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REVIEW ARTICLE

Engineered exosomes in dermatology: Design strategies, functional advantages, and therapeutic translation

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Abstract

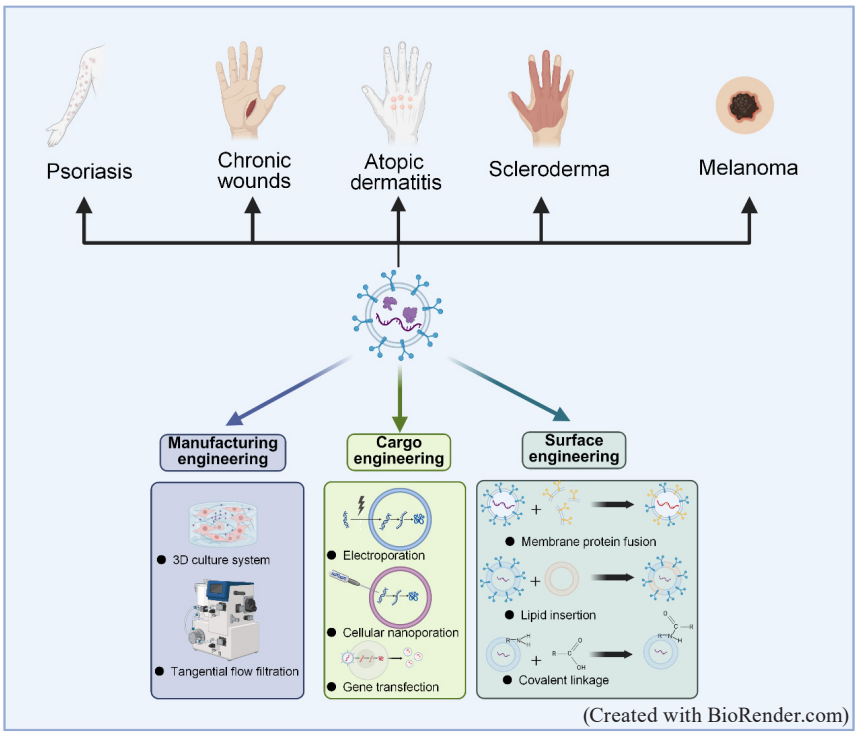
Given the complex pathogenesis of skin diseases, current treatments are not always adequate or suitable for all patients. This highlights the necessity for a multi-target therapeutic nanoplatform. Owing to their intrinsic biological functions, exosomes have emerged as a promising transdermal drug delivery system. However, native exosomes face bottlenecks in drug loading efficiency, tissue specificity, and scalability. This article aims to review the advances in engineered exosomes, focusing on cargo engineering, surface engineering, and manufacturing engineering. We outline the methods and strategies deployed for encapsulating functional molecules into exosomes or remodeling vesicle interface properties, with particular attention to the advantages and disadvantages of different technologies employed for engineering exosomes. Through rational design, exosomes can be engineered to achieved precise targeting, controlled delivery, combination therapeutic effects, and scalable production. They exhibit therapeutic potential in refractory skin diseases, including psoriasis, atopic dermatitis, scleroderma, chronic wounds, and skin malignancies, but there are still challenges regarding clinical standardization and quality control. Overall, engineered exosomes represent a new type of nanotherapeutic platform in the field of transdermal drug delivery. Exosome-based drug formulations have the potential to serve as delivery vehicles with more predictable and reproducible therapeutic effects.

Keywords: Dermatology, Engineered exosomes, Engineering strategies, Functional advantages, Therapeutic translation

Highlights

- Exosome engineering encompasses cargo, surface, and manufacturing engineering.
- Engineered exosomes show superior efficacy over native exosomes in skin diseases.
- Clinical translation is hindered by standardization and regulatory issues.

Graphical abstract



1 INTRODUCTION

Skin diseases place a heavy burden on health-care systems worldwide. Chronic skin disorders are rarely life-threatening, but their long-term management continues to pose major clinical challenges [1]. These difficulties are partly related to the unique biological nature of the skin, which functions as an active immune interface continuously exposed to the external environment. In dermatologic disease, barrier dysfunction, immune activation, inflammation, and tissue repair are often interconnected and may change as the disease progresses [2, 3]. Established therapies involve the use of topical corticosteroids, systemic immunosuppressants, and targeted biologic drugs. These treatments can effectively ameliorate symptoms, but their prolonged use is limited by the risk of relapse, adverse effects, or incomplete restoration of skin homeostasis [4, 5]. As a consequence, investigators in this field are now searching for strategies that can facilitate the coordinated regulation of these interconnected processes.

Exosomes are nanoscale vesicles generated through the endosomal-multivesicular body pathway. They serve as natural carriers for bioactive cargo and mediators of intercellular communication [6]. Typically, 30–150 nm in diameter, these vesicles are enclosed by a phospholipid bilayer and carry nucleic acids, proteins and lipids derived from their parental cells [7]. Compared with many synthetic nanocarriers, native exosomes generally exhibit stability in physiological environments, favorable biocompatibility, and low immunogenicity [8-10]. Moreover, they offer practical advantages over cell-based therapies, including easier storage, repeated administration, and a lower theoretical risk of tumorigenicity [11]. A growing body of evidence supports their value in dermatology. Exosomes derived from skin cells, blood, and mesenchymal stem cells (MSCs) can promote angiogenesis and re-epithelialization while attenuating local inflammation, thereby supporting tissue repair in several experimental models [12-15]. Research interest has recently extended to plant-derived exosome-like nanoparticles (PDELNs), especially those isolated from traditional Chinese medicinal plants [16]. These PDELNs retain bioactive molecules from their source tissues and have shown antioxidant, anti-inflammatory, and tissue-repair activities [17]. Accessible sources and potential scalability render PDELNs even more attractive candidates for translational development.

Despite the therapeutic promise described above, native exosomes are not inherently suitable for efficient transdermal delivery. Their cargo composition is largely determined by the physiological state of donor cells, and consequently, targeting behavior, loading capacity, and batch consistency are often difficult to control [6, 18]. Engineering strategies have thus emerged to convert native exosomes into more programmable platforms. The methodological basis of this field can be traced to early work on cell-mediated drug packaging and targeted nucleic acid delivery. Pascucci *et al.* attempted to incorporate paclitaxel into secreted vesicles during exosome biogenesis,

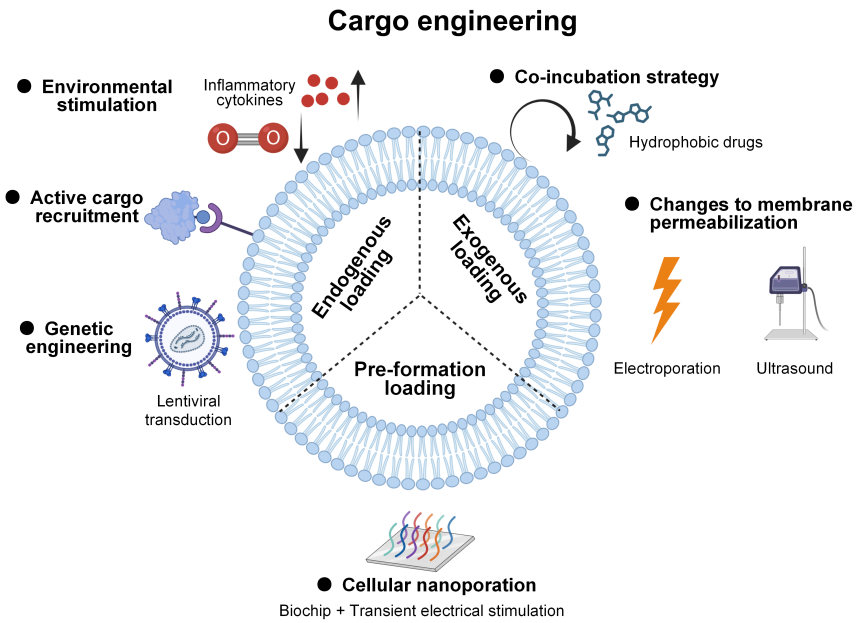


Figure 1. Cargo-engineering strategies for exosomes. Created with BioRender.com.

suggesting that MSCs could function as factories for effectively packaging antineoplastic molecules into vesicles [19]. A particularly interesting study was based on the fusion of the membrane protein lysosome-associated membrane protein 2b (LAMP2b) with targeting peptides. The results showed that this fusion protein could be transferred from donor cells to the exosomes they secreted and ultimately displayed on the vesicle surface [20]. Since then, interest in engineered exosomes has grown quickly and has gradually converged on two major directions: cargo loading to enhance bioactivity and surface modification to improve delivery specificity [21, 22]. For dermatologic diseases, such engineering is particularly important. Multifunctional vesicles are needed both to address interconnected pathological networks and to precisely target cells within inflammatory microenvironments. Further breakthroughs are required given that exosome populations are by nature heterogeneous, and this heterogeneity can compromise the production of stable therapeutic products. Therefore, scalable manufacturing, quality control, and process standardization are considered key priorities for clinical translation [7, 23].

Through engineering, exosomes can be transformed from natural intercellular messengers into more controllable and effective delivery platforms. This article seeks to systematically summarize the main modification techniques available, evaluate how these methods improve therapeutic performance, and highlight their applicability in treating representative dermatological diseases. By discussing current advances and remaining challenges, this review aims to provide a framework for understanding the role of engineered exosomes in the future development of precision dermatology.

2 STRATEGIES FOR CONSTRUCTING ENGINEERED EXOSOMES

To enable the therapeutic application of exosomes, it is necessary to determine which cargo they should carry, how they can be directed to their targets, and how they can be manufactured on a large scale.

2.1 Cargo engineering

The functionalization of exosomes is primarily achieved through cargo engineering. As depicted in **Figure 1**, cargo-engineering strategies can be categorized into endogenous loading, exogenous loading, and pre-formation loading. Pre-formation loading integrates cargo during exosome biogenesis and serves as a complementary engineering strategy.

2.1.1 Endogenous loading

Exosomes loaded with a specific cargo are often generated through plasmid-based transfection or lentivirus-based transduction. This is possible because endogenous loading relies on exosome biogenesis rather than external physical methods. Cells overproduce the target cargo and package these molecules into exosomes [24]. Recent combinatorial designs have enabled the concurrent loading of nucleic acids and proteins. Yueh *et al*. clearly demonstrated this capability [25]. Moreover, fusing cargo with ubiquitin tags greatly increases protein loading [26]. Nevertheless, the abundance of molecules in the cytoplasm does not guarantee their incorporation into exosomes. The sorting ability of transmembrane proteins can help overcome this limitation [27, 28]. Passive diffusion alone is rarely sufficient for large cargo molecules. Large CRISPR-associated protein 9–single-guide RNA ribonucleoprotein complexes enter exosomes through a cluster of differentiation 63 (CD63)–MS2 coat protein (MCP) scaffold [29]. A strong interaction between the MCP domain and MS2 aptamers in the single-guide RNA drives the recruitment of editing tools. Later, tuning this MCP-MS2 interaction was shown to balance loading stability and intracellular release [30]. In this way, the system is able to incorporate different CRISPR-associated protein 9 variants without compromising efficiency.

In a low-oxygen environment, cells increase overall vesicle production, and the transcriptomic profile of their exosomes differs from that observed under normoxic conditions [31]. Energy metabolism shifts toward glycolysis, and angiogenesis is promoted. Such reactions are aimed at alleviating hypoxic stress across tissues [32]. Supplementation of the culture medium with melatonin enhances the regenerative properties of the resulting exosomes, as evidenced by elevated levels of the

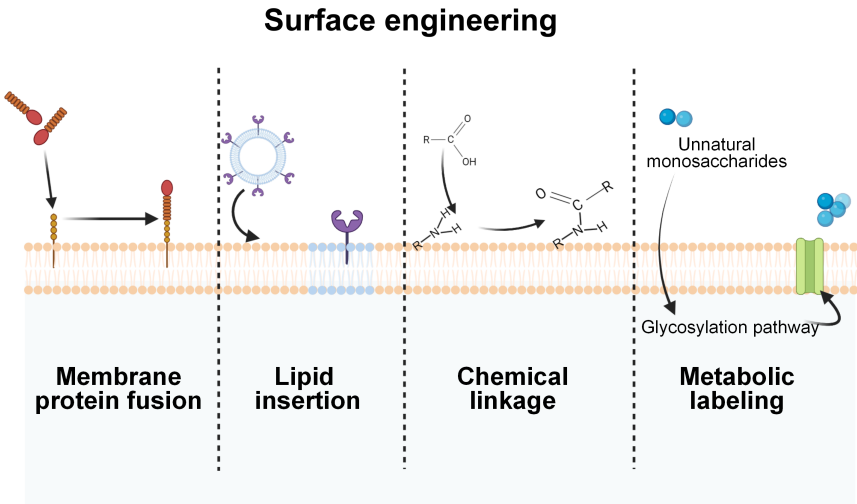


Figure 2. Surface-engineering strategies for exosomes. Created with BioRender.com.

microRNAs let-7b-5p, miR-23a-3p, and miR-100-5p [33]. Exposure to tumor necrosis factor-α upregulates the autophagy-related protein 16-like 1, accelerating multivesicular body formation and, consequently, the packaging of the functional cargo [34]. These natural adaptive stress responses can be harnessed to produce engineered exosomes with an optimized payload landscape. In some cases, pharmacological stimulation can even induce exosomes to encapsulate entire mitochondria [35].

2.1.2 Exogenous loading

Curcumin, paclitaxel, and rapamycin can be easily loaded into isolated exosomes [8, 36-38]. Diffusion and hydrophobic interactions are the primary driving forces. This post-loading strategy simply involves incubating exosomes with these lipophilic molecules, which naturally partition into the lipid bilayer. However, it often suffers from low loading efficiency. Some vesicles are heavily loaded and others stay empty. Freeze-thaw cycles offer a low-cost approach, but due to the difficulty in maintaining membrane integrity, this technique has gradually fallen out of favor [39]. Active loading methods apply physical stimuli to transiently disrupt the membrane. Additionally, these direct-loading methods enable efficient processing. For example, electroporation or sonication can rapidly deliver larger amounts of cargo into exosomes, with loading efficiencies of up to 90% [40, 41]. Rather than relying on sorting by parent cells, such methods are relatively controllable. It is also possible to determine how much of the drug has successfully been encapsulated in the carrier. Following extrusion through a microporous membrane, the particles are nearly uniform in size [42]. The exosome membrane is transiently disrupted and then reseals, entrapping the drug inside.

There is emerging evidence that hybrid vesicles formed by combining exosomes with liposomes can deliver messenger RNA (mRNA) and peptide drugs [43, 44]. Fusogenic lipid nanoparticles termed cubosomes even load large therapeutic macromolecules into exosomes within minutes [45]. Pure exosomes generally lag behind synthetic nanocarriers in payload capacity. To overcome this limitation, hybrid vesicles merge the biocompatibility of exosomes with the physicochemical advantages of liposomes. Smaller and more uniform nanoparticles exhibit higher contact probability and undergo accelerated membrane fusion [46].

2.1.3 Pre-formation loading

To overcome low loading efficiency while avoiding damage to cell membranes, researchers have developed a series of strategies, one of which is cellular nanoporation (CNP) [47]. In this technique, cells cultured on a biochip are subjected to brief electrical pulses. Compared with bulk electroporation, CNP enables exosomes to accommodate large nucleic acids, leading to a more than 1,000-fold increase in exosomal mRNA transcripts. You *et al.* subsequently utilized CNP to deliver COL1A1 mRNA for photoaged skin and vascular endothelial growth factor A mRNA for ischemic injury, demonstrating a safer and more effective therapeutic strategy in both settings [48, 49]. In fact, this method still represents an improved form of genetic modification. Using a quantitative assay, RNA transfection efficiencies of 90–100% have been reported [50]. The term "pre-formation loading" was formally defined by Ramon *et al.*, who employed photoporation to deliver cargo directly into the cytoplasm of producer cells [51]. As a result, different types of molecules can be encapsulated within the exosomes as they are assembled. Moreover, this flexible approach has minimal impact on vesicle characteristics.

2.2 Surface engineering

Surface engineering constitutes an equally critical strategy for optimizing exosome functionality and encompasses four primary approaches: membrane protein fusion, membrane insertion, chemical linkage, and metabolic labeling (**Figure 2**). These techniques equip exosomes to display targeting ligands or stealth molecules on their surface and fine-tune their interactions with recipient cells.

2.2.1 Membrane protein fusion

Membrane protein fusion is a widely used genetic strategy for exosome surface engineering. By fusing functional peptides, ligands, or protein domains with exosomal membrane scaffolds such as CD63, CD9, CD81, and LAMP2b, donor cells can produce engineered exosomes displaying selected surface motifs that are readily accessible to receptors on recipient cells. This

approach allows vesicles to acquire additional functions, including selective cell recognition, improved tissue penetration, immune regulation, and reduced clearance.

A CD63 fusion with a thrombopoietin receptor-binding peptide is able to selectively guide exosomes toward leukemia cells [52]. Similar principles have been applied to overcome biological barriers. Angiopep-2, a ligand associated with blood-brain barrier transport, can improve vesicle access to glioblastoma lesions, whereas TAT peptides enhance membrane penetration and cellular uptake [53, 54]. Programmed death-ligand 1 (PD-L1)-enriched exosomes confine immunosuppressive signaling to inflamed sites [55]. Owing to its favorable membrane topology, LAMP2b is preferred as a scaffold for the co-display of PD-L1 and galectin-9. This dual-ligand design suppresses excessive immune activation and further promotes the silencing or removal of activated effector T cells [56]. Immune evasion is also an important goal of membrane protein fusion. CD47 expressed on host cells binds to signal regulatory protein α on macrophages and limits phagocytic clearance. Exosomes can inherit this "don't eat me" signal from parental cells, while those with enhanced CD47 presentation are advantageous for systemic delivery, repeated dosing, or the treatment of deep inflammatory lesions that require prolonged vesicle retention [57, 58].

However, the performance of membrane protein fusion depends strongly on the choice of scaffold. Conventional exosomal membrane scaffolds are constrained by their topology, orientation, and sorting efficiency. To address these limitations, Plexin A1 has been proposed as an alternative display scaffold [59]. Plexin A1 is a type I transmembrane protein and remains functional after truncation. Its N-terminal region provides flexible sites for ligand insertion, supporting complex surface designs.

2.2.2 Lipid insertion

Membrane insertion is a post-isolation engineering technique in which lipid anchors are inserted into the exosomal phospholipid bilayer. This approach is straightforward to implement and can modify vesicles under mild conditions, thereby preserving membrane integrity and fluidity. Hydrophilic ligands, aptamers, or small interfering RNA (siRNA) molecules are usually conjugated to lipid anchors for display on the exosome surface. For this purpose, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine–polyethylene glycol (PEG) is an amphiphilic linker. The 1,2-distearoyl-sn-glycero-3-phosphoethanolamine–PEG–aptamer module has been developed by Zhao *et al.* to direct exosomes to $CD31^{+}EMCN^{+}$ vessels in diabetic wounds [60]. The PEG segment positions the aptamer at an appropriate distance from the vesicle surface, thereby facilitating CD31 recognition. Conversely, compact RNA nanostructures that integrate both targeting ligands and siRNA require shorter spacers to maintain structural integrity [61].

For membrane insertion, the choice of lipid moiety is critical, as it influences insertion efficiency and retention time. Among the available lipids, 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine represents a well-balanced and adaptable option. This lipid anchor can be coupled with fluorescent probes, targeting peptides, or albumin-binding groups [62].

2.2.3 Chemical linkage

Chemical linkage takes advantage of reactive groups that are naturally exposed on the exosome surface. Targeting ligands can be covalently attached to the vesicle membrane via amino, carboxyl, or thiol groups on membrane proteins and lipids. This chemistry, however, is sensitive to reaction conditions. Without tight control over reaction time, pH, and activation states, there is a substantial risk of disrupting the native folding of membrane proteins. It is also important to minimize residual coupling reagents or by-products. Chemical conjugation usually provides more durable modification than lipid anchoring because the ligand is irreversibly attached and is less likely to dissociate.

Commonly employed reactions include carbodiimide-mediated amide bond formation and thiol-maleimide coupling. Carbodiimide coupling using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and N-hydroxysuccinimide (NHS) is well established and frequently adopted for surface engineering. The carbodiimide reagent (─N=C=N─) activates free carboxyl groups on exosomal membrane proteins. It induces the formation of O-acylisourea intermediates, which then react with NHS to form a more stable NHS ester. The modified AS1411 ultimately displaces NHS through the nucleophilic attack of its primary amines on the NHS ester [63]. However, this method lacks site selectivity since carboxyl groups are widely distributed on the surface. As a result, the final product may contain a heterogeneous population of exosomes with variable ligand density and orientation. Thiol-maleimide coupling offers higher site selectivity. Free sulfhydryl groups are less abundant. This narrows the range of reactive sites but also limits the total modification capacity. To create more available thiols, disulfide bonds can be reduced with reagents such as tris(2-carboxyethyl)phosphine [64]. Since reductive treatment may disturb protein conformation, milder enzymatic methods have also been explored. Chen *et al.* reported that, at physiological pH, phospholipase D exposed hidden thiol sites, enabling conjugation with maleimide-functionalized alcohols and achieving modification efficiencies above 90% [65].

2.2.4 Metabolic labeling

Surface modification is valuable only when it does not erase the biological identity of exosomes. Although the post-isolation methods mentioned above are convenient, they may still interfere with membrane structure or surface proteins to some extent. Metabolic glycoengineering, also referred to as meta-

bolic labeling, addresses this limitation by shifting the modification process upstream to the donor cells. Instead of genetic decoration, cells are supplied with unnatural monosaccharide precursors, which enter the glycosylation pathway and are incorporated into newly synthesized glycans. The secreted exosomes therefore inherit bioorthogonal chemical handles on their surface. Azide groups ($–N_3$) and alkynes, particularly strained alkynes such as dibenzocyclooctyne, are commonly selected for this purpose [66]. They are largely absent from native biomolecules and remain relatively inert under physiological conditions. Chen *et al.* applied this principle by using azide-labeled exosomes as a clickable scaffold for the conjugation of dibenzocyclooctyne-modified dextran sulfate [67]. This modification improved targeting to pro-inflammatory M1 macrophages and promoted macrophage polarization toward an M2-like phenotype.

Notably, metabolic labeling should not be regarded as completely passive. As Agatemor *et al*. discussed in their review, the competition between unnatural sugar substrates and endogenous sugars may alter cellular metabolism. They also suggested that unlabeled controls and natural sugar rescue experiments are useful for distinguishing labeling effects from broader metabolic perturbations [66].

2.3 Manufacturing engineering

2.3.1 Cell sources and three-dimensional (3D) culture

Manufacturing engineering begins with the producer cell. All functionally viable cells secrete exosomes. Natural sources, such as plants or biological fluids, have clear advantages in production and collection. MSCs remain a major research focus in the treatment of skin diseases, as the regenerative and immunomodulatory effects of their exosomes are difficult to replicate. The challenge is that primary mammalian cells have limited expansion capacity, and their characteristics and functions change during prolonged culture. Therefore, immortalized cell lines have been explored. Tong *et al.* introduced simian virus 40 large T antigen into human placental chorionic MSCs, achieving long-term expansion for over 50 passages [68]. This antigen disrupts cell-cycle regulation and places cells in a less physiologically relevant proliferative state. Alternatively, human telomerase reverse transcriptase-based immortalization, which extends cellular lifespan through telomere maintenance, may raise fewer concerns regarding oncogenicity [69]. Exosomes from these immortalized cells, even after several passages, showed similar proteomic profiles to those from primary cells.

The culture method is equally important for improving exosome yield. Conventional two-dimensional culture is easy to implement, but it is not suitable for sustained production. Cells grow on a flat surface and their growth soon becomes constrained by the available area. In contrast, 3D culture overcomes this spatial limitation. Adherent cells grow on suspended microcarriers rather than on the bottom of culture dishes [70]. This greatly increases production within a short time. To produce 10^{12} particles, one microcarrier system required only a single shake flask and 488 mL of conditioned medium [71]. More advanced 3D systems using flexible substrates and microgravity culture are designed to better mimic *in vivo* tissues [72, 73]. These methods may help prevent the reduction in exosome release associated with excessive cell spreading. In microfluidic chips, fluid shear stress can be controlled to stimulate secretory activity [74, 75].

2.3.2 Isolation and purification

Downstream isolation is a decisive step in exosome manufacturing. The aim is not simply to collect more vesicles, but to remove soluble proteins, protein aggregates, lipoproteins, and other particles.

Differential ultracentrifugation has long been regarded as a classical laboratory method. Repeated centrifugation and resuspension can improve purity, but also make the workflow time-consuming and difficult to scale. Thus, centrifugation-based methods are useful for concentration and initial enrichment, but they are not ideal as stand-alone methods for manufacturing [76]. For larger sample volumes, filtration is more practical. Tangential flow filtration is particularly effective for plant-derived samples, where fibrous residues and polysaccharides may accelerate membrane fouling. Still, filtration mainly retains vesicles based on a molecular weight cutoff, so protein aggregates, lipoproteins, and other particles of similar dimensions may also be retained in the final product. It is therefore commonly combined with size exclusion chromatography, a gentle method that further separates exosomes from soluble contaminants [77]. Affinity capture enriches exosomes through defined surface markers, making it suitable for well-characterized exosome subpopulations or genetically engineered exosomes carrying specific tags [78].

Recently, several emerging platforms have been developed to simplify operation. Photosensitive lipid nanoprobes, for example, exploit the biotin-avidin interaction to enable labeling, capture, and release within a short workflow [79]. Ion chromatography employs the negative charge of phospholipids to bind exosomes to the stationary phase, and has been applied to the rapid processing of liquid biopsy samples [80, 81]. Exosome detection via the ultrafast-isolation system represents another automated platform capable of isolating exosomes from diverse biological fluids [82]. Even so, the value of these technologies for exosome manufacturing should not be judged by novelty alone. Scalability, cost, sample compatibility, release efficiency, and preservation of vesicle function all need to be considered.

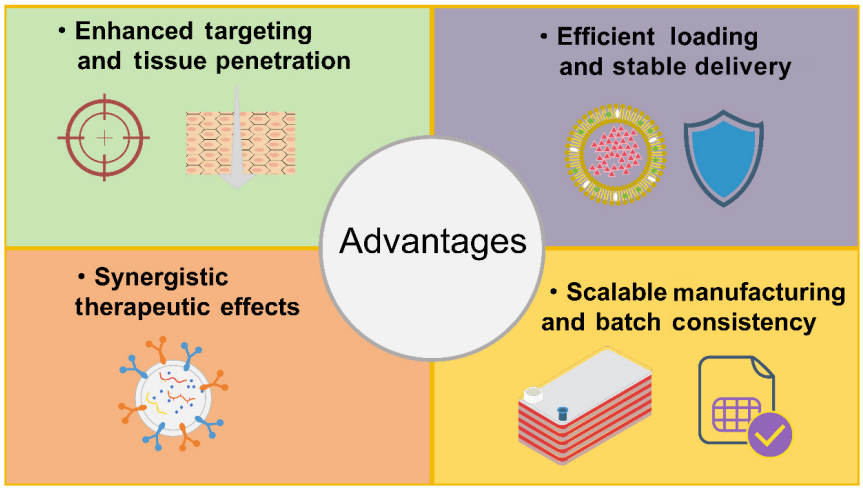


Figure 3. Advantages of engineered exosomes in dermatology. Created using Microsoft PowerPoint.

3 FUNCTIONAL ADVANTAGES OF ENGINEERED EXOSOMES

Engineered exosomes offer distinct functional advantages over native vesicles, including enhanced targeting and tissue penetration, efficient cargo loading and stable delivery, synergistic therapeutic effects, and greater feasibility for scalable manufacturing with improved batch consistency (**Figure 3**).

3.1 Enhanced targeting and tissue penetration

In some skin diseases, pathological changes are located deep within the dermis. Some stem cells and their exosomes possess homing properties. However, this natural tendency is insufficient when specific interactions with certain target cells are required [11]. Surface engineering addresses this limitation by exploiting receptor-ligand interactions. Vesicles enriched with PD-L1 can directly inhibit T cells [55]. Synthetic aptamers were used by Zhao *et al.* to label exosomes, increasing the binding selectivity of the exosomes toward endothelial cells by more than tenfold [60]. Similar ideas appear in other surface modification strategies. Metabolic glycoengineering or membrane fusion, for instance, endows engineered exosomes with higher affinity for particular macrophage subpopulations [67, 83]. Some engineering designs incorporate stimulus-responsive elements rather than relying on cell-type recognition. pH-sensitive peptides stay quiescent under physiological conditions but become activated in the acidic microenvironment. These peptides are anchored on the surface of exosomes, so that cargo release mainly occurs at tumor sites or sites of active inflammation [84, 85].

Nevertheless, if the engineered exosomes fail to enter the skin, the value of targeting becomes limited. The stratum corneum functions as a strong barrier. Exosomes may cross it through hair follicles or along intercellular lipid channels. Some evidence supports this possibility, but when the skin is intact, the contribution of these routes to penetration is relatively small [86, 87]. Among invasive techniques, microneedle platforms are frequently used to deliver vesicles deep into tissues [88]. Li *et al.* aimed to enable light-controlled and deep transdermal delivery, so they developed a spherical nucleic acid that integrates gas-generating molecules [89]. The 3D nanostructure can penetrate to a depth of up to 120 μm into the dermis.

3.2 Efficient loading and stable delivery

Free drugs are frequently degraded in the body. Exosomes have a relatively stable lipid bilayer structure, which protects the cargo inside. For instance, anthocyanins are highly sensitive to environmental conditions. When such unstable compounds are encapsulated within vesicles, their retention is much higher than that of the corresponding free compounds [39]. Drug-loaded vesicles represent a major category of engineered exosomes. Besides maintaining product quality, cargo engineering also seeks to enhance efficacy. The employment of an engineered CD63 scaffold makes autonomous cargo selection possible [90]. Compared to simple passive loading, the ultrasonic incubation method has been reported to raise loading efficiency to around 85% [91].

Loading the cargo is only one part of the process. The more critical question is whether the payloads are released once exosomes enter the target cells. Several factors influence this step, including temperature and pH, both of which can affect cellular uptake behavior [92]. Even after exosomes are internalized, delivery is not yet complete. The cargo still has to evade lysosomal degradation before it can eventually reach the cytoplasm [93]. Avoiding lysosomal degradation is one of the main obstacles to the application of natural exosomes. Some engineering strategies have been proposed for this stage. Vesicular stomatitis virus glycoprotein promotes membrane fusion between exosomes and endosomes. Through the resulting fusion pore, mRNA contained in the vesicle lumen escapes into the recipient cell [27]. At the same dose, these engineered exosomes enable nearly complete cytoplasmic delivery of mRNA. The lipid composition of the exosomal membrane also influences this process [94]. Certain lipid metabolic signatures have been found to promote macrophage uptake of anti-inflammatory exosomes [95]. Further analyses suggest that palmitoylation of membrane lipids is closely associated with the membrane anchoring of fusion proteins [96]. Once inside the endosome, such palmitoylated lipids may increase the probability of triggering membrane fusion.

3.3 Synergistic therapeutic effects

Even without synthetic drugs or exogenous nucleic acids, engineered exosomes still exhibit biological activity. This activity arises from their complex endogenous cargo. Synthetic lipid nanoparticles also serve as drug carriers, but they do not naturally contain proteins and microRNAs [97, 98]. Exosomes also carry nucleic acids. In particular, their microRNAs modulate gene expression networks in recipient cells [99, 100]. Membrane lipids are also frequently discussed components. Abundant phospholipids are present on the exosome surface, some of which participate in cell-to-cell recognition and inflammation-related signaling pathways [101]. The significance of engineered exosomes lies in their ability to rationally amplify or expand these intrinsic functions.

One approach is to modify the genetic program of donor cells to alter their secretory profile. The exosomes produced in this way acquire additional functional molecules. Vesicles rich in the transcriptional repressor Foxp1 promote the conversion of conventional T cells into regulatory T cells (Tregs) [102]. Stem cells are engineered to overexpress interferon regulatory factors. This change in turn leads to elevated levels of miR-16-5p in the released exosomes. Target cells take up miR-16-5p, which gradually alleviates the inhibitory effect on wound healing [103]. Another type of exosome carries cytotoxic molecules that induce apoptosis in melanoma cells. After loading these vesicles with chlorin e6, researchers utilized their photoresponsive behavior for precise photodynamic elimination of tumor cells [104].

In the treatment of skin diseases, exosomes are generally used for local immunomodulation, making it particularly difficult for them to rapidly suppress acute, severe inflammatory storms. Conventional dermatological drugs are potent but non-specific. Dexamethasone is a representative example, but relapse after drug withdrawal and adverse effects remain concerns. The combination of dexamethasone and exosomes was demonstrated by Ma *et al.* to exert a synergistic biological effect against systemic lupus erythematosus [105]. Dimethyl fumarate is suitable for adult patients with moderate to severe psoriasis. Treg exosomes loaded with dimethyl fumarate not only alleviate skin symptoms, but also overcome immune dysfunction. This comprehensive approach is superior to either component deployed individually [106].

3.4 Scalable manufacturing and batch consistency

Clinical translation of engineered exosomes requires more than simply scaling up production volume. The final product must also remain consistent in terms of identity, potency, and safety. Many early-stage studies still depend on two-dimensional culture and differential ultracentrifugation, which are suitable for exploratory experiments but difficult to adapt to mass production. In static mammalian cell culture, the restricted growth area requires frequent monitoring and adjustment of cell state. As a result, the secretory profile of producer cells may vary between batches with changes in cell density, nutrient consumption, and harvest timing [107]. For plant-derived exosomes, additional variables arise during sample pretreatment. When plant homogenates are processed by ultracentrifugation, mechanical stress may lead to variable vesicle loss. Fluctuations that seem acceptable at laboratory scale can become amplified during scale-up.

Industrial experience with biological products offers a more practical direction for exosome manufacturing. Perfusion culture maintains a continuous flow of fresh medium and enables vesicles to be harvested soon after secretion [108]. This shortens their residence time in the bioreactor and may minimize aggregation or degradation. When tangential flow filtration is integrated with bioreactors, a closed and automated production workflow can be established [109, 110]. Once key parameters are defined in advance, each batch is more likely to follow a consistent and stable production pattern, with minimal variation introduced by external factors. In this sense, clinical scalability depends not only on production capacity, but also on whether the process can repeatedly generate vesicles with comparable quality.

4 ENGINEERED EXOSOMES IN SKIN DISEASE THERAPY

Diverse pathological mechanisms drive the development of chronic skin diseases, ranging from immune dysregulation and fibrotic abnormalities to impaired tissue repair. However, they share a common imbalance in the microenvironment, primarily due to the dysregulation of interconnected signaling networks. Engineered exosomes, as a customizable platform, can meet the needs of different pathological stages.

4.1 Psoriasis

The interleukin-23/T helper 17 cell signaling pathway plays a central role in psoriasis, and its influence extends well beyond immune activation, as it also triggers extensive immunometabolic dysregulation [111-113]. Rapid keratinocyte proliferation follows chronic inflammation, while the lipid metabolites generated in the process further fuel inflammation [114]. Elevated glycolysis supports the pathogenic differentiation of effector T cells and macrophages [115]. Current biologic therapies mainly focus on single cytokines such as interleukin-17, interleukin-23, or tumor necrosis factor-α. These therapies control only parts of the inflammatory cascade. Such treatments lack metabolic regulatory functions [116, 117].

The coexistence of immune dysregulation and metabolic reprogramming has motivated the use of engineered exosomes as multifunctional delivery platforms. One strategy focuses on polyamine metabolism [118]. MSC-derived exosomes have

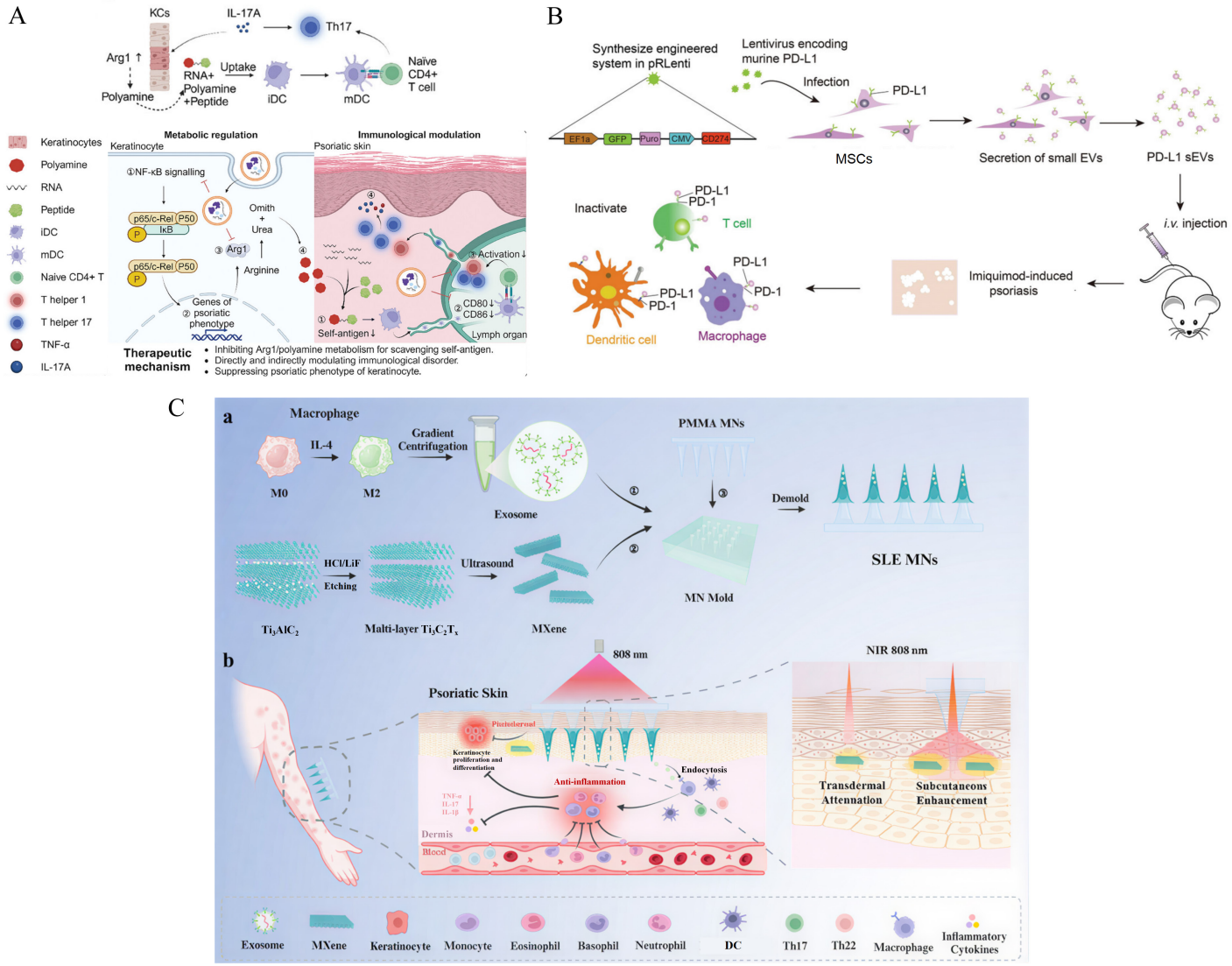


Figure 4. Engineered extracellular vesicle-based strategies for psoriasis therapy. (A) A synergistic strategy for regulating polyamine metabolism and the immune microenvironment, in which engineered MSC-derived extracellular vesicles disrupt the metabolic–immune vicious cycle in psoriasis. Adapted from [118] (Copyright © 2024, Zhou *et al.* Advanced Science published by Wiley-VCH GmbH); (B) MSC-derived small extracellular vesicles with high PD-L1 expression inhibit the activation of T cells, macrophages, and DCs. Adapted from [55] (Copyright © 2021, Xu *et al.* Advanced Materials published by Wiley-VCH GmbH); (C) A light-responsive microneedle system integrating immunomodulation with transdermal near-infrared light delivery. Adapted from [126] (Copyright © 2025, Zhao *et al.* ACS applied materials & interfaces published by ACS). Arg1, arginase 1; CD4, cluster of differentiation 4; CD80, cluster of differentiation 80; CD86, cluster of differentiation 86; CD274, cluster of differentiation 274; CMV, cytomegalovirus; DC, dendritic cell; EF1α, elongation factor 1 alpha; EV, extracellular vesicle; GFP, green fluorescent protein; HCl, hydrochloric acid; iDC, immature dendritic cell; IL-4, interleukin-4; IL-17A, interleukin-17A; i.v., intravenous; IκB, inhibitor of nuclear factor κB; KC, keratinocyte; LiF, lithium fluoride; M0, unpolarized macrophage; M2, alternatively activated macrophage; mDC, mature dendritic cell; MN, microneedle; MSC, mesenchymal stem cell; NF-κB, nuclear factor κB; NIR, near-infrared; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PMMA, poly(methyl methacrylate); RNA, ribonucleic acid; sEV, small extracellular vesicle; SLE MN, subcutaneous light response-enhanced microneedle; Th2, T helper 2 cell; Th17, T helper 17 cell; p65, RELA p65 subunit; p50, nuclear factor κB1 p50 subunit; c-Rel, REL proto-oncogene, NF-κB subunit; Puro, puromycin-resistance marker; Ti_3AlC_2, titanium aluminum carbide; $Ti_3C_2T_x$, titanium carbide MXene with surface terminations; MXene, a class of two-dimensional transition-metal carbides and nitrides; pRLenti, lentiviral expression vector.

been engineered to carry an arginase-1 inhibitor that depletes precursors for polyamine synthesis (**Figure 4A**). Autoantigen levels and the activity of related antigen-presentation pathways are markedly reduced. Researchers have also attempted combinatorial loading to influence several pathways at the same time. Ultraviolet B exposure upregulates platelet-activating factor in keratinocytes, thereby transmitting immunosuppressive signals to neighboring keratinocytes [119]. This effect can

be enhanced by loading exosomes with JPH203, an L-type amino acid transporter 1 inhibitor [120]. Excessive activation of the mechanistic target of rapamycin (mTOR) is a major factor contributing to keratinocyte proliferation. Extracellular leucine turns on this cascade by binding to sestrin2 and inducing its dephosphorylation [121]. JPH203 can occupy the binding site, thereby hindering leucine transport. Exosomes also serve as carriers for natural bioactive molecules from medicinal plants, including epigallocatechin-3-gallate and anhydroicaritin [122, 123]. The lipid bilayer protects these molecules from rapid degradation, reducing the skin irritation that may occur during topical application.

Another advantage is that engineered exosomes can precisely target inflamed lesions. Damaged tissue releases chemotactic signals that recruit reparative exosomes, reflecting the body's natural compensatory response. In particular, vesicles derived from MSCs have intrinsic homing properties, which facilitate the delivery of antisense oligonucleotides targeting miR-210 to $CD4^+$ T cells, thereby regulating the balance among $CD4^+$ T-cell subtypes [11, 124]. Liu *et al.* chose melanoma cells as the source because these cells naturally express PD-L1, the ligand for programmed cell death protein 1 (PD-1) on T cells [125]. Genetic engineering can further increase the amount of PD-L1 carried by exosomes, so that significant therapeutic effects can be achieved at lower doses (**Figure 4B**) [55].

Psoriasis lesions are accompanied by epidermal hyperplasia and hyperkeratosis, and the thickened plaques that form make drug penetration challenging [112]. Microneedle-assisted systems can penetrate this barrier, allowing engineered exosomes to enter the skin through the resulting micropores. Dissolvable microneedle patches are more convenient and less invasive [106]. Traditional phototherapy for psoriasis has poor efficacy, largely because the epidermis intercepts and absorbs much of the light. An optical microneedle system constructed by Zhao *et al.* guided the energy directly to the deep subcutaneous tissues [126]. Under controlled light exposure, it additionally released anti-inflammatory exosomes in the same vicinity (**Figure 4C**).

4.2 Atopic dermatitis (AD)

AD is characterized by recurrent episodes and an immune response dominated by T helper 2 (Th2) cells [127, 128]. Due to immune bias, even some harmless stimuli can activate Th2 cells, which then release large amounts of interleukin-4 and interleukin-13 that aberrantly inhibit the normal synthesis of ceramides, cholesterol, and fatty acids. The "brick-and-mortar" structure of the skin becomes disrupted, facilitating the penetration of exogenous allergens. Breaking this positive feedback loop requires targeting multiple pathogenic factors: topical moisturizers strengthen the skin barrier, while abrocitinib or dupilumab block inflammatory signals.

Hereditary filaggrin deficiency is a major genetic risk factor [129, 130]. This could partly explain the high prevalence of AD observed in early childhood. When the filaggrin gene was knocked out, keratinocytes released altered exosomes with an abnormal lipid composition [131]. Such vesicle changes are often present in AD patients, and interleukin-13 levels are likely to be elevated. These findings suggest exosomes may be part of a vicious circle. As a consequence, exogenously introducing therapeutic exosomes seems to be a reasonable strategy. Evidence suggests that this approach may provide both anti-inflammatory effects and tissue repair [132, 133]. Optimizing the cell source further improves their potential. MSCs can be licensed by inflammatory cytokines to function in a highly activated state. Interferon-γ is a well-documented and stable licensing factor [134]. In experiments by Kim *et al.*, exosomes obtained from interferon-γ-primed MSCs suppressed the expression of interleukin receptors for Th2 cytokines, including interleukin-4 receptor α, interleukin-13 receptor α1, and interleukin-31 receptor α [135]. The damaged skin barrier was restored, as evidenced by the recovery of key genes involved in epidermal differentiation and lipid synthesis from inhibitory effects (**Figure 5A**, **5B**). Moreover, engineered exosomes are being redefined as versatile delivery platforms. Given its associations with improved sleep quality, skin cell protection, and reduced serum immunoglobulin E levels, a transdermal exosome-based delivery system for melatonin could be beneficial for AD therapy [136]. Attention is increasingly turning to cross-species membrane fusion, a novel, low-cost approach to integrating the benefits of distinct species. Easily obtainable exosomes—from sources such as Portulaca oleracea L., turmeric, or grapefruit—are known to alleviate symptoms of AD [137-139]. When such vesicles are fused with stem cell membranes, the resulting hybrid vesicles preferentially accumulate in regions enriched with chemokines [139]. RNA polymerase I inhibitors are then released to increase the proportion of Tregs within the inflamed lesion (**Figure 5C**).

4.3 Scleroderma

Systemic sclerosis (SSc), at its core, is a disease of progressive fibrosis [140]. Inflammation and vasculopathy are the initial events, but extensive damage results from uncontrolled fibroblast activation. These activated fibroblasts produce excessive extracellular matrix, disrupting homeostasis and leading to fibrosis and stiffening of the skin and internal organs [141, 142].

Small RNA profiling of circulating exosomes isolated from blood shows downregulation of anti-fibrotic microRNAs and upregulation of pro-fibrotic microRNAs [143]. Accordingly, unaffected cells may take up these pathological exosomes and acquire a fibrotic phenotype. Wermuth *et al.* instead focused on fingertip ulcers, a complication of SSc. They found that serum exosome levels were decreased in patients with SSc, possibly because of severe microvascular injury [144]. Only a small number of exosomes are released from dermal fibroblasts, whereas the secretion of inherently reparative exosomes is

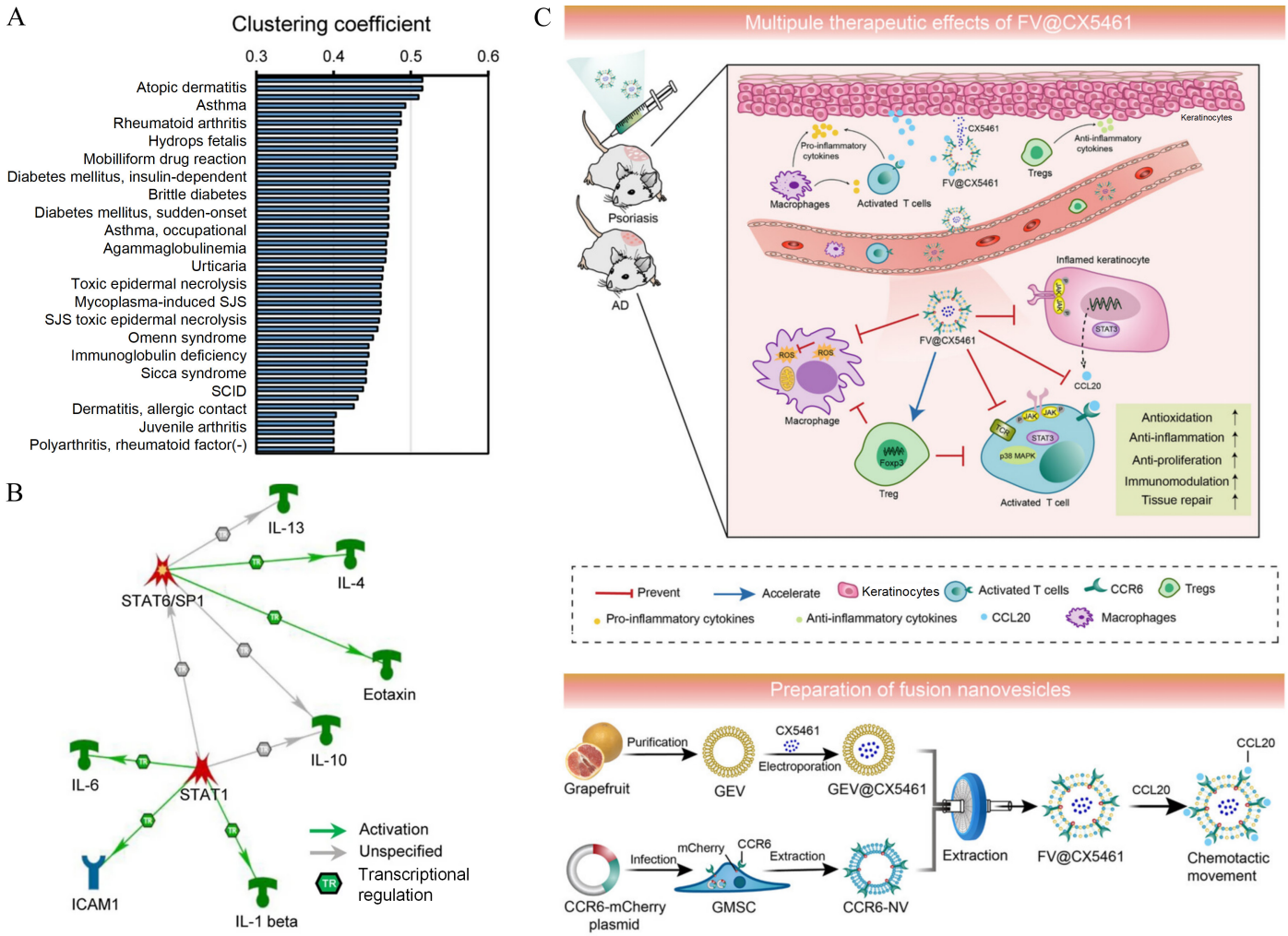


Figure 5. Engineered exosomes in atopic dermatitis. (A) Differential proteins identified in engineered exosomes show a significant association with the AD-associated gene set. Adapted from [135] (Copyright © 2022, Kim *et al.* Journal of Nanobiotechnology published by Spring Nature); (B) Engineered exosomes ameliorate Th2-type inflammation and downstream pathology in AD by modulating the IL-4/IL-13-STAT6/STAT1 signaling axis. Adapted from [135] (Copyright © 2022, Kim *et al.* Journal of Nanobiotechnology published by Spring Nature); (C) Design and function of the FV@CX5461 hybrid vesicle. Adapted from [139] (Copyright © 2023 Huang *et al.* Journal of Extracellular Vesicles published by Wiley Periodicals LLC on behalf of International Society for Extracellular Vesicles). AD, atopic dermatitis; CCL20, C-C motif chemokine ligand 20; CCR6, C-C motif chemokine receptor 6; FV, fusion vesicle; GEV, grapefruit-derived exosome-like nanovesicle; GMSC, gingiva-derived mesenchymal stem cell; ICAM1, intercellular adhesion molecule 1; IL-1β, interleukin-1β; IL-4, interleukin-4; IL-6, interleukin-6; IL-10, interleukin-10; IL-13, interleukin-13; MS, multiple sclerosis; NV, nanovesicle; SCID, severe combined immunodeficiency; SJS, Stevens–Johnson syndrome; SP1, specificity protein 1; STAT1, signal transducer and activator of transcription 1; STAT6, signal transducer and activator of transcription 6; Th2, T helper 2 cell; Treg, regulatory T cell.

compromised. This hypothesis was supported in a mouse model in which normal serum-derived exosomes were applied to full-thickness skin wounds. Platelets may be the main contributors. In the context of SSc, natural exosomes present both challenges and therapeutic opportunities that warrant further investigation. Rozier *et al.* provided evidence that miR-29a-3p from MSC-derived exosomes can target genes related to apoptosis and methylation [145]. DNA methyltransferase 3 alpha, in particular, plays a critical role in epigenetic dysregulation during disease progression. Jin *et al.* identified miR-143-3p as a critical antifibrotic factor and demonstrated that miR-143-3p-enriched extracellular vesicles represent a potential therapeutic strategy for localized scleroderma [146]. Another important finding from their study is that this microRNA can be loaded into exosomes at high levels to more effectively inhibit extracellular matrix deposition, fibroblast differentiation, and epithelial cell activation.

4.4 Chronic wound healing in diabetes

Chronic wound healing continues to be a significant clinical issue. This is especially true for patients with metabolic disor-

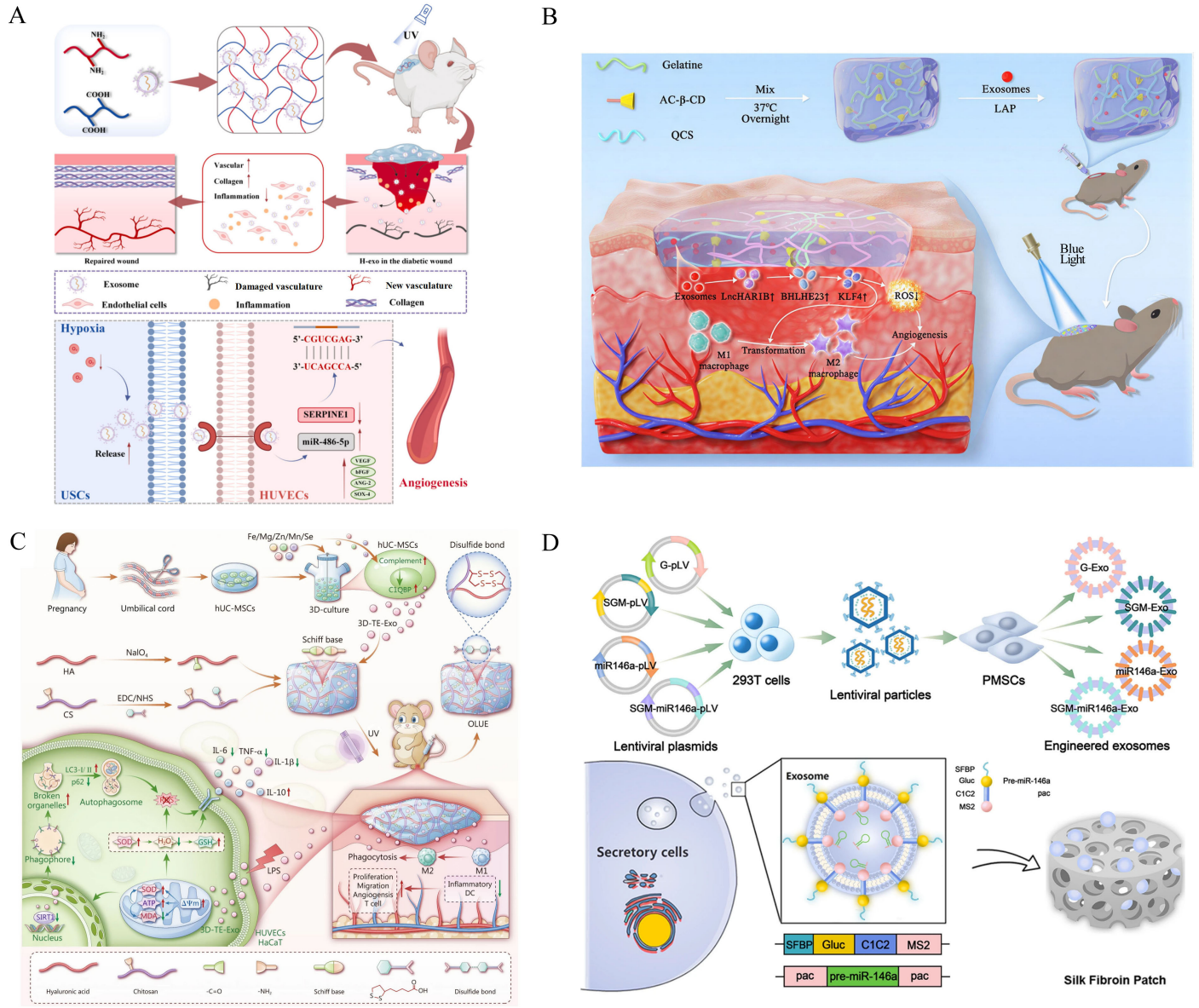


Figure 6. Engineered exosomes in diabetic wound healing. (A) A hydrogel system loaded with hypoxia-preconditioned exosomes promotes angiogenesis and collagen deposition and alleviates inflammation through increased miR-486-5p levels. Adapted from [154] (Copyright © 2024, Fan *et al.* Biomaterials published by Elsevier Ltd); (B) A hydrogel system loaded with hypoxia-preconditioned exosomes promotes M2 macrophage polarization and angiogenesis through lncHAR1B upregulation. Adapted from [155] (Copyright © 2023, Cheng *et al.* Bioactive Materials published by Elsevier B.V. on behalf of KeAi Communications Co. Ltd); (C) Exosomes generated through synergistic supplementation with Fe, Mg, Zn, Mn, and Se and 3D dynamic culture suppress inflammation and enhance angiogenesis. Adapted from [158] (Copyright © 2025, Wang *et al.* Military Medical Research published by Springer Nature); (D) A silk fibroin patch for the delivery of miR-146a-loaded engineered exosomes. Adapted from [162] (Copyright © 2023, Li *et al.* Signal Transduction and Targeted Therapy reproduced with permission from Nature). H-exo, hypoxic urine-derived stem cell exosomes; HUVECs, human umbilical vein endothelial cells; miR-486-5p, microRNA-486-5p; SERPINE1, serpin family E member 1; USCs, urine-derived stem cells; UV, ultraviolet; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; ANG-2, angiopoietin-2; SOX-4, SRY-box transcription factor 4; Ac-β-CD, acrylate β-cyclodextrin; BHLHE23, basic helix-loop-helix family member e23; KLF4, Krüppel-like factor 4; LAP, lithium phenyl-2,4,6-trimethylbenzoylphosphinate; lncHAR1B, long non-coding RNA HAR1B; M1, classically activated macrophage; M2, alternatively activated macrophage; QCS, quaternized chitosan; ROS, reactive oxygen species; 3D, three-dimensional; 3D-TE-Exo, exosomes derived from trace element-supplemented three-dimensional culture; C1QBP, complement C1q-binding protein; CS, chitosan; DC, dendritic cell; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; GSH, glutathione; HA, hyaluronic acid; hUC-MSCs, human umbilical cord mesenchymal stem cells; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-10, interleukin-10; LC3, microtubule-associated protein 1 light chain 3; LPS, lipopolysaccharide; MDA, malondialdehyde; NHS, N-hydroxysuccinimide; OLUE, ultraviolet-irradiated oxidized hyaluronic acid/lipoic acid-grafted chitosan hydrogel containing exosomes; p62, sequestosome 1; SIRT1, sirtuin

1; SOD, superoxide dismutase; H_2O_2, hydrogen peroxide; TNF-α, tumor necrosis factor-α; ATP, adenosine triphosphate; ΔΨm, mitochondrial membrane potential; HaCaT, human immortal keratinocyte line; Exo, exosome; G-Exo, Gaussia luciferase-labeled exosomes; Gluc, Gaussia luciferase; G-pLV, Gaussia luciferase lentiviral plasmid; miR-146a, microRNA-146a; pLV, lentiviral plasmid; PMSCs, placental mesenchymal stem cells; SFBP, silk fibroin-binding peptide; SGM, SFBP–Gluc–MS2; MS2, bacteriophage MS2 coat protein; C1C2, C1 and C2 domains of lactadherin; pac, MS2 coat protein-binding RNA packaging site; 293T, human embryonic kidney 293T cell line.

ders [147]. In diabetes, hyperglycemia disrupts cell function, predisposing patients to chronic ulcers, most commonly diabetic foot ulcers (DFUs). Acute inflammation is a beneficial early stage for normal wound repair. However, DFUs often remain in a state of low-grade but persistent inflammation. The accumulation of advanced glycation end products and reactive oxygen species traps macrophages in an inflammatory M1 state [148]. This inflammatory environment is exacerbated by protease imbalance. Abnormally elevated matrix metalloproteinases rapidly degrade growth factors and matrix [149]. If left uncontrolled, these alterations eventually lead to severe microvascular dysfunction and tissue hypoxia.

Wound healing typically goes through four phases. Unlike acute wounds, chronic ulcers bypass the hemostatic stage because platelets fail to aggregate and initiate the repair cascade. Platelet-rich plasma appears attractive, and it is frequently employed in regenerative medicine. When neutrophils take up platelet-rich plasma-derived exosomes, the suppressive miR-26b-5p is released to target matrix metalloproteinase-8, an important enzyme involved in the formation of neutrophil extracellular traps [150]. Damage-associated molecular patterns are attenuated, creating a favorable microenvironment for wound healing. Moreover, exosome therapy promotes the crosstalk between keratinocytes and macrophages. Sharma *et al.* found that macrophages enriched in the mitochondrial membrane protein TOMM70 often localize to leading-edge keratinocytes to rescue their mitochondrial metabolism [151]. In turn, keratinocytes deliver exosomal microRNAs to M1 macrophages, signaling that inflammation has already resolved [152].

To better counteract pathological cascades in DFUs, engineering strategies have been applied to enhance exosomal efficacy. Stem cells have excellent regenerative capabilities. Those isolated from hypoxic tissues are more likely to maintain their stemness. Hypoxic preconditioning shifts the microRNA composition of exosomes, resulting in the upregulation of miR-21-3p, miR-126-5p, and miR-31-5p [153]. Fan *et al.* uncovered an association among exosomal miR-486-5p, the negative regulator of angiogenesis SERPINE1, and the hypoxia-inducible factor 1α signaling pathway (**Figure 6A**) [154]. In addition, differentially expressed long non-coding RNAs have been identified in exosomes from human umbilical vein endothelial cells. Cheng *et al.* ultimately pinpointed long non-coding RNA HAR1B, which exerts specific dual functions rather than broad-spectrum regulation (**Figure 6B**) [155]. Other types of nucleic acids, circular RNAs, work mainly as "molecular sponges". Once inside diseased cells, they sequester microRNAs that would otherwise block repair-related gene expression. Thus, downstream genes, like those involved in hypoxia response and growth regulation, can be restored [156, 157]. Adding trace elements to a 3D dynamic culture system is also a method for manufacturing highly active exosomes (**Figure 6C**), which target multiple pathways through a complement–mitochondria–autophagy loop [158]. IMMUNEPOTENT CRP has recently been considered for DFU treatment, and its exosomes indeed promote tissue regeneration, with targets including but not limited to the phosphatidylinositol (3,4,5)-trisphosphate/protein kinase B signaling pathway [159]. IMMUNEPOTENT CRP-derived exosomes can also work alongside conventional drugs (insulin, gentamicin, etc.) to improve the wound microenvironment and help manage infection [160, 161].

Since diabetic wounds are rich in proteases, clinical formulations are mostly prepared using hydrogels, microneedles, or other biomaterial platforms, such as silk fibroin [162]. The enzymatic degradation of this material is relatively slow, and when exosomes are anchored to such a silk fibroin patch via binding peptides, they can be released in a sustained and stable manner as the matrix degrades (**Figure 6D**). In recent years, exosomes intended for treating diabetic ulcers have been increasingly derived from medicinal or edible plants (**Table 1**).

4.5 Melanoma

Skin cancer accounts for only a small proportion of cancer-related mortality, and most cases are relatively indolent types, such as basal cell carcinoma and squamous cell carcinoma, which originate from epidermal cells. Melanoma, however, is notably aggressive [170]. Its survival outcomes are even poorer than those of many advanced visceral cancers, largely due to its high metastatic potential. Some tumor cells can rapidly penetrate the basement membrane and seed the dermis at an early stage. This vertical invasion may be attributed to the epithelial-mesenchymal transition. A subset of macrophages ($APOE^+CD163^+$) was considered a potential initiator, and Liu *et al*. identified four invasion-associated driver genes: NRAS, KRAS, NF1, and KIT [171]. Mutant KRAS often activates the mitogen-activated protein kinase signaling pathway. Downstream transcription factors then bind to the death receptor 5 (DR5) promoter, resulting in high DR5 expression on the surface of tumor cells [172]. A single-chain variable fragment is a versatile antibody fragment that can be engineered as DR5-single-chain variable fragment to specifically target this antigen. A single immunoglobulin G molecule has only two binding sites, and its binding is stochastic. Exosomes aggregate on

Table 1. Delivery platforms integrated with plant-derived vesicles for diabetic wound healing

Source	Matrix	Delivery system	Reference
Lemon	Gelatin methacryloyl and dialdehyde starch	Hydrogel patch	[163]
Bitter gourd	Gelatin methacryloyl and dopamine	Hydrogel	[164]
Purslane	Gelatin methacryloyl	Hydrogel	[165]
Siberian ginseng	Chitosan and carboxymethyl chitosan and chondroitin sulfate	Dissolving microneedle	[166]
Chinese motherwort	Gelatin methacryloyl	Hydrogel	[167]
Kelp	Octenyl succinic anhydride-grafted agarose and polydopamine-decorated carbon nanotubes	Conductive microneedle	[168]
Aloe, neem, and ginger	Chitosan and polyvinyl alcohol	Nanomembrane	[169]

Note: Plant sources: Lemon, *Citrus limon*; Bitter gourd, *Momordica charantia*; Purslane, *Portulaca oleracea*; Siberian ginseng, *Acanthopanax senticosus*; Chinese motherwort, *Leonurus japonicus*; Kelp, *Saccharina japonica*; Aloe, *Aloe barbadensis*; Neem, *Azadirachta indica*; Ginger, *Zingiber officinale*.

the membrane of $DR5^+$ melanoma cells, effectively inducing conformational changes in the intracellular death domain of DR5 [173]. To meet the demand for clinical applications, Chintapula *et al.* scaled up production using microfluidic technology [75]. They additionally loaded extracellular signal-regulated kinase inhibitors to enhance the anti-tumor effect (**Figure 7A**). Altanerova *et al.* proposed a novel prodrug therapy based on the yeast cytosine deaminase::uracil phosphoribosyl transferase suicide fusion gene [174]. After the exosomes are internalized, the yeast cytosine deaminase::uracil phosphoribosyl transferase mRNA is translated into an enzyme that converts co-administered, harmless 5-fluorocytosine into the chemotherapeutic drug 5-fluorouracil (**Figure 7B**). This method can be further enhanced. For example, they later turned to tumor-derived exosomes as carriers, thereby reducing off-target damage to healthy tissues [175].

Beyond direct elimination, the modified exosomes can also reprogram the tumor immune microenvironment. Different stages of the immune response determine which antigenic molecules are displayed on the exosome surface. Peptide-loaded major histocompatibility complex molecules and co-stimulatory molecules provide activation signals, enabling exosomes to function similarly to antigen-presenting cells (**Figure 7C**) [176]. They exert either positive or negative stimulation on $CD4^+$ and $CD8^+$ T cells (**Figure 7D**) [177]. PD-1 and PD-L1 are a typical pair of negative co-signaling molecules, commonly expressed on T cells and tumor cells. When T cells infiltrate the tumor, it is undesirable for them to be in an exhausted state. Immune checkpoint blockade therapy is appropriate for the immune-inflamed phenotype. Kandimalla *et al.* chose to package PD-L1 siRNA into exosomes, silencing PD-L1 on both tumor cells and tumor-associated macrophages, rather than treating with anti-PD-1 or anti-PD-L1 antibodies [178]. However, boosting the host immune response alone is insufficient because T cells can become functionally suppressed again within the complex tumor immune microenvironment. Recognizing this limitation, Liu *et al.* extended their investigation beyond PD-L1 to explore Wnt signaling and its associated immune checkpoint escape mechanisms [179]. They compared engineered exosomes with bispecific antibodies. Although both restored the infiltration of $CD8^+$ T cells, the effect of the latter was less pronounced than that of the former. Despite advances in immunotherapy, its efficacy against melanoma remains limited in aged individuals, particularly because of the age-related decline in dendritic cell function. An engineered nano-vaccine has been introduced to restore dendritic cell activity [180]. This nano-vaccine, based on highly immunogenic tumor exosomes, is also functionalized with potent immune adjuvants. Following vaccination, the combined use of doxorubicin and anti-PD-1 drugs formed a self-sustaining immune cycle that significantly delayed tumor progression.

4.6 Other skin diseases

So far, we have focused on inflammation, autoimmunity, fibrosis, wound healing, and cancer. However, the same logic extends to other skin conditions that do not respond well to conventional treatments—pigmentary disorders, physical trauma, and cutaneous appendage diseases. Representative strategies are summarized in **Table 2**, ranging from melanin regulation to hair follicle regeneration.

5 CONCLUSION

Engineered exosomes represent a promising new tool for dermatology. Modifications can be introduced in terms of cargo, membrane, and production process. These rational designs translate into precise targeting, stronger therapeutic effects, and greater flexibility, enabling engineered exosomes to perform functions beyond those of natural vesicles. This implies that a single platform could perform multiple therapeutic functions. Due to this synergistic advantage, engineered exosomes have been applied to distinct types of skin diseases, including inflammatory disorders, fibrosis, impaired wound healing, and skin tumors.

Most studies focus on how to enhance the performance of engineered exosomes. Although a range of surface engineering strategies is available, it is essential to verify that these modifi-

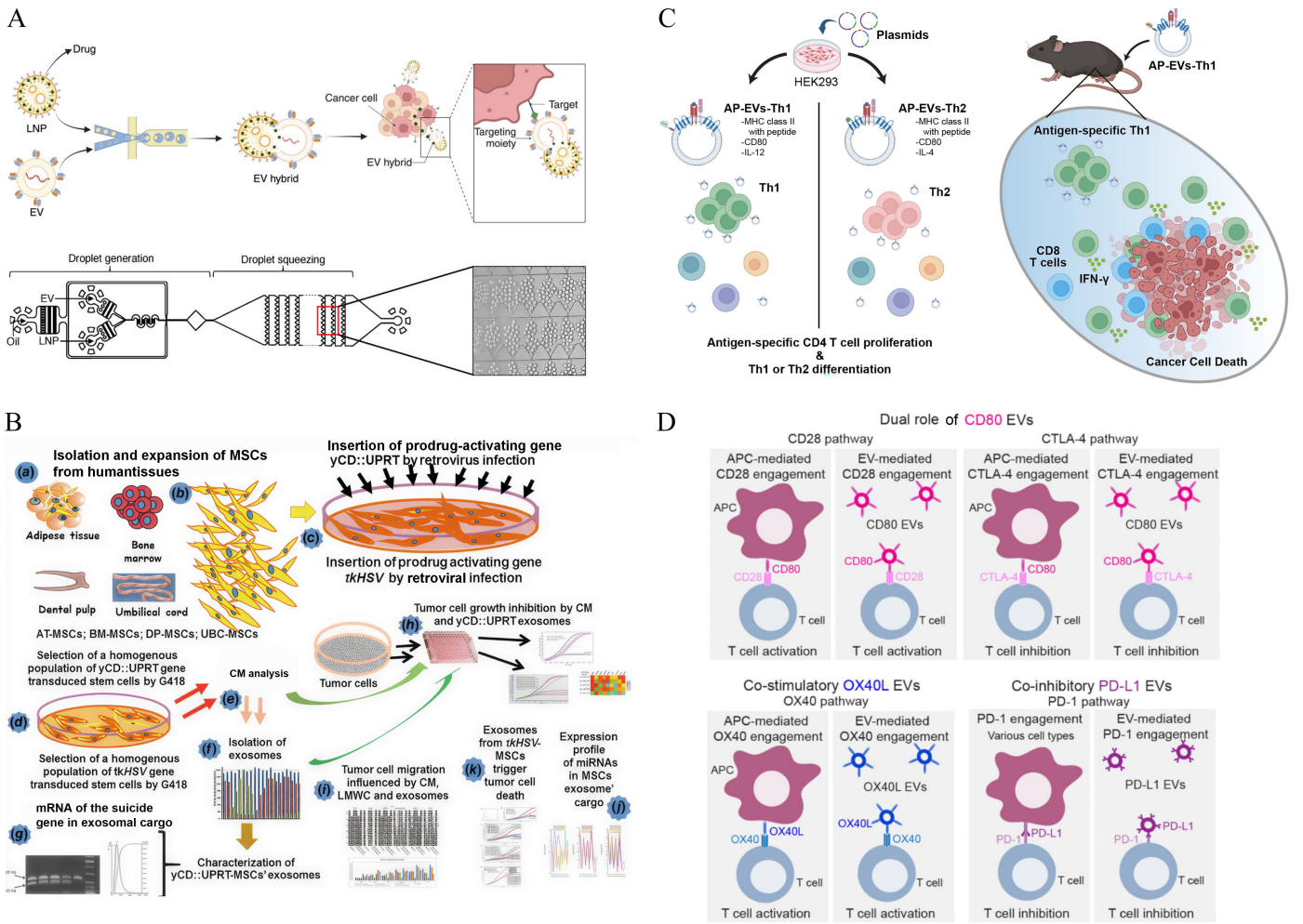


Figure 7. Engineered extracellular vesicle-based strategies for melanoma therapy. (A) A DR5-targeted hybrid vesicle for the delivery of ulixertinib and ravoxertinib, and a schematic of a microfluidic device featuring droplet-squeezing geometries to fuse DR5-targeted exosomes with LNPs. Adapted from [75] (Copyright © 2025, Chintapula *et al.* Small published by Wiley-VCH GmbH); (B) An engineered exosome-mediated prodrug suicide gene therapy for tumors. Adapted from [174] (Copyright © 2018, Altanerova *et al.* International Journal of Cancer published by John Wiley and Sons); (C) Precise polarization of Th1/Th2 subsets through the presentation of antigenic peptides. Adapted from [176] (Copyright © 2025, Kimura *et al.* Drug Delivery published by Informa UK Limited, trading as Taylor & Francis Group); (D) Modified extracellular vesicles enable dual regulation of T-cell immunity through the CD28/CTLA-4, OX40, and PD-1 pathways. Adapted from [177] (Copyright © 2025, Luo *et al.* ACS Nano published by ACS). DR5, death receptor 5; EV, extracellular vesicle; LNP, lipid nanoparticle; AT-MSCs, adipose tissue mesenchymal stem cells; BM-MSCs, bone marrow mesenchymal stem cells; CM, conditioned medium; DP-MSCs, dental pulp mesenchymal stem cells; LMWC, low-molecular-weight components; miRNA, microRNA; mRNA, messenger RNA; MSC, mesenchymal stem cell; tkHSV, herpes simplex virus thymidine kinase; UBC-MSCs, umbilical cord mesenchymal stem cells; yCD::UPRT, yeast cytosine deaminase::uracil phosphoribosyl transferase suicide fusion gene; G418, geneticin; AP-EVs, antigen-presenting extracellular vesicles; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CD80, cluster of differentiation 80; HEK293, human embryonic kidney 293 cell line; IFN-γ, interferon-γ; IL-4, interleukin-4; IL-12, interleukin-12; MHC, major histocompatibility complex; Th1, T helper 1 cell; Th2, T helper 2 cell; APC, antigen-presenting cell; CD28, cluster of differentiation 28; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; OX40, OX40 receptor (CD134); OX40L, OX40 ligand; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

cations do not alter native protein conformations or compromise the integrity of the lipid bilayer. This is a particular concern with chemical conjugation, as residual coupling reagents may persist and contribute to adverse reactions. Cargo loading presents a comparable constraint. In practice, many researchers apply mechanical treatments to exosomes, yet capacity and stability impose an upper limit on the number of molecules a single vesicle can accommodate. Liposome-exosome fusion is often used to increase drug loading, but it also blurs the boundary between exosomes and biomimetic vesicles. When typical markers such as CD63 and CD81 are weakened or lost, these hybrid vesicles may be better described as exosome mimetics rather than conventional exosomes. Protein nanoparticle co-assembly supraparticles offer a new strategy for enhancing payload capacity. Their compact size favors subsequent packaging into exosomes before secretion [189].

Table 2. Applications of engineered exosomes in other skin diseases

Disease type	Exosome source	Specific methods	Mechanism	Reference
Vitiligo	Keratinocytes	H_2O_2 preconditioning	miR-31-3p-enriched exosomes impair melanocyte survival and melanogenesis via the MITF signaling pathway and concurrently activate $CD8^+$ T cells	[181]
Skin wounds	MSCs	GelMA-based 3D culture	Delays cellular senescence, increases exosome yield, and augments pro-angiogenic activity	[182]
Bacterial infection in atopic dermatitis	*Staphylococcus epidermidis*	Freeze-thaw-mediated loading of levofloxacin	Selectively eradicates *Staphylococcus aureus*, alleviates cutaneous inflammation, and, in combination with microneedle delivery, promotes dermal repair and epidermal barrier restoration	[183]
Wound infection management	Monocytes	Preconditioning with 1α,25-dihydroxyvitamin D_3 and CYP24A1 inhibitor	Exhibits broad-spectrum bactericidal activity against Gram-negative and Gram-positive bacteria via enrichment of the antimicrobial peptide cathelicidin (LL-37)	[184]
Wound infection management	Lactic acid bacteria	Culture condition optimization (pH, incubation time, and medium concentration)	Optimized bioprocessing enhances production of exosomes with potent anti-*Staphylococcus aureus* activity	[185]
Radiation dermatitis	*Spirulina platensis*	Ultrasound-assisted astaxanthin encapsulation	Activates the Nrf2/Keap1 pathway, scavenges radiation-induced reactive oxygen species, and restores mitochondrial integrity	[186]
Alopecia	MSCs	Rapamycin preconditioning	Activates hair follicle stem cells by upregulating Wnt/β-catenin signaling, growth factors, and autophagy-related genes, thereby promoting telogen-to-anagen transition and enhancing angiogenesis to support follicular nutrition	[187]
Alopecia	Hair follicle stem cells	Liposome membrane fusion followed by sonication-mediated loading of finasteride and gold nanoparticles	Enhances follicular retention; finasteride inhibits 5α-reductase and reduces DHT production to prevent follicular miniaturization, while AuNPs induce photothermal vasodilation to improve follicular nutrient supply	[188]

Note: 3D, three-dimensional; AuNPs, gold nanoparticles; CD8, cluster of differentiation 8; CYP24A1, cytochrome P450 family 24 subfamily A member 1; DHT, dihydrotestosterone; GelMA, gelatin methacryloyl; H_2O_2, hydrogen peroxide; Keap1, Kelch-like ECH-associated protein 1; LL-37, human cathelicidin antimicrobial peptide LL-37; miR-31-3p, microRNA-31-3p; MITF, microphthalmia-associated transcription factor; MSCs, mesenchymal stem cells; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species.

Vesicles derived from different sources possess distinct advantages, and those secreted by probiotics or beneficial skin commensals have attracted increasing interest as potential therapeutic agents for dermatologic intervention [183, 190]. Nevertheless, extraction and purification methods for microbial exosomes are still technically demanding. For scalable manufacturing, low-cost and readily accessible feedstocks, like plants and biofluids, are preferred. Milk exosome production, in particular, has reached a relatively mature stage of industrial development [191]. Regardless of scale, batch-to-batch consistency remains a critical requirement. Minor variations can lead to differences in the final product, so processing steps should ideally be carried out within an integrated, continuous workflow. Critical quality attributes and process parameters are central to regulatory approval. No universally accepted standard has yet been established for defining exosome purity, whether by particle number, protein content, or surface markers. To date, no drug regulatory agency has issued dedicated technical guidelines specific to exosomes, and classification varies across jurisdictions [192]. The core debate lies in whether exosomes should be classified as drugs or biologics. Xu *et al.* argued for positioning exosomes within the framework of advanced therapy medicinal products [193]. They also advised implementing refined oversight that distinguishes native from engineered exosomes. Engineered exosomes have opened a new avenue for the treatment of refractory skin diseases. Future progress will depend on closer coordination among design, manufacturing, quality control, and clinical translation, along with genuine interdisciplinary collaboration.

DECLARATIONS

Author contributions

Jiayi Wang and Junkun Qu performed the image processing and wrote the manuscript. Don Green helped with language polishing of the manuscript. Yangyang Zhang and Yuling Chen contributed significantly to the analysis and manuscript editing. Yongtai Zhang contributed to the analysis through constructive discussions. Teng Guo and Nianping Feng performed the manuscript review, project administration, and resource acquisition.

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Data availability

No new data were created or analyzed in this study.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have read the manuscript and agreed to its publication.

Competing interests

All authors declare that there are no competing interests.

Acknowledgements

Not applicable.

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