 15 psoriasis patients and 10 healthy controls found that serum exosomal miR-6785-5p was significantly upregulated.<sup>42</sup> This miRNA can be taken up by KCs, where it targets MNK2 and inhibits its downstream phosphorylated eukaryotic translation initiation factor 4E (p-eIF4E) axis, thereby suppressing abnormal proliferation and inflammation. Collectively, these studies demonstrate that circulating exosomal miRNAs are sensitive indicators reflecting disease severity and that their dynamic changes may encompass rich information ranging from pathogenic drivers to protective feedback mechanisms.

## Differential Diagnosis of Psoriatic Arthritis

Accurate differentiation between cutaneous-only psoriasis (PsO) and psoriatic arthritis (PsA) is crucial for clinical decision-making, and circulating exosomes provide a highly promising noninvasive tool for this purpose. The current diagnosis of PsA relies on the CASPAR criteria and imaging techniques (ultrasound and MRI) that are often insensitive to subclinical joint inflammation. A blood-based exosomal miRNA panel could identify individuals at risk before erosive damage occurs.

Studies have revealed systematic differences in the molecular profiles of plasma exosomes between PsA patients and PsO patients. In the Han Chinese population, a study of 42 patients (25 PsO, 17 PsA) identified significantly reduced plasma extracellular vesicle miR-218-5p in PsA versus PsO via next-generation sequencing.<sup>43</sup> ROC analysis showed its

diagnostic value (AUC=0.758, 95% CI: 0.535–0.982, P=0.023; sensitivity 73.3%, specificity 87.5%). Western blotting confirmed elevated ADP-ribosylation factor 6 (ARF6) and tumor necrosis factor alpha-induced protein 3 (TNFAIP3) in PsA, with ARF6 positively correlated with TNFAIP3 and inversely related to miR-218-5p. Both genes are involved in the regulation of inflammatory pathways such as NF- $\kappa$ B, suggesting that this axis may play a role in PsA-specific joint inflammation. Broader omics studies have confirmed the universality of these differences. In 12 psoriasis vulgaris (PsV), 12 PsA, and 12 healthy controls, serum EV miRNAs were profiled by RNA sequencing after size-exclusion chromatography. Compared with PsV, PsA had eight differentially enriched miRNAs (FDR  $\leq$  0.1), including upregulated miR-33a-5p (1.82-fold) and downregulated miR-671-3p (0.43-fold); miR-10b-5p was also lower in PsA versus controls (0.46-fold). Pathway analysis of target genes implicated arthritis-related processes (methyl CpG binding protein 2, circadian rhythm, dopamine release cycle), suggesting that circulating EV miRNAs reflect joint-specific pathology in PsA.<sup>44</sup> Additionally, studies indicate that the expression of let-7b-5p and miR-30e-5p in the plasma exosomes of PsA patients is significantly lower than that in the plasma exosomes of PsO patients.<sup>45</sup> The former can target and inhibit the key proinflammatory factor IL-6, while the latter targets genes such as BMI1, an activator of the NF- $\kappa$ B pathway. Their downregulation may promote joint inflammation.<sup>46</sup> These findings collectively highlight that circulating exosomes carry molecular information reflecting systemic disease involvement. By analyzing their specific miRNA profiles, efficient and noninvasive differentiation between PsA and PsO may be achieved, guiding early therapeutic interventions. However, direct comparisons with established imaging or serological biomarkers (eg, ultrasound-detected enthesitis, CRP) are still lacking, and such validation studies should be a priority for translation.

## Exosomes as a Promising Therapeutic Strategy

Therapeutic exosomes, which leverage their inherent biocompatibility, low immunogenicity, and targeting capabilities, are emerging as a cutting-edge approach in the field of cell-free therapy, with a trend toward diversified sources. Current research not only systematically elucidates the core effector molecules and signaling pathways of exosomes from various sources but also enhances their functions through engineering strategies, revealing a developmental trajectory from natural biological agents to intelligent drug systems.

### Mesenchymal Stem Cell-Derived Exosomes

Mesenchymal stem cell-derived exosomes (MSC-Exos) have emerged as the most promising therapeutic carriers because of their ability to inherit the immunomodulatory and tissue repair properties of MSCs while avoiding the risks associated with live cell transplantation, such as potential tumorigenesis and embolism. Their efficacy has been extensively validated in preclinical studies, with meta-analyses confirming their ability to significantly reduce the PASI score and epidermal thickness, as well as downregulate key inflammatory cytokines such as TNF- $\alpha$  and IL-17A.<sup>47</sup>

The efficacy of these methods is closely related to the tissue source and pretreatment strategy. A comparative study revealed that human umbilical cord-derived MSCs (hUCMSC-Exos) are superior to adipose-derived exosomes in reversing epidermal acanthosis and reducing CD3<sup>+</sup> T-cell and CD68<sup>+</sup> macrophage infiltration without the common side effects of topical corticosteroids, such as skin thinning. Their superiority may be associated with the enrichment of hepatocyte growth factor (HGF) revealed by proteomics.<sup>48</sup> More innovatively, the “inflammatory cytokine pretreatment” strategy involves stimulating MSCs with a mixture of IL-17, IL-22, and TNF- $\alpha$  (10–50 ng/mL for 24 h), after which the secreted exosomes (MSC-Exo 3C) exhibit a qualitative improvement in efficacy, even surpassing that of the parent cells. In an imiquimod-induced psoriasis-like mouse model, subcutaneous injection of MSC-Exo 3C on days 1 and 4 significantly reduced the cumulative PASI score from 11.5 (control) to 4.0 on day 8 (65.2% reduction), outperforming intact hUCB-MSCs (PASI 7.0) and the parent cells. The molecular mechanism involves the “reprogramming” of exosomes by pretreatment, enabling them to carry more targeted immunomodulatory signals, such as increasing the secretion of regulatory cytokines such as transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1), thereby more effectively correcting the Th17/Treg imbalance *in vivo*.<sup>49</sup>

Analysis of its active components revealed precise molecular targets. miR-100-5p in human placental MSC-Exos is one of the core effector molecules. It directly targets the messenger RNA of the mammalian target of rapamycin (mTOR), inhibiting the phosphorylation and activation of mTOR and its downstream ribosomal protein S6 kinase 1

(S6K1). Topical MSC-Exos reduced epidermal thickness by  $\approx 50\%$  and the PASI score from 7.83 to 2.00 on day 4. The suppression of this pathway blocks keratinocyte hyperproliferation and alleviates inflammation, achieving dual anti-proliferative and anti-inflammatory effects.<sup>50</sup> Additionally, MSC-Exos have been shown to induce the expression of transforming growth factor- $\beta 2$  (TGF- $\beta 2$ ), which interferes with another critical pathological process of psoriasis—angiogenesis—by inhibiting the abnormal proliferation of dermal microvascular endothelial cells.<sup>51</sup>

Research on the molecular mechanisms of topical application provides insights for clinical positioning. Studies indicate that topically applied MSC-Exos localize primarily to the stratum corneum of the skin and that the surface marker CD59 effectively inhibits the assembly of the terminal complement complex C5b-9. Moreover, C5b-9 is a key trigger for inducing neutrophils to undergo neutrophil extracellular traps (NETosis) and release IL-17. Topical MSC-Exos significantly reduced IL-17 and C5b-9 levels in the skin. Therefore, MSC-Exos exert anti-inflammatory effects by inhibiting complement activation, reducing NETosis, and lowering IL-17 levels, which is particularly suitable for mild psoriatic phenotypes.<sup>52</sup> This mechanism also partially explains its limited efficacy in deep or severe inflammation—due to insufficient transdermal delivery depth. To repair more extensive cellular damage, ADSC-Exos have been shown to reverse keratinocyte dysfunction induced by serum exosomes (Ps-Exos) from psoriasis patients. The mechanism involves the following mechanisms for restoring multidimensional homeostasis: reinstating autophagy function to clear damaged organelles; alleviating oxidative stress by downregulating NADPH oxidase 2/4 and upregulating nuclear factor erythroid 2-related factor 2 (NRF2); and simultaneously inhibiting the NF- $\kappa$ B and p38 MAPK signaling pathways activated by Ps-Exo.<sup>53</sup>

Encouragingly, clinical translation has achieved positive progress. In terms of safety, a Phase I open-label trial confirmed that topical MSC exosome ointment was well tolerated, with no treatment-related adverse events or abnormal laboratory indicators observed.<sup>54</sup> In terms of efficacy, a randomized, double-blind, controlled study in 12 patients with bilateral psoriasis utilized Wharton's jelly MSC secretome (exosome-enriched) combined with hyaluronic acid in a lyophilized sponge for topical treatment over 30 days. The results revealed an average 33% reduction in the modified PASI (mPASI) score, a 41% decrease in the target plaque area, and improvements in skin barrier function (transepidermal water loss) and elasticity.<sup>55</sup> A dose-finding study in 12 patients with mild-to-moderate plaque psoriasis (divided into three groups receiving single intradermal injections of 50, 100, or 200  $\mu\text{g}/\text{cm}^2$  autologous ADSC-exosomes) identified 200  $\mu\text{g}/\text{cm}^2$  as the optimal regimen, which reduced lesional IL-17 and CD3 expression and increased FOXP3, with no severe adverse events.<sup>56</sup> A systematic review of multiple clinical studies (totaling >30 patients with moderate-to-severe psoriasis) revealed that ADSCs and their exosomes exert therapeutic effects through multiple pathways, including secretion of IL-10, prostaglandin E2 (PGE2), and other molecules, as well as direct regulation of keratinocyte autophagy and oxidative stress; clinical improvements included significant PASI reductions (eg, from 24.0 to 8.3, or complete resolution of plaques) with no serious adverse events reported.<sup>57</sup>

## Plant-Derived Nanovesicles

Plant-derived exosome-like nanovesicles (PDNVs) are emerging as a highly promising direction in the field of psoriasis treatment because of their unique advantages of wide availability, low cost, and rich natural bioactive components. These natural nanostructures derived from plants demonstrate therapeutic potential comparable to or even superior to that of some traditional drugs by regulating key inflammatory pathways and oxidative stress responses in psoriasis, and they have garnered significant attention for their excellent biocompatibility.

Various plant-derived PDNVs have been demonstrated to be effective through different molecular mechanisms. For example, PDNVs extracted from garlic and shallot significantly alleviated psoriasis symptoms. The mechanism involves dual synergistic effects: inhibition of IL-17 signaling (downregulating downstream proinflammatory cytokines such as TNF- $\alpha$ ) and activation of the NRF2 antioxidant pathway (inducing protective proteins such as HMOX1). This dual regulatory effect makes their therapeutic efficacy comparable to that of topical glucocorticoids while avoiding the associated side effects.<sup>58</sup>

Another groundbreaking study revealed the astonishing cross-kingdom regulatory capabilities between plants and mammals. Extracellular vesicle-like particles (PLEVPs) derived from *Perilla frutescens* leaves carry the unique plant microRNA Pab-miR-396a-5p. When delivered to psoriatic skin lesions, Pab-miR-396a-5p crosses species barriers, is

taken up by keratinocytes, and directly targets heat shock protein 90 (HSP90), inhibiting its expression. This suppresses the NF- $\kappa$ B and JAK-STAT pathways, blocks IL-17 signaling, and reduces epidermal thickness and PASI scores, with efficacy even surpassing that of topical tacrolimus.<sup>59</sup>

Furthermore, rose hip-derived nanoparticles (RNPs) provide another mechanism to directly combat oxidative stress in psoriasis. Unlike those that activate the endogenous NRF2 pathway, RNPs possess a strong ability to scavenge reactive oxygen species (ROS) directly. After entering keratinocytes through clathrin-mediated endocytosis and other pathways, RNPs can directly eliminate excess ROS, alleviating oxidative damage. Simultaneously, they inhibit the phosphorylation of Akt, thereby interfering with the cell cycle and suppressing the abnormal proliferation of keratinocytes.<sup>60</sup>

## Probiotic/Microbial-Derived Vesicles

With a focus on the “gut–skin axis” and the regulation of local skin microecology, the use of probiotics and symbiotic microbe-derived vesicles provides a novel approach for modulating systemic and local immunity in psoriasis. They circumvent the potential colonization and infection risks associated with live bacterial therapies by carrying specific bacteria-derived active metabolites, precisely regulating the host immune response and microenvironment homeostasis. In a study by Xie et al<sup>61</sup> using an IMQ-induced psoriasis mouse model (n=5/group), oral administration of *Lactobacillus plantarum*-derived cytoplasmic membrane vesicles (CMVs) reduced PASI scores by approximately 73–78% and decreased epidermal thickness by 56% compared to the IMQ group. The therapeutic effect was attributed to the enrichment of the endogenous cannabinoid ligand anandamide (AEA) within CMVs. Despite these promising preclinical results, the clinical translation of *L. plantarum*-derived CMVs requires further investigation into optimal dosing, long-term safety, and scalable production.

The outer membrane vesicles of the gut commensal bacterium *Parabacteroides goldsteinii* (Pg OMVs) exert systemic regulatory effects through their ability to carry the active lipid pentadecanoic acid (PEA). Pg OMVs can be administered via two routes, oral (acting on the gut) or local subcutaneous injection, both of which effectively inhibit psoriasis-like skin inflammation, reducing PASI scores and epidermal thickness. At the molecular level, PEA effectively inhibits the activation of NF- $\kappa$ B and STAT3, two core inflammatory transcription factors in psoriasis, thereby downregulating the expression of downstream cytokines such as IL-17 and IL-23 and restoring the Th17/Treg balance.<sup>62</sup> Multiomics analysis revealed its dual regulatory mechanisms: direct action on the skin to inhibit the local mTOR/NF- $\kappa$ B pathway; oral administration also reshaped the disordered gut microbiota, increased the abundance of beneficial Bacteroidetes, and alleviated systemic inflammation.<sup>63</sup> Despite these preclinical efficacy data, clinical translation of Pg OMVs requires further evaluation of long-term safety and optimal dosing. These exosomes, which have diverse origins and mechanisms, significantly expand the diversity and precision of psoriasis treatment strategies. To clearly outline the main strategies and molecular mechanisms of therapeutic exosomes, key points are summarized in [Table 1](#).

## Engineering and Delivery Strategies for Exosomes

To overcome the limitations of natural exosomes in targeting, efficacy, and stability, the integration of engineered modifications and innovative delivery technologies is driving their evolution into intelligent nanomedicines that can be designed on demand and precisely regulated.

### Engineering Modifications of Exosomes

Engineering modifications aim to endow exosomes with novel functions through rational design, with core strategies including loading therapeutic molecules, modifying membrane properties and engineering parent cells. Loading strategies focus on encapsulating exogenous active substances into exosomes to achieve precise intervention in specific pathological processes. For example, nor@MSC-EVs were constructed by loading the arginase 1 (Arg1) inhibitor nor-NOHA into MSC-derived vesicles and effectively inhibited Arg1 activity and reduced polyamine production upon uptake by keratinocytes, thereby blocking the key step of protein citrullination in autoantigen formation and subsequently suppressing downstream inflammatory pathways such as NF- $\kappa$ B activation.<sup>65</sup> Its efficacy in animal models even surpasses that of clinical anti-interleukin-17A antibodies. Similar loading strategies have been applied to improve existing drugs, such as TFC-Exos, which are formed by loading the JAK inhibitor tofacitinib (TFC) into keratinocyte-

**Table 1** Therapeutic Strategies of Diverse Exosomes in Psoriasis

Exosome Type	Exosome Source	Key Molecular Cargo/Effector	Target Cells	Specific Molecular Targets/Pathways	Therapeutic Mechanism	Translational Stage	Refs.
Mesenchymal Stem Cell (MSC)-Derived	Human Umbilical Cord MSCs	HGF; growth factors (FGFs, PDGFs, TGF- $\beta$ , VEGF)	T cells, Macrophages, KCs	<ol style="list-style-type: none"> <li>T cells: <math>\downarrow</math>T-bet (Th1), <math>\downarrow</math>ROR<math>\gamma</math>t (Th17)</li> <li>Macrophages: <math>\downarrow</math>CD86, <math>\uparrow</math>CD206</li> <li>KCs: <math>\downarrow</math>Kl6, <math>\downarrow</math>S100A7</li> <li>Immune infiltration: <math>\downarrow</math>CD3<math>^+</math>/CD4<math>^+</math>/CD8<math>^+</math> T cells, <math>\downarrow</math>CD68<math>^+</math> macrophages, <math>\downarrow</math>CD117<math>^+</math> mast cells</li> </ol>	<ol style="list-style-type: none"> <li>Cellular: Suppresses Th1/Th17; expands Tregs (Foxp3<math>^+</math>)</li> <li>Histological: Reduces epidermal hyperplasia and immune infiltration</li> <li>Comparative: Superior to ADSC-Exo; safer than corticosteroids (no skin thinning)</li> </ol>	Preclinical (in vivo)	[48]
	Cytokine-Preconditioned MSCs (IL-17/IL-22/TNF- $\alpha$ )	TGF- $\beta$ 1, IL-6, PGE2	T cells	<ol style="list-style-type: none"> <li>Treg: <math>\uparrow</math>p-SMAD2/3</li> <li>Th17: <math>\downarrow</math>p-STAT3</li> </ol>	<ol style="list-style-type: none"> <li>Reprogramming: Enhances MSC secretome potency</li> <li>Immune balance: Rebalances Th17/Treg axis; superior to unpreconditioned exosomes and parent cells</li> </ol>	Preclinical (in vivo)	[49]
	Human Placental MSCs	miR-100-5p	KCs	mTOR/S6K1: targets 3'UTR of mTOR $\rightarrow$ $\downarrow$ p-mTOR (Ser2448) and $\downarrow$ p-S6K1 (Thr389)	<ol style="list-style-type: none"> <li>Proliferation: Inhibits KC hyperproliferation via mTOR/S6K1 blockade</li> <li>Inflammation: Reduces IL-6, TNF-<math>\alpha</math> secretion</li> <li>Efficacy: Comparable to hUCMSC-Exo</li> </ol>	Preclinical (in vivo)	[47,50]
	MSC-Exos (General/Topical)	CD59; miR-146a; TGF- $\beta$ 2	Complement, DCs, KCs, endothelial cells	<ol style="list-style-type: none"> <li>Complement: inhibits C5b-9 <math>\rightarrow</math> <math>\downarrow</math>NETosis</li> <li>DCs: targets IRAK1/TRAF6 <math>\rightarrow</math> <math>\downarrow</math>NF-<math>\kappa</math>B <math>\rightarrow</math> <math>\downarrow</math>IL-23</li> <li>KCs: <math>\downarrow</math>p-STAT3 (Tyr705), <math>\uparrow</math>TGF-<math>\beta</math>2/SMAD2</li> <li>Endothelial: <math>\downarrow</math>proliferation</li> </ol>	<ol style="list-style-type: none"> <li>Immune: Inhibits IL-23/Th17 axis; reduces complement-driven inflammation</li> <li>Tissue: Suppresses KC hyperplasia</li> <li>Clinical: Safe and well-tolerated in human Phase I trial; suitable for mild psoriasis</li> </ol>	Clinical (Phase I)	[51,52,54,55]
	Adipose-Derived MSCs (ADSC-Exo)	miRNAs, antioxidative enzymes	KCs	<ol style="list-style-type: none"> <li>Autophagy: <math>\uparrow</math>ATG5, Beclin1, LC3B</li> <li>Oxidative stress: <math>\downarrow</math>NOX2/4, <math>\uparrow</math>NRF2</li> <li>Inflammation: <math>\downarrow</math>p-p65 (NF-<math>\kappa</math>B), <math>\downarrow</math>p-p38 (MAPK)</li> </ol>	<ol style="list-style-type: none"> <li>Homeostasis restoration: Reverses KC dysfunction induced by psoriatic serum exosomes</li> <li>Multi-target: Restores inflammation, redox, and autophagy balance</li> <li>Cytokine suppression: <math>\downarrow</math>IL-1<math>\beta</math>, IL-6, TNF-<math>\alpha</math></li> </ol>	Preclinical (in vivo)	[53,56,57]

Plant-Derived Nanovesicles (PDNVs)	Garlic/Onion PDNVs	Flavonoids (eg, quercetin), organosulfur compounds	KCs	<ol style="list-style-type: none"> <li>① Antioxidant: activates NRF2 (nuclear translocation, ↑HO-1, ↑NQO1)</li> <li>② Anti-inflammatory: inhibits IL-17R downstream (↓LCN2, ↓CCL20)</li> </ol>	<ol style="list-style-type: none"> <li>① Dual regulation: ROS scavenging (antioxidant) + IL-17 pathway blockade (anti-inflammatory)</li> <li>② Efficacy: Comparable to topical glucocorticoids without side effects</li> </ol>	Preclinical (in vivo)	[58]
	Perilla Leaf EVs (PLEVPs)	Pab-miR-396a-5p (plant miRNA); ceramides, hexosylceramides, flavonoids	KCs	Cross-kingdom: targets HSP90 3'UTR → destabilizes client proteins → ↓NF-κB (↓p-p65) and ↓JAK-STAT (↓p-STAT3)	<ol style="list-style-type: none"> <li>① Cross-kingdom RNAi: Disrupts multiple inflammatory pathways via HSP90 degradation</li> <li>② Cellular effects: Reduces ROS, promotes KC apoptosis, enhances Treg activity</li> <li>③ Delivery: Hydrogel formulation improves stability and transdermal delivery</li> </ol>	Preclinical (in vivo)	[59]
	Rose Hip-Derived NPs (RNPs)	Polyphenols (gallic acid), carotenoids (β-carotene)	KCs, RAW264.7 macrophages	<ol style="list-style-type: none"> <li>① ROS: directly scavenges</li> <li>② Akt: ↓p-Akt (Ser473) → ↓Cyclin D1</li> <li>③ Macrophages: ↓intracellular ROS</li> </ol>	<ol style="list-style-type: none"> <li>① Oxidative stress reduction: Direct ROS scavenging</li> <li>② Cell cycle arrest: Induces G1 arrest via Akt inhibition</li> <li>③ Anti-proliferative: Suppresses KC hyperproliferation and macrophage infiltration</li> </ol>	Preclinical (in vivo)	[60]
Probiotic/Microbial-Derived	<i>Lactobacillus plantarum</i> CMVs	AEA (Anandamide)	Macrophages, KCs	<ol style="list-style-type: none"> <li>① Macrophages: inhibits NF-κB p65 nuclear translocation → ↓iNOS, ↓TNF-α</li> <li>② KCs: ↓ROS, ↓Ki67</li> </ol>	<ol style="list-style-type: none"> <li>① Cannabinoid receptor-mediated: Immunomodulation via AEA</li> <li>② Phenotype shift: Reduces M1 polarization</li> <li>③ Anti-proliferative: ↓KC proliferation and oxidative damage</li> </ol>	Preclinical (in vivo)	[61]
	<i>Parabacteroides goldsteinii</i> OMVs (Pg OMVs)	PEA (Pentadecanoic Acid); Lipids/Proteins	Macrophages, DCs, KCs; Gut microbiota	<ol style="list-style-type: none"> <li>① Myeloid cells: inhibits mTOR/NF-κB (↓p-p65, ↓p-S6)</li> <li>② Gut: restores microbiota (↑Bacteroidetes, ↓F/B ratio)</li> </ol>	<ol style="list-style-type: none"> <li>① Dual action: Direct cutaneous NF-κB suppression + indirect gut-skin axis modulation</li> <li>② Anti-inflammatory: Reduces LPS-induced TNF-α/IL-6 in HaCaT cells</li> <li>③ Microbiota restoration: Increases beneficial bacteria</li> </ol>	Preclinical (in vivo)	[62,63]
	<i>Cutibacterium acnes</i> EVs (CA-EVs)	Unknown (proteins/lipids)	ILCs; skin microbiota	<ol style="list-style-type: none"> <li>① ILCs: inhibits ILC2-to-ILC3 transition (↓RORγt) → ↓IL-17, ↓IL-22</li> <li>② Microbiota: ↑diversity, ↓<i>S. aureus</i></li> </ol>	<ol style="list-style-type: none"> <li>① Immune-microbiota dual regulation: Restores skin immune homeostasis via ILC plasticity</li> <li>② Microbial rebalancing: Suppresses <i>S. aureus</i> overcolonization</li> <li>③ Sustained effect: Hydrogel encapsulation prolongs efficacy</li> </ol>	Exploratory	[64]

**Notes:** ↑ indicates increase/upregulation; ↓ indicates decrease/downregulation. Translational stage definitions: Clinical = entered Phase I/II trials; Preclinical (in vivo) = validated in animal models; Preclinical (in vitro) = only cell-based evidence; Exploratory = preliminary concept. For full references, see the main text.

**Abbreviations:** ADSC, adipose-derived mesenchymal stem cell; AEA, anandamide; ATG5, autophagy related 5; C5b-9, terminal complement complex; CA-EVs, *Cutibacterium acnes*-derived extracellular vesicles; CCL20, C-C motif chemokine ligand 20; CD, cluster of differentiation; CMVs, cytoplasmic membrane vesicles; DC, dendritic cell; F/B ratio, Firmicutes/Bacteroidetes ratio; FGF, fibroblast growth factor; Foxp3, forkhead box P3; HGF, hepatocyte growth factor; HO-1, heme oxygenase 1; hUCMSC, human umbilical cord mesenchymal stem cell; IGF-1, insulin-like growth factor 1; IGF1BP3, insulin-like growth factor binding protein 3; IL, interleukin; ILC, innate lymphoid cell; iNOS, inducible nitric oxide synthase; JAK-STAT, Janus kinase-signal transducer and activator of transcription; KC, keratinocyte; LCN2, lipocalin 2; MAPK, mitogen-activated protein kinase; miR, microRNA; MSC, mesenchymal stem cell; mTOR, mammalian target of rapamycin; NETosis, neutrophil extracellular trap cell death; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOX2/4, NADPH oxidase 2/4; NPs, nanoparticles; NQO1, NAD(P)H quinone dehydrogenase 1; NRF2, nuclear factor erythroid 2-related factor 2; OMVs, outer membrane vesicles; PASI, Psoriasis Area and Severity Index; PDGF, platelet-derived growth factor; PDNVs, plant-derived nanovesicles; PEA, pentadecanoic acid; PGE2, prostaglandin E2; RORγt, RAR related orphan receptor γt; ROS, reactive oxygen species; S6K1, ribosomal protein S6 kinase 1; S100A7, psoriasin; STAT, signal transducer and activator of transcription; T-bet, T-box transcription factor TBX21; TGF-β, transforming growth factor beta; Th, T helper cell; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

derived exosomes via probe sonication.<sup>66</sup> This system leverages the natural skin affinity of exosomes to significantly increase drug accumulation and cellular uptake in the skin layer. By more efficiently inhibiting the JAK-STAT pathway, it achieves robust downregulation of inflammatory factors such as TNF- $\alpha$  and IL-23, while its sustained release reduces its cytotoxicity. However, a limitation of this study is the use of exosomes derived from A-431 cancer cells, which may carry potential safety risks for clinical translation. Additionally, exosomes loaded with naturally active ingredients such as green tea polyphenol epigallocatechin-3-gallate nanoparticles (EGN-Exos) can synergistically downregulate NF- $\kappa$ B inflammatory signaling and modulate apoptosis balance (reducing Bax and increasing Bcl-2), demonstrating multitarget synergistic advantages.<sup>67</sup>

Membrane modification and fusion strategies endow exosomes with new capabilities, such as active targeting by altering their surface properties or integrating other membrane structures. Inspired by tumor immune evasion mechanisms, melanoma-derived exosomes (B16-Exos) were found to possess unique transdermal capabilities (dependent on transcytosis mediated by the membrane protein RhoA) and immunosuppressive cargo (mmu-miR-320-3p targeting IL-17a mRNA). The biomimetic formulation ExoLipo, which uses B16-Exo as a template, incorporates a RhoA membrane protein and is loaded with therapeutic miRNA, not only inheriting the dual functions of natural exosomes—transdermal delivery and immune regulation—but also effectively avoiding the potential safety risks associated with the direct use of tumor-derived exosomes.<sup>68</sup> Another approach involves membrane fusion technology, where T-cell exosomes overexpressing the anti-inflammatory protein annexin A1 (ANXA1) are fused with M2 macrophage membranes, enabling the resulting engineered vesicles to simultaneously possess the direct anti-inflammatory activity of ANXA1 and the inherent natural homing-targeting ability of M2 cell membranes. In an IMQ-induced psoriasis mouse model, subcutaneous injection of these engineered EVs enhances the polarization of local macrophages toward the M2 anti-inflammatory phenotype, downregulating M1 markers such as CD86 and IL-6, thereby significantly alleviating skin inflammation in psoriasis animal models and demonstrating superior stability compared with nonfused vesicles.<sup>69</sup> A more innovative strategy is cross-species fusion, such as fusing grapefruit exosomes (GEVs) with mesenchymal stem cell membrane nanovesicles (CCR6-NVs) that overexpress the chemokine receptor CCR6 on their surface. The resulting intelligent hybrid vesicles can actively target inflammatory sites via the CCR6–CCL20 axis and synergistically load the cell cycle inhibitor CX5461 while retaining the plant-derived miR-159a with regulatory functions. This enables cross-kingdom suppression of inflammatory factors such as IL-6 and TNF- $\alpha$ , promotes regulatory T-cell infiltration, and polarizes macrophages toward the M2 anti-inflammatory phenotype, achieving multitarget synergistic therapy.<sup>70</sup> The use of *Cutibacterium acnes*-derived extracellular vesicles encapsulated in sustained-release hydrogel microspheres (CA-EVs@GHMs) represents another functionalized delivery system. They enable sustained vesicle release, inhibiting the conversion of skin innate lymphoid cells (ILCs) into pathogenic ILC3 subtypes and restoring skin microbiota diversity, thereby suppressing the overcolonization of harmful bacteria such as *Staphylococcus aureus*. This system exerts a dual-target “immune microbiota” regulatory effect.<sup>64</sup>

The parental cell engineering strategy achieves precise intervention in diseases by accurately manipulating the source cells that secrete exosomes, thereby directionally regulating the cargo composition and function of exosomes. The most representative method involves genetic engineering to overexpress specific therapeutic molecules in parental cells. For example, lentiviral vectors can be used to induce MSCs to overexpress the immune checkpoint protein programmed death ligand 1 (PD-L1). The engineered small extracellular vesicles (MSC-sEVs-PD-L1) secreted by these cells consequently exhibit high PD-L1 expression on their surfaces. These vesicles can target psoriatic inflammatory sites and, by binding to programmed death receptor 1 (PD-1) on activated T cells, efficiently activate the PD-1/PD-L1 inhibitory signaling pathway. This leads to more effective suppression of pathogenic Th1 and Th17 cell proliferation, promotes the differentiation of Treg cells, and inhibits dendritic cell maturation. The in vivo therapeutic efficacy of these vesicles even surpasses that of PD-L1-overexpressing MSCs themselves while avoiding the risk of pulmonary embolism associated with cell infusion.<sup>71</sup> Additionally, physical or chemical pretreatment of parental cells serves as an efficient nongenetic modification approach. Studies have shown that exposing keratinocytes to UVB irradiation can “reprogram” their secreted exosomes (UV KEV) into potent immunomodulatory carriers. The mechanism involves UVB-induced enrichment of platelet-activating factor (PAF) in exosomes, which, via its receptor pathway, remotely promotes mast cell migration to lymph nodes and the secretion of IL-10. This systemically expands the Treg cell population and decreases

mature dendritic cell numbers, inducing systemic immune tolerance.<sup>72</sup> A codelivery system (J@EV) was developed by loading UV-KEV with the metabolic inhibitor JPH203. This system synergistically combines the anti-inflammatory effects of the IL-1RA/NF- $\kappa$ B axis with the antimetabolic proliferation effects of the JPH203/mTORC1 axis.<sup>73</sup> Another parental cell strategy leverages the natural “organelle transfer” capability of platelet-derived extracellular vesicles (PEVs). PEVs can directly transfer their intact, functional mitochondria to macrophages, fundamentally reprogramming the latter’s energy metabolism from proinflammatory glycolysis to anti-inflammatory, reparative oxidative phosphorylation.<sup>74</sup> This profound metabolic reprogramming is a key mechanism driving macrophage polarization toward the M2 anti-inflammatory phenotype. In summary, through genetic modification, physical stimulation, or the utilization of inherent properties of parental cells, engineered exosomes carrying specific therapeutic cargos can be directionally produced, significantly enhancing the precision of exosome-based strategies for psoriasis treatment.

## Exosome Local Delivery System

Efficient local delivery is the key to the therapeutic efficacy of exosome therapy. Microneedle-based delivery systems overcome the skin barrier by physically creating micron-sized channels, providing a minimally invasive and efficient solution. The basic microneedle platform can serve as a carrier for codelivery, such as loading Treg cell-derived exosomes (rExos) with the anti-inflammatory drug dimethyl fumarate (DMF) into hyaluronic acid microneedle patches (rExo@DMF MNs). Among these, rExos can induce the generation of tolerogenic dendritic cells and Tregs, whereas DMF enhances anti-inflammatory signaling and activates the NRF2 antioxidant pathway. The two synergistically inhibit NF- $\kappa$ B, thereby locally remodeling the immune microenvironment.<sup>75</sup> Another study addressed the clinical translation bottleneck of storage stability for exosome formulations. Researchers have developed microneedles composed of hyaluronic acid and the protective agent trehalose for delivering natural killer cell-derived extracellular vesicles (NK-EVs). These microneedles not only effectively treated psoriasis-like skin lesions but also demonstrated a prominent advantage: the addition of trehalose enabled the loaded vesicles to retain their anti-inflammatory activity after room temperature storage for up to 6 months, offering a highly promising solution for the long-term storage and transportation of exosome formulations.<sup>76</sup>

Intelligent responsive microneedle systems represent a more advanced direction, achieving integrated diagnosis and treatment through the integration of environmentally responsive components. For example, a dual-segment subcutaneous light-responsive enhanced microneedle (SLE MN) system features an upper section composed of polymethyl methacrylate optical fibers, which efficiently transmit near-infrared light irradiated on the surface to the epidermal basal layer. The lower drug-loaded matrix encapsulates M2 macrophage-derived exosomes and the photothermal conversion material MXene. Under near-infrared light irradiation, MXene generates localized mild photothermal effects, directly inducing apoptosis in hyperproliferative basal layer keratinocytes. Simultaneously, the photothermal trigger enables the rapid release of exosomes, thereby regulating the polarization of local macrophages toward the M2 anti-inflammatory phenotype.<sup>77</sup>

In summary, through the deep integration of diverse engineering modification strategies and advanced delivery systems, exosomes have evolved from natural messengers to programmable, targetable, and controllable intelligent therapeutic platforms, opening a promising new pathway for the precise treatment of psoriasis. The main approaches and characteristics are summarized in [Table 2](#).

## Challenges and Future Prospects

Although exosomes have demonstrated disruptive potential in mechanistic research and therapeutic exploration of psoriasis, their translation from basic discoveries to clinical routines still faces a series of fundamental scientific and translational challenges. The essence of these obstacles largely stems from the inherent complexity of exosomes as endogenous nanoscale vesicles and the vast gap between this complexity and the rigor required to reshape them into standardized “pharmaceutical products”.

The core challenge stems from the dual dilemma of standardization and mechanistic understanding. The primary bottleneck is the lack of standardization in production processes and quality control. Currently, there is no global consensus on isolation and purification methods for obtaining exosomes from different cell sources, leading to significant

**Table 2** Engineering and Delivery Strategies for Exosome-Based Psoriasis Therapy

Strategy Category	Specific Subtype/Carrier	Method/Design	Molecular Modification/Cargo	Target Cells/Molecules	Molecular Target/Pathway	Therapeutic Advantage/Limitation	Translational Stage	Refs.
Cargo Loading	nor@MSC-EVs	Loading ArgI inhibitor into MSC-EVs	nor-NOHA (ArgI inhibitor)	KCs (intracellular ArgI); DCs/Th17 (self-antigen sensing)	① Metabolic: inhibits ArgI → ↓polyamines (PUT/SPD) → ↓RNA <sup>+</sup> polyamine <sup>+</sup> peptide self-antigens ② Immune: blocks DC maturation (↓CD80/86/MHC II) and Th1/Th17 differentiation; ↓NF-κB (↓p-p65) in KCs	① Metabolic-immunological crosstalk: Novel mechanism ② Superior efficacy: ↓epidermal thickness and PASI scores vs. MSC-EVs and anti-IL17A ③ Limitation: limited storage stability (5 days at 4°C)	Preclinical (in vivo)	[65]
	TFC-Exo	Probe-sonication loading into KC-Exo	Tofacitinib (pan-JAK inhibitor)	KCs (JAK-STAT); immune cells	JAK-STAT: inhibits JAK1/JAK3 → blocks STAT1/STAT3 phosphorylation (Tyr701/Tyr705) → ↓transcription of TNF-α, IL-23, IL-6	① Enhanced delivery: Improved transdermal penetration and skin retention ② Lower cytotoxicity: Higher IC <sub>50</sub> than free TFC ③ Sustained release: Prolonged effect ④ In vivo efficacy: ↓ear thickness, PASI, and histopathological scores vs. free TFC ⑤ Limitation: Exosomes from A-431 cancer cells may pose safety risks	Preclinical (in vivo)	[66]
	EGN-Exo	EGCG nanoparticles loaded into exosomes	EGCG (green tea polyphenol)	KCs (NF-κB, Bcl-2/Bax); immune cells	① Inflammation: inhibits IKKα/β → ↓p-p65 (Ser536) ② Apoptosis: ↓Bax, ↑Bcl-2 ③ Cytokines: ↓IL-17A, ↓TNF-α	① Synergistic: Combined anti-inflammatory and pro-apoptotic effects ② Multi-target: Outperforms single agents ③ In vivo efficacy: ↓IL-6, NF-κB, CDC25B; ↑IL-4, Bcl-2; histopathological improvement ④ Limitations: Animal model may not fully replicate human psoriasis; small sample size; lack of long-term safety data	Preclinical (in vivo)	[67]

Membrane Engineering	ExoLipo (Biomimetic hybrid)	Fusion of B16-Exo with liposome (retaining RhoA membrane protein + loading miRNA)	RhoA (membrane protein); mmu-miR-320-3p	Keratinocytes (transcytosis); Th17 cells (IL-17a mRNA)	<ol style="list-style-type: none"> <li>① Transdermal: RhoA-mediated transcytosis across epidermal barrier</li> <li>② Immune: miR-320-3p targets IL-17a 3'UTR → ↓IL-17a</li> <li>③ ↓TNF-α, IL-6, IL-1β; ↓splenomegaly; ↓PASI</li> </ol>	<ol style="list-style-type: none"> <li>① Biomimetic: avoids safety risks of tumor-derived exosomes</li> <li>② Dual function: transdermal + immunomodulatory</li> <li>③ Superior to plain liposomes</li> <li>④ Limitation: long-term safety and dosing need evaluation</li> </ol>	Preclinical (in vivo)	[68]
	EAM/JAM (Fusion)	ANXA1-OV T-cell Exo fused with M2 macrophage membrane	ANXA1; M2 membrane proteins (CD163, CCR2)	Macrophages (FPR2/ALX); inflammatory lesions	Receptor: ANXA1 binds FPR2 → activates SHIP-1 → inhibits PI3K/Akt → induces M2 polarization (↑CD206, ↑IL-10, ↓CD86, ↓IL-6)	<ol style="list-style-type: none"> <li>① Enhanced targeting: Homing ability from M2 membrane</li> <li>② Superior stability: Resists degradation</li> <li>③ Systemic repair: Ameliorates organ damage</li> <li>④ In vivo efficacy: ↓PASI, ↓epidermal thickness, ↓IL-1β/IL-6/TNF-α, ↑Arg-1</li> <li>⑤ Limitation: Long-term safety and dosing need further evaluation</li> </ol>	Preclinical (in vivo)	[69]
	FV@CX5461 (Cross-species fusion)	Grapefruit Exo fused with CCR6-OV MSC-NV	CCR6 (targeting); miR-159a (plant); CX5461 (loaded)	Inflammatory site (CCL20 <sup>+</sup> ); KCs, T cells, macrophages	<ol style="list-style-type: none"> <li>① Targeting: CCR6 → CCL20-rich lesions</li> <li>② RNAi: miR-159a inhibits IL-6/TNF-α</li> <li>③ Cell cycle: CX5461 arrests G2/M</li> <li>④ Polarization: promotes M2 and Treg infiltration</li> </ol>	<ol style="list-style-type: none"> <li>① Multi-target synergistic: Combines targeting, RNAi, and cell cycle arrest</li> <li>② Intelligent targeting: Chemokine axis-guided delivery</li> <li>③ In vivo efficacy: ↓PASI/severity scores, ↓splenomegaly, ↓epidermal thickness, ↓IL-1β/TNF-α/IL-17/IL-22, ↑Tregs</li> <li>④ Limitation: Cross-border mechanism of plant miRNA unclear; needs validation in other autoimmune diseases</li> </ol>	Exploratory	[70]

(Continued)

Table 2 (Continued).

Strategy Category	Specific Subtype/Carrier	Method/Design	Molecular Modification/Cargo	Target Cells/Molecules	Molecular Target/Pathway	Therapeutic Advantage/Limitation	Translational Stage	Refs.
Parental Cell Engineering	MSC-sEVs-PD-L1 (Genetic modification)	Lentiviral PD-L1 overexpression in MSCs → collect sEVs	PD-L1 (high surface expression)	T cells (PD-1); DCs (PD-1)	Checkpoint: PD-L1 engages PD-1 → recruits SHP-2 → dephosphorylates TCR signaling (↓ZAP70) → induces anergy/apoptosis in Th1/Th17; inhibits DC maturation; ↓cutaneous CD45 <sup>+</sup> /CD4 <sup>+</sup> T-cell infiltration	<ol style="list-style-type: none"> <li>① Superior to cell therapy: No embolism risk</li> <li>② Targeted checkpoint modulation: Efficient suppression of pathogenic T cells</li> <li>③ In vivo efficacy (n=6/group, IMQ model): ↓clinical scores, ↓skin/epidermal thickness, ↓IFN-<math>\gamma</math>/IL-17/IL-6/TNF-<math>\alpha</math>, ↑Tregs</li> <li>④ Limitation: Long-term safety still needs evaluation</li> </ol>	Preclinical (in vivo)	[71]
	UV KEV (Physical stimulation)	UVB irradiation (3 mW/cm <sup>2</sup> , 2 min) of KCs	PAF enrichment; IL-10	Mast cells (PAFR); Tregs, DCs, KCs	PAF/PAFR: promotes mast cell migration to lymph nodes → IL-10 secretion → ↑Tregs (CD25 <sup>+</sup> Foxp3 <sup>+</sup> ), ↓mature DCs (↓CD80/86); stimulates KCs to secrete PGE <sub>2</sub> /IL-10	<ol style="list-style-type: none"> <li>① Systemic immune tolerance: Induces tolerance without direct UV carcinogenic risk</li> <li>② Cross-disease efficacy: Treats both psoriasis and IBD</li> <li>③ In vivo efficacy: ↓PASI (erythema/thickness/scaling), ↓epidermal thickness, ↓Ki67<sup>+</sup> cells, ↑splenic Tregs, ↓mature DCs</li> <li>④ Limitation: Long-term safety and off-target effects need evaluation</li> </ol>	Preclinical (in vivo)	[72]
	J@EV (Combined)	UVB irradiation (1.8 kJ/m <sup>2</sup> , 2 h) of HaCaT cells preincubated with JPH203 → collect EVs (centrifugation)	IL-1RA (UV-induced); JPH203 (LAT1 inhibitor)	KCs (NF- $\kappa$ B, mTOR); Th17 cells	<ol style="list-style-type: none"> <li>① Inflammation: IL-1RA blocks IL-1/NF-<math>\kappa</math>B</li> <li>② Metabolism: JPH203 inhibits LAT1-mediated leucine uptake → blocks mTOR pathway</li> </ol>	<ol style="list-style-type: none"> <li>① Dual targeting: Inflammation + metabolism</li> <li>② Etiological intervention: Targets metabolic dysregulation</li> <li>③ In vivo efficacy: ↓PASI (erythema/scaling/thickness), ↓epidermal thickness, ↓Ki67<sup>+</sup> cells, ↓splenic Th17 (19.6%→4.25%)</li> <li>④ Limitation: clinical studies lacking</li> </ol>	Preclinical (in vivo)	[73]
	PEVs (Organelle transfer)	Platelet-derived EVs	Functional mitochondria	Macrophages (metabolism); KCs	Metabolic reprogramming: transfers intact mitochondria → ↑OXPHOS, ↓glycolysis (↓HK2, ↓LDHA) → reprograms macrophages to M2 phenotype (↑CD163, ↑IL-10); ↓KC inflammation	<ol style="list-style-type: none"> <li>① Novel mechanism: Metabolic reprogramming via organelle transfer</li> <li>② Immune cell repolarization: Shifts macrophages to anti-inflammatory phenotype</li> <li>③ In vivo efficacy: ↓PASI, ↓epidermal thickness, ↓Ki67<sup>+</sup> cells, ↓IL-1<math>\beta</math>/TNF-<math>\alpha</math>/IL-17A, ↑IL-10</li> <li>④ Limitation: Long-term safety and off-target effects need evaluation</li> </ol>	Preclinical (in vivo)	[74]

Local Delivery Systems	rExo@DMF MNs	HA-MN loaded with Treg-Exo + DMF	rExo (CTLA-4, LAG-3, IL-10); DMF (Nrf2 activator/NF-κB inhibitor)	DCs, T cells, KCs, lymph nodes/spleen	<ol style="list-style-type: none"> <li>① rExo: induces tolerogenic DCs (↓CD80/86) → promotes Tregs (↑Foxp3)</li> <li>② DMF: activates Nrf2 (↑HO-1) and inhibits NF-κB; MNs enhance transdermal delivery</li> </ol>	<ol style="list-style-type: none"> <li>① Synergistic: Local Treg induction + systemic antioxidant/anti-inflammatory effects</li> <li>② Biocompatible: Uses natural components</li> <li>③ In vivo efficacy: ↓PASI (induration/erythema/desquamation), ↓epidermal thickness (111.9→22.9 μm), ↓Ki67<sup>+</sup> cells, ↓IL-6/IL-23/IL-17A/IFN-γ, ↑Tregs (11.6%→20.6%), ↑IL-10</li> <li>④ Limitation: Long-term safety and off-target effects need evaluation</li> </ol>	Preclinical (in vivo)	[75]
	NK-EV MNs	HA + trehalose MN loaded with NK-EVs	NK-EVs (miR-21, Granzyme B, FasL)	KCs, macrophages, inflammatory cells	<ol style="list-style-type: none"> <li>① Percutaneous delivery; ↓IL-6, TNF-α, IL-17, Ki67; miR-21 modulates cytokines; Granzyme B/FasL enhance efficacy</li> </ol>	<ol style="list-style-type: none"> <li>① Room-temperature stable: 6 months stability without cold chain</li> <li>② Minimally invasive: Microneedle platform</li> <li>③ In vivo efficacy: ↓PASI, ↓epidermal thickness, ↓Ki67<sup>+</sup> cells, ↓IL-6/TNF-α/IL-17</li> <li>④ Limitation: Long-term safety and off-target effects need evaluation</li> </ol>	Preclinical (in vivo)	[76]
	Smart MN (Dual-layer)	PMMA (light guide) + MXene (photothermal) + M2-Exo	M2-Exo (IL-10, TGF-β); NIR light (trigger)	Basal KCs (heat); macrophages (M2-Exo)	<ol style="list-style-type: none"> <li>① Photothermal: NIR via PMMA triggers MXene (42–45°C) → induces HSP70 in KCs, inhibiting proliferation</li> <li>② Immunomodulation: M2-Exo drives macrophage M2 polarization (↓IL-1β, ↓TNF-α)</li> </ol>	<ol style="list-style-type: none"> <li>① Spatiotemporal control: Light-triggered, deep-penetrating (500 μm)</li> <li>② Synergistic: Photothermal killing + immunomodulation</li> <li>③ In vivo efficacy: ↓epidermal thickness (111.9→38.5 μm), ↓PASI scores, ↓Ki67, ↓IL-17/TNF-α/iNOS, ↑CD206, ↓splenomegaly</li> <li>④ Limitation: High production cost, scalability issues, long-term stability needs evaluation</li> </ol>	Exploratory	[77]
	CA-EVs@GHM (Hydrogel microspheres)	CA-EVs encapsulated in gelatin methacryloyl hydrogel microspheres	CA-EVs (active proteins/lipids)	ILCs; skin microbiota ( <i>S. aureus</i> )	<ol style="list-style-type: none"> <li>① Immune: sustained release inhibits ILC2-to-ILC3 conversion (↓IL-17/IL-22)</li> <li>② Microbiota: restores diversity (↑alpha diversity, ↓<i>Staphylococcus</i>); enhances fatty acid/tryptophan metabolism</li> </ol>	<ol style="list-style-type: none"> <li>① Dual-target: Immune + microbiota regulation</li> <li>② Sustained release: Prolonged efficacy vs. free CA-EVs</li> <li>③ In vivo efficacy: ↓mPASI, ↓epidermal thickness, ↓IL-17/IL-22, ↑skin barrier markers (K10, loricrin, claudin-1)</li> <li>④ Limitation: Active components unknown; clinical trials lacking</li> </ol>	Exploratory	[64]

**Notes:** ↑ indicates increase/upregulation; ↓ indicates decrease/downregulation. Translational stage definitions: Clinical = entered Phase I/II trials; Preclinical (in vivo) = validated in animal models; Preclinical (in vitro) = only cell-based evidence; Exploratory = preliminary concept with limited data. For full references, see the main text.

**Abbreviations:** ANXA1, annexin A1; Arg1, arginase 1; CA-EVs, *Cutibacterium acnes*-derived extracellular vesicles; CCL20, C-C motif chemokine ligand 20; CCR6, C-C chemokine receptor type 6; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte associated protein 4; DC, dendritic cell; DMF, dimethyl fumarate; EGCG, epigallocatechin gallate; EVs, extracellular vesicles; FPR2, formyl peptide receptor 2; GEV, grapefruit-derived exosome; GHM, gelatin methacryloyl hydrogel microspheres; HA, hyaluronic acid; HK2, hexokinase 2; HO-1, heme oxygenase 1; HSP70/90, heat shock protein 70/90; IC<sub>50</sub>, half-maximal inhibitory concentration; IKKα/β, IκB kinase α/β; IL, interleukin; ILC, innate lymphoid cell; IRAK1, interleukin-1 receptor associated kinase 1; JAK, Janus kinase; KC, keratinocyte; LAG-3, lymphocyte activation gene 3; LAT1, L-type amino acid transporter 1; LDHA, lactate dehydrogenase A; MAPK, mitogen-activated protein kinase; MeCP2, methyl CpG binding protein 2; MHC II, major histocompatibility complex class II; miR, microRNA; MN, microneedle; MSC, mesenchymal stem cell; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIR, near-infrared; NK-EVs, natural killer cell-derived extracellular vesicles; nor-NOHA, N<sup>ω</sup>-hydroxy-nor-L-arginine; Nrf2, nuclear factor erythroid 2-related factor 2; OXPHOS, oxidative phosphorylation; PAF, platelet-activating factor; PAFR, platelet-activating factor receptor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PMMA, polymethyl methacrylate; PUT, putrescine; rExo, regulatory T-cell-derived exosomes; S6K1, ribosomal protein S6 kinase 1; sEV, small extracellular vesicle; SHIP-1, SH2 domain containing inositol 5' phosphatase 1; SPD, spermidine; STAT, signal transducer and activator of transcription; TCR, T-cell receptor; TFC, tofacitinib; TGF-β, transforming growth factor beta; Th, T helper cell; TLR7, Toll-like receptor 7; TNF-α, tumor necrosis factor alpha; TRAF6, TNF receptor associated factor 6; Treg, regulatory T cell; UV, ultraviolet; UVB, ultraviolet B; ZAP70, zeta-chain-associated protein kinase 70.

variations in product purity, subgroup heterogeneity, and biological activity. Large-scale, high-purity, low-cost manufacturing processes compliant with good manufacturing practices are lacking, and their industrial pathways, along with strict quality control systems encompassing attributes such as potency, purity, and sterility, urgently need to be established, which directly hinders their clinical translation. A deeper challenge lies in the “black box of effector components” for therapeutic exosomes. Although a few studies have identified active molecules such as miR-100-5p, AEA, and PEA, for the vast majority of exosomes, it remains unclear whether their therapeutic effects are attributable to a single star molecule, specific molecular combinations, or the synergistic effects of the vesicle as a whole. This mechanistic ambiguity hinders rational process design on the basis of quality attributes, precise potency evaluation, and targeted engineering modifications.

The depth and breadth of clinical translation evidence have significant limitations. Current human trials are generally small in scale and short in duration and lack reliable long-term safety and sustained efficacy data. Study designs predominantly use open-label or single-arm formats, and there is an urgent need for randomized, double-blind, head-to-head superiority comparisons with existing standard therapies to clarify their therapeutic position. The optimal dosing regimen (formulation, dose, and course) has not undergone systematic pharmacokinetic/pharmacodynamic optimization. Additionally, the potential immunogenicity, off-target effects, and long-term biodistribution risks of allogeneic or engineered exosomes must be evaluated through more rigorous preclinical and clinical monitoring.

Future breakthroughs rely on technological innovation and paradigm shifts. Advancing the field requires focusing on several key directions: 1) Establishing standards and regulatory consensus: Through international collaboration, developing guiding principles for critical quality attributes of therapeutic exosomes, standardized testing methods, and regulatory pathways. 2) Deepening mechanism analysis and rational design: Single-vesicle analysis, spatial omics, and gene editing technologies can be utilized to clarify the causal contributions of functional components at the donor cell level, and predictable, modular engineering platforms can be developed to achieve “on-demand customization”. 3) Innovative production paradigms: Exploring cell-free synthetic biology or robust microbial expression systems to achieve truly standardized and scalable production. 4) Conduct high-level clinical validation: Design large-scale, multicenter, randomized controlled trials and conduct comparative or combination therapy studies with existing standard treatments (eg, biologics) while systematically establishing pharmacokinetic/pharmacodynamic models. 5) Promotion of integrated diagnosis and treatment: Accelerate the validation of circulating exosome biomarkers; develop companion diagnostic tools for patient stratification, efficacy prediction, and dynamic monitoring; and advance toward personalized precision medicine.

Beyond these technical and regulatory priorities, several biologically intriguing questions merit future investigation. Although genetic association studies have linked IL19/IL20/IL24 polymorphisms to psoriasis susceptibility,<sup>78,79</sup> whether exosomal cargo of these cytokines contributes to subtype-specific diagnosis (eg, palmoplantar pustulosis vs. psoriasis vulgaris) remains unknown. Transcriptomic analyses have revealed differential expression of repetitive elements (REs), such as LINE-1, Alu, and HERV-K, in psoriatic skin,<sup>80</sup> but whether these REs are selectively packaged into exosomes and contribute to disease pathogenesis is an open question. Likewise, exosomes can carry functional apoptosis-inducing factors, as shown by placental exosomes expressing oligomerized FasL and TRAIL.<sup>81</sup> In psoriasis, TRAIL and its death receptors DR4/DR5 are upregulated in lesional skin,<sup>82</sup> raising the possibility that psoriatic exosomes may similarly transport these molecules and modulate immune cell survival or keratinocyte apoptosis. Addressing these questions will help bridge the gap between basic exosome biology and clinical application.

Only through deep interdisciplinary integration and systematic resolution of these scientific challenges—from molecular mechanisms to industrial implementation—can exosomes transform from a broad research blueprint into tangible clinical breakthroughs benefiting psoriasis patients.

## Conclusion

Exosomes play dual roles in psoriasis as both core pathogenic mediators and versatile translational tools. Mechanistically, diseased cells release exosomes that carry not only non-coding RNAs but also proteins, lipids, and metabolites, which collectively program CD4<sup>+</sup> T cells toward Th17 polarization, drive M1 macrophage activation, and establish a positive inflammatory feedback loop with neutrophils, thereby amplifying the IL-23/Th17 axis. Therapeutically, this natural

delivery system has been successfully repurposed: circulating exosomal fingerprints enable non-invasive diagnosis and subtype differentiation, while exosomes derived from mesenchymal stem cells, plants, and microorganisms offer cell-free, multi-mechanistic synergy (anti-inflammatory, immunoregulatory, antioxidant, and microecological repair). Engineering modifications and intelligent delivery platforms, particularly microneedle-based systems, are further advancing exosomes into targeted, smart nanomedicines. What is most promising today is the clinical translation of mesenchymal stem cell-derived exosomes, which have shown safety and preliminary efficacy in early-stage trials, and microneedle-mediated local delivery, which overcomes skin barriers and enhances retention. The key remaining barriers to clinical adoption are standardized good manufacturing practice production, identification of core effector components, and rigorous Phase II/III validation against current standards (eg, biologics). Overcoming these challenges will transform exosome-based strategies into precision tools for psoriasis management.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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