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Review

Therapeutic roles of natural and engineered mesenchymal stem cells and extracellular vesicles in atopic dermatitis

Tingting Ren [a,b,d,1], Kang He [b,1], Donghua Xu [c,e,1], Yuxiang Kong [a,d], Shuyue Jiang [b], Jinjin Chu [c], Yi Sun [a], Jie Zang [c,*], Zhenhua Wang [a,d,**]

[a] Department of Dermatology, Weifang People's Hospital, Shandong Second Medical University, Weifang 261041, Shandong, China
[b] School of Clinical Medicine, Shandong Second Medical University, Weifang 261000, Shandong, China
[c] Central Laboratory, Weifang People's Hospital, Shandong Second Medical University, Weifang 261041, Shandong, China
[d] Shandong Provincial Key Medical and Health Laboratory of Skin Immunology (Weifang People's Hospital), Shandong Second Medical University, Weifang 261041, Shandong, China
[e] Department of Rheumatology and Immunology, Weifang People's Hospital, Shandong Second Medical University, Weifang 261041, Shandong, China

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ABSTRACT

Atopic dermatitis (AD) is a chronic and inflammatory disease characterized by skin barrier destruction, sustained inflammation, and immune imbalance. Increasing evidence has suggested mesenchymal stem cells (MSCs) exhibit great potentials in treating AD due to the strong anti-inflammatory, immunomodulatory, and regenerative repair properties. As a cell-free nanocarrier, MSC-derived extracellular vesicles (MSC-EVs) play critical roles in mediating intercellular communications. Recent advance has suggested some bioengineering strategies have greatly improved the therapeutic potentials of MSCs and MSC-EVs in AD treatment, such as genetic reprogramming, biomimetic scaffold integration, and precision surface functionalization. In this comprehensive review, we systematically evaluate the current landscape of both natural and engineered MSCs and MSC-EVs to provide updated insights into the exploration of therapeutic strategies for AD.

Contents

Abbreviations: AD, Atopic dermatitis; MSCs, Mesenchymal stem cells; MSC-EVs, MSC-derived extracellular vesicles; FLG, Filaggrin; SA, Staphylococcus aureus; IL, Interleukin; TSLP, Thymic stromal lymphopoietin; Th, T helper; JAK, Janus kinase; PDE-4, Phosphodiesterase-4; MSC, Mesenchymal Stem Cell; Exos, Exosomes; TLR, Toll-like receptor; S1P, Sphingosine-1-phosphate; TNF-α, Tumor necrosis factor-α; Cldn, Claudin; K1, Keratin 1; LOR, Loricrin; INV, Involucrin; DNCB 2, 4-dinitrochlorobenzol; Hrh2, Histamine receptor H2; Bdkrb, Bradykinin receptors; MSCs-CM, MSCs culture medium; PGE2, Prostaglandin E 2; EGF, Epidermal growth factor; TARC, Thymus activation-regulated chemokine; IFN-γ, Interferon-γ; IgE, Immunoglobulin E; MC, Mast cells; MIP-2, Macrophage inflammatory protein-2; SOCS1, Suppressor of cytokine signaling 1; CXCL13, C-X-C motif chemokine 13; ATRP, Atom transfer radical polymerization; MSM, Molecular sorting module; TEWL, Transepidermal water loss; CAFs, Cancer-associated fibroblast; TGF-β, Transforming growth factor-β; IDO, 2,3-dioxygenase; SOD3, Superoxide dismutase 3; H4R, Histamine H4 receptor; miR-147a, microRNA-147a; VEGFA, Vascular endothelial growth factor A; HUVEC, Human umbilical vein endothelial cells; HA, Hyaluronic acid; HMNVs, Hybrid membrane nanovesicles; PDNVs, Plant-derived nanovesicles; GEVs, Grapefruit-derived nanovesicles; EASI, Eczema area and severity index; SCORAD, Scoring atopic dermatitis index; IGA, Investigator's global assessment; BSA, Body surface area.

* Corresponding author.
** Corresponding author. Department of Dermatology, Weifang People's Hospital, Shandong Second Medical University, Weifang 261041, Shandong, China.
E-mail addresses: 2457232961@qq.com (J. Zang), wfzcwzh@126.com (Z. Wang).
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1. Introduction

Atopic dermatitis (AD) is a chronic and inflammatory disease, characterized by dry skin, erosion, desquamation, and varying degrees of itching [1]. The global prevalence of AD is rising with a higher incidence in children than in adults, resulting in a significant social and economic burden worldwide [2–4]. The pathogenesis of AD is potentially associated with various risk factors, including genetic predispositions, environmental factors, and skin microbiomes imbalance [5]. The diagnosis of AD primarily relies on characteristic rash examinations and careful medical history inquiries. However, some patients may present with atypical clinical manifestations, making diagnosis challenging. Traditional treatment methods often show inadequate efficacy or poor safety profiles in AD. Although biologic agents such as dupilumab represent an important therapeutic option for AD, the long-term effectiveness and safety warrant further investigations. Due to the chronic and recurrent nature of AD, long-term management becomes complex and different. Moreover, AD significantly impairs the quality of life and imposes a substantial socioeconomic burden. Therefore, elucidating the precise pathogenic mechanisms of AD and developing more effective and safe therapeutic strategies are crucial directions for current research.

Mesenchymal stem cells (MSCs) are multipotent stem cells found in various tissues, including bone marrow, peripheral blood, umbilical cord, placenta, and adipose tissue. MSCs possess anti-apoptotic activity, anti-fibrotic effects, regenerative capabilities, and immunomodulatory properties, making them highly promising for the treatment of various diseases [6,7]. Numerous preclinical and clinical studies have been conducted on MSC-based therapies for AD [8]. As the primary way of paracrine regulation of MSCs, MSC-derived extracellular vesicles (MSC-EVs) are rich in genetic substances, enzymes, signal transduction proteins, immune regulatory factors, and growth factors produced by MSCs [9]. MSC-EVs are classified into apoptotic bodies, microvesicles, and exosomes (Exos) based on their diameter and cellular origins. EVs have “homing” properties, allowing them to travel to target locations via body fluids. They can bind to specific membrane receptor or directly fuse with the cellular membrane, thereby releasing active components that regulate the target cells [9]. MSCs and MSC-EVs have shown great potentials in the treatment of AD. However, the heterogenicity of MSCs is significant. In recent years, engineering strategies have been introduced to enhance the functions of MSCs and MSC-EVs, such as ways of physical, chemical, and genetic approaches [10–12]. The engineered MSCs and MSC-EVs possess enhanced ability, efficiency, and stability, thereby augmenting their therapeutic effects.

This review summarizes recent advances in both natural and engineered MSCs and MSC-EVs for the treatment of AD. We also discuss the advantages and challenges associated with engineered MSCs and MSC-EVs in order to outline future research directions.

2. Regulatory roles of natural MSCs and MSC-EVs in AD

2.1. Improvement of skin barrier

Restoring the physiological function of the skin barrier is crucial for AD treatment. We have summarized the common causes of AD-related skin barrier disruption and the mechanisms by which MSCs and MSC-EVs contribute to barrier repair from the following aspects.

2.1.1. Inhibition of Staphylococcus aureus activity

A reduction in microbial diversity and an increase in the colonization of *Staphylococcus aureus* (SA) are correlated with the severity of AD [13]. SA can secrete superantigens, various toxins, and proteases to aggravate AD [14]. The activation of the Toll-like receptor (TLR) pathway by these toxins contributes to the destruction of skin barrier and immune dysfunction, thereby inducing AD [15]. Thus, SA is closely associated with AD barrier dysfunction. The antimicrobial peptide LL-37 produced by MSCs has been found to exhibit antibacterial activity against SA through the vitamin D receptor signaling [16]. Besides, MSC-conditioned medium can reduce the hydrophobicity of the SA membrane and inhibit SA biofilm formation, thereby achieving effective antibacterial activity [17]. Marx C. et al. have demonstrated that conditioned medium from horse peripheral blood-derived MSCs significantly inhibited the growth of SA depending on the cysteine protease released by MSCs [18]. Similarly, MSCs treatment can prevent skin infections and reduce infection-induced inflammatory response in AD mice [19]. Accordingly, MSCs and MSC-conditioned medium can prevent or alleviate infections caused by SA colonization. AD patients with SA colonization infections may be potential candidates for MSC therapy.

2.1.2. Regulating barrier-belated genes expression and function

Normal skin structure consists of the epidermis and the dermis, collectively establishing the skin barrier. The skin barrier restricts the penetration of microorganisms, allergens, irritants, and toxins, while simultaneously preventing the percutaneous loss of skin

moisture [20]. However, external stimuli, genetic defects, and internal immune disorders can lead to an impaired skin barrier in patients with AD.

MSCs and MSC-EVs have been shown to promote the repair of skin barrier in AD. Subcutaneous injection of human adipose tissue-derived Exos in AD mice increased long-chain ceramide production through de novo synthesis, which is the crucial component of the epidermal permeability barrier [21]. Besides, human adipose MSCs-derived Exos are also demonstrated to enhance keratinocyte differentiation and form an appropriate epidermal permeation barrier by regulating the activity of enzymes involved in the synthesis and cleavage of sphingosine-1-phosphate (S1P), which promotes the continued conversion of ceramide to S1P [21]. Human immortal keratinocytes (HaCaT cells) play a vital role in maintaining the biochemical and physical integrity of the skin. Co-culturing MSCs or their medium with human immortal keratinocytes (HaCaT) cells can promote the migration and proliferation of HaCaT cells, suggesting that MSCs and MSCs cultural medium may contribute to the repair of epidermal cells and skin barrier [22]. Furthermore, increasing evidence suggests multiple genetic variants exist in AD patients. The most common genetic mutation in AD is the loss-of-function mutation in the Filaggrin (FLG) gene, encoding FLG protein essential for the skin barrier [23,24]. FLG gene mutation leads to impaired skin barrier function. It has been found that MSC-conditioned medium could reduce fibroblast senescence and the generation of IL-1α and tumor necrosis factor-α (TNF-α), but increase extracellular matrix secretion and the expression of the skin barrier protein FLG, thereby improving skin inflammation [25]. In mouse models, MSCs have been shown to increase the expression of FLG and Claudin (Cldn 3 and Cldn 23) in the skin, particularly at the tight junctions between cells [19]. The adipose tissue-derived MSCs are also found to upregulate FLG expression a canine AD model [26]. These findings have suggested the anti-inflammatory effect of MSCs secretome during skin barrier repair. Additionally, in a mouse AD model, some other epidermal differentiation proteins, such as keratin 1 (K1), Loricrin (LOR), and involucrin (INV), are significantly reduced, while MSCs and MSC-EVs treatment can markedly upregulate them [27]. The canine fat tissue-derived MSCs or MSC-EVs are demonstrate to alleviate the epidermal hyperplasia and edema in AD, accompanied by a reduction in epidermal thickness [27–29]. Therefore, MSCs and MSC-EVs can promote skin barrier repair via restoring the expression and function of barrier-related genes.

2.2. Regulating immune and inflammatory disorders

An imbalance between Th2 and Th1 immune responses contributes to the development of AD, and the type 2 inflammation mediated by Th2 is predominant in AD [30]. Besides, the abnormal activation of innate immune cells is common in AD, such as mast cells, macrophages, and granulocytes [31]. In the acute phase of AD, Th22 cell-mediated inflammation can occur in conjunction with type 2 inflammation, whereas Th1 and Th17 cell-mediated inflammation is progressively exacerbated in the chronic phase [32]. MSCs and MSC-EVs have the ability to regulate excessive or dysregulated innate and adaptive immunity, alleviating the immune and inflammatory response in AD [33]. Many studies have suggested MSCs or MSC-EVs can significantly reduce the trans-epidermal water loss, itch score, and increase the hydration of the stratum corneum in AD by controlling inflammation and immune imbalance [21,27,28,34,35]. A previous study has suggested the subcutaneous injection of bone marrow-derived MSCs or the culture supernatant could inhibit the activation of astrocytes and microglia associated with chronic itch in the AD model [22]. The treatment with MSCs and MSC-EVs can effectively alleviate IL-31-induced itch symptoms via inhibiting the activation of STAT1 and STAT3 signaling and the expressions of IL-31 receptor and TRPA 1 expression in 2, 4-dinitrochlorobenzol (DNCB)-induced AD mice [27]. Hua, C. et al. have found that MSCs can also interrupt the itch-scratching cycle by targeting neuroimmune receptors and reducing cytokine levels [19]. MSCs and MSCs-EVs can alleviate AD by reducing the infiltration of inflammatory T cells, mast cells and dendritic cells [19,29,34,36–41]. MSCs co-cultured with immature B cells can inhibit B cell maturation [38]. TGF-β secreted by MSCs can inhibit the activation of mast cells by reducing TNF-α and histamine release through the ERK and STAT3 signaling pathways, thereby alleviating AD [38]. MSC-secreted PGE2, TGF-β, and IDO significantly alleviates AD and psoriasis by upregulating Treg cells and inhibiting T cell apoptosis depending on Fas and Fas ligand signaling [42]. MSCs can also ameliorate AD by secreting epidermal growth factor (EGF) to regulate inflammation in keratinocytes, Th2 cells, and mast cells [43]. Fat-derived MSCs are found to inhibit IL-4R expression in mouse skin tissues and significantly suppressed Th17 cell proliferation and inflammatory cytokines expression via RORγt and PD-L1, TGF- β and PGE2 [37]. All these findings have strongly supported that MSCs and MSC-EVs play critical roles in the regulation of immune balance in AD. They not only attenuate the inflammatory activation of mast cells, the excessive Th2 and Th17 responses, but also increase the immunosuppressive activity of Treg subsets (Table 1). In addition, MSCs and MSC-EVs possess strong anti-inflammatory effects by reducing the production of IL-4, IL-23, IL-31, IL-17, IL-1β, tumor necrosis factor-α(TNF-α), interferon-γ(IFN-γ), and immunoglobulin E(IgE) [19,21,27,29,34–37,40,41].They can also promote the production of anti-inflammatory mediators, such as PPARα, IκB, IL-10, and TGF-β1 [35,41]. Compared to JAK inhibitors, MSCs can more extensively downregulate the expression of IL-4 receptor, IL-13 receptor, IgE receptor, toll-like receptor, and JAK1/2/3 in the skin and blood samples of AD [19]. Interestingly, when MSCs were co-cultured with PBMC from patients with AD, the Th2 transcription factor GATA3 is downregulated, while the Th1 transcription factor T-bet1 is upregulated, suggesting the pivotal immunomodulatory role of MSCs in treating AD [42]. Studies have found that AD mice exhibit an increased number of degranulated mast cells (MCs) and elevated expression of Th1 and Th2 cytokines, which is dependent on macrophage inflammatory protein-2 (MIP-2) or suppressor of cytokine signaling 1 (SOCS1). MSCs can prevent AD development by facilitating the downregulation of MIP-2, SOCS1, and C-X-C motif chemokine 13 (CXCL13) [39]. In summary, MSCs and MSC-EVs show significant advantages in alleviating AD by controlling inflammation and maintaining the immune balance.

3. Roles of engineered MSCs and MSC-EVs in AD

Engineered MSCs and MSC-EVs have been extensively studied in chronic lung diseases, neurological diseases, bone regeneration, cardiovascular diseases, cancer, and inflammatory diseases [12,44–49], offering new strategies to improve the therapeutic efficacy of MSCs and MSC-EVs. To facilitate an understanding of what engineered MSCs and EVs are and the engineering strategy available, we provide a brief introduction from the following aspects. This will help us better summarize the current advances of engineered MSCs and EVs in treating AD.

Compared to natural MSCs, engineered MSCs exhibit enhanced cellular functions, which are expected to improve therapeutic efficiency, reduce toxicity, and broaden the clinical application of MSCs [50]. MSCs can be used to overexpress genes associated with disease treatment, augmenting the therapeutic effects. The technical approaches include gene transduction via viral vectors, gene

transfection via non-viral vectors, and gene conversion through nanoinjection and electroporation [51]. Studies have shown that combining MSCs and EVs with biological scaffolds, such as hydrogels and 3D-printed porous scaffolds, can create a favorable environment for cell adhesion, proliferation, and differentiation. These scaffolds provide physical protection for cells and vesicles, allowing them to be released in response to environmental changes upon reaching specific sites. This enables precise and sustained therapy, enhancing the immunomodulatory and tissue repair functions of MSCs and EVs [52–55]. Additionally, surface engineering modifications of MSCs, employing peptides and glycan engineering, can improve their homing and transport capabilities (decorating peptides and polymers on the surface of MSCs using covalent modification, noncovalent modification, and atom transfer radical polymerization (ATRP) methods can improve their homing and transport capacity) [56]. MSCs can be pre-activated with specific inflammatory mediators, allowing MSCs and secreted EVs to contain higher concentrations of active substances, thereby promoting the therapeutic efficacy of MSCs [57–59].

The engineering of EVs for disease treatment mainly involves two strategies: engineering parental cells and modifying the EVs. The parental cell engineering strategy refers to loading desired molecules or drugs into parental cells through co-incubation and electroporation, leading to the secretion of EVs containing specific molecules or drugs. Parental cells can also use the molecular sorting module (MSM) and plasmid transfection to ensure that target proteins are encapsulated by or expressed on the surface of EVs. Engineering methods of EVs include chemical modification, surface functionalization, polymer nanoparticle modification, etc. Chemical modification refers to introducing peptide sequences, immunomodulatory molecules, antibodies, cholesterol, and other affinity molecules on the surface of EVs through covalent coupling, non-covalent chimerism, and electrostatic interactions. These methods also enable the surface functionalization of EVs. Polymer nanoparticle modification involves combining biocompatible polymers with EVs to form EVs-polymer hybrid nanocarriers by ultrasound, freeze-thawing, and coextrusion, which retain the endogenous properties of EVs while gaining the controllability of polymers. This hybrid carrier overcomes the limitations of using each component alone and facilitates the development of a drug delivery system. These engineering methods enhance EV's delivery capacity and targeting, improving the effectiveness of bioactive molecules and drug delivery [60,61]. Ongoing research has applied engineered MSCs and MSC-EVs in AD treatment to enhance the efficacy (Fig. 1). The engineering strategies and the altering effects of engineered MSCs and MSC-EVs have been listed as follows.

3.1. Induction by inflammatory mediators

Research indicates that stimulation by inflammatory mediators can induce nuclear reprogramming in MSCs, leading to increased expression of immunomodulatory molecules. These changes caused by inflammatory mediators are reversible [62]. Strategies involving inflammatory mediator induction suggest that the immunomodulatory functions of MSCs and their EVs can be enhanced with increased secretion of immunosuppressive factors [63]. The pre-treating MSCs with inflammatory mediators potentially increases their survival rate and manipulates their secretion profiles, thereby improving their therapeutic efficacy [64].

3.1.1. Toll-like receptor 3 agonist induction

Priming with the Toll-like receptor 3 agonist poly (I: C) or IFN-γ enhanced the therapeutic efficacy of MSC in a mouse model of AD, which reduced clinical symptom scores, transepidermal water loss, epidermal thickness, and inflammatory cell infiltration. The MSCs priming with poly (I: C) and IFN-γ exhibited significant enrichment of the synthetic mRNA in immune-related classical pathways. Specifically, poly (I: C) influences the function of MSCs in regulating cell apoptosis, death, and survival. IFN-γ can regulate complex functions of MSCs, such as development, growth, proliferation, and intercellular signaling and interaction [65].

IDO inhibits the activation of effector T cells activation and the function of natural killer cells, stimulates T cell apoptosis, reduces the immunogenicity of dendritic cells, and promotes the conversion of Treg cells. Some researchers found that IFN-γ can increase the expression of 2,3-dioxygenase (IDO) in induced pluripotent stem cell-derived MSCs (iMSCs). The iExos derived from IFN-γ pre-treated MSCs improved the clinical symptom score, transepidermal water loss, skin thickness, and inflammatory cell

Table 1
Effects of MSCs and MSCs-derived biological mediators on immune cells.

Immune cells		MSCs-derived biological mediators	Mechanisms	Major effects	References
T cell	Unclassified/$CD4^+$ T cell	PGE2	PGE2 pathway	Fas expression significantly; decreases on naive T cells.	[42]
	Th2 cell	EGF	Inhibition of TARC/CCL17 expression.	Th2 cell maturation is inhibited.	[43]
	Th17 cell	PD-L1, TGF-β, PGE2	Reduced expression of transcription factors RORγ T and IL-17A	Inhibition of proliferation and activation of Th17 cells	[37]
	Treg cell	PGE2,TGF-β,IDO	PGE2 and TGF-β pathway.	An increase in the number of tregs.	[42]
Mast cell		TGF-β	Activation of ERK and STAT3 signaling in mast cells.	Histamine and TNF-α release reduction.	[38]
Microglia		/	Inhibition of cell activation	Alleviate neuropathic itch	[22]
B cell		TGF-β	Directly inhibits the maturation and proliferation of B cells; indirectly suppresses B cell activation by inhibiting TNF-α released from mast cells	Reduced serum IgE levels; alleviation of AD symptoms	[38]

MSCs: mesenchymal stem cell; Th: helper T; Treg: regulatory T; PGE2: prostaglandin E2; EGF: epidermal growth factor; PD-L1: programmed death-ligand 1; TGF-β: transforming growth factor-β; IDO: indoleamine 2,3-dioxygenase; TARC: thymus activation regulated chemokine; CCL17: chemokine (C–C motif) ligand 17; RORγ T: retinoid-related orphan receptor gamma T; IL-17A: interleukin-17A; ERK: extracellular regulated protein kinases; STAT3: signal transducer and activator of transcription 3; TNF-α: tumor necrosis factor-α.

infiltration in AD mice. Bioinformatic analysis of mouse skin mRNA revealed that this treatment primarily affected skin barrier function and T cell immune response [66]. The study has shown that IFN-γ induces iMSCs, producing transcriptional changes related to immune regulation, such as upregulation of genes that regulate Treg cell activation. The molecular and biological alterations in the iMSCs caused by IFN-γ can also cause corresponding changes in the composition of the EVs' protein cargo. Among them, AD and infant eczema are the immune diseases with the highest association with EVs proteins induced by IFN-γ. This study shows that EVs obtained after pretreatment reduced the expression of the Th2 cytokine receptor and the corresponding activation of intracellular JAK/STAT signaling molecules. Additionally, EVs can improve skin inflammation and prevent itching by reducing the NF-κB pathway activity, inhibiting TSLP expression and IL-31R-STAT signaling, and repairing skin barrier dysfunction and abnormal lipid synthesis in AD [67]. Proteomics and transcriptome sequencing analyses revealed that EVs, secreted by MSCs induced by poly (I: C) had increased levels of innate immune defense proteins, while miRNA and antimicrobial peptide content remained largely unchanged [68]. Furthermore, priming with Toll-like receptor 3 agonists can alter the composition of different functional mRNA and proteins in

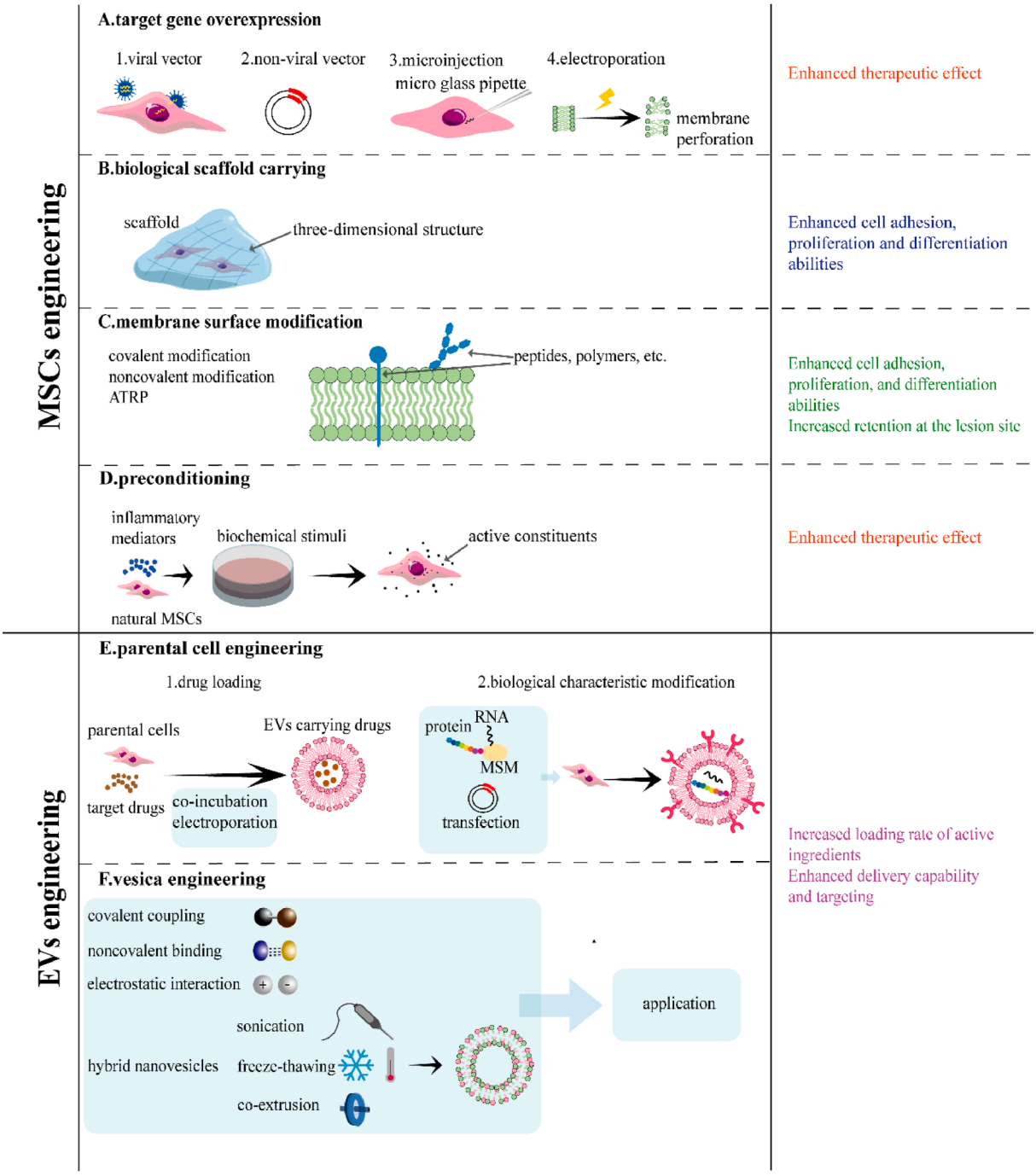

Fig. 1. Engineering methods for MSCs and EVs. MSCs: mesenchymal stem cells; EVs: Extracellular vesicles; ATRP: atom transfer radical polymerization; MSM: molecular sorting module.

MSCs and EVs, increasing the production of active substances and enhancing their anti-inflammatory effects.

3.1.2. Mast cell granules induction

Mast cells (MCs) are crucial effector cells in AD and play a significant role in allergic reactions. MCs become sensitized by IgE and are activated upon binding to allergen. Once activated, MCs secrete several molecules that trigger allergic responses, such as itching and Th2 inflammation. Since MCs contain various disease-triggering molecules and pro-inflammatory cytokines, MC particles have been considered for the pretreatment of MSCs. Notably, MSCs can inhibit MC degranulation and reduce TNF-α production and mast cell growth factor-mediated cell migration. However, following the induction of MC granules, MSCs exhibited increased secretion of COX2, which stimulated MSC growth via the COX2-PGE2 signaling pathway, enhancing their self-renewal and immunosuppressive properties. The pretreatment of MC particles enhanced the inhibitory effect of MSCs on both MCs and B cells. MSCs pretreated with MC particles significantly reduced IgE expression, accelerated skin lesion healing, and notably alleviated the clinical severity in AD mice [69]. MCs particle pretreatment operates similarly to Toll-like receptor 3 agonists, as both alter the biological properties of MSCs through inflammatory stimuli. Conversely, COX2, an inflammatory mediator whose secretion increases in MSCs after pretreatment with MC particles, is used to promote MSCs self-enhancement. Following this "self-reinforcement," MSCs effectively alleviate AD inflammation.

3.2. Genetic modifications

The strategies for genetic alteration of MSCs include changing DNA by viral transduction, nuclear transfer or transfection, gene editing techniques, and various other approaches to achieve the desired phenotype. Gene manipulation can improve the migration and homing ability of MSCs and enhance the paracrine effects [70–72].

Extracellular superoxide dismutase 3 (SOD3), an extracellular antioxidant enzyme, has been shown to regulate adaptive immune responses. MSCs genetically modified to overexpress SOD3 (SOD3-MSCs) can regulate immune cells, reduce proinflammatory mediators, and inhibit the expression and activation of the histamine H4 receptor (H4R). SOD3-MSCs also mitigate splenomegaly, lymphadenopathy, and levels of reactive oxygen species in the skin, while altering the composition of effector cells in the spleen and lymph nodes. Besides, they reduce the phosphorylation levels of signaling pathway molecules such as ERK1/2, p38, NF-κB, and JAK/STAT, alleviating inflammation associated with AD. Moreover, SOD3 interacts with H4R and the IL-4 receptor α to suppress the pathogenesis of AD, showing a stronger inhibition compared to native MSCs [73]. SOD3-MSCs cells overexpressing SOD3 preserved the migratory capacity of MSCs, enhanced the anti-inflammatory properties, and inhibited the Th cell differentiation and mast cell degranulation. The EVs derived from SOD3-MSCs retain the ability of MSC and deliver SOD3 to modulate immune cells and anti-fibrosis [74].

Some researchers found that the expression level of microRNA-147a (miR-147a) was significantly downregulated in both the serum and skin tissues of AD mice. Moreover, the expression of miR-147a was also negatively correlated with the level of vascular endothelial growth factor A (VEGFA) and TSLP in AD mice, suggesting a potential role in the pathogenesis of the condition. To investigate the therapeutic potential of MSC-Exos enriched with miR-147a in AD, miR-147a mimics were transfected into MSCs, resulting in a significant increase in miR-147a levels within Exos. Compared to Exos without transfection, those with miR-147a transfection significantly reduced the inflammatory response and apoptosis of HaCaT cells induced by TNF-α/IFN-γ and inhibited the angiogenesis of human umbilical vein endothelial cells (HUVEC). The transcription factor MEF2A acts as an activator of TLSP transcription during the progression of AD. miR-147a-overexpressing Exos directly target VEGFA and MEF2A-TSLP axis, suppressing pathological angiogenesis and inflammatory damage in AD through a direct binding relationship [75]. Gene overexpression not only has barely negative effects on the properties of MSCs but also enhances the functions of MSCs and EVs. Therefore, the genetic engineering better improves the therapeutic efficacy of MSCs and MSC-EVs in AD beyond their original capabilities.

3.3. Gel loading project

With their chemical, physical, and biological properties similar to the extracellular matrix in natural tissues, gels can provide a suitable environment for cells, regulate cell function, and support cell attachment, proliferation, and differentiation. The three-dimensional hierarchy of gels allows cells to accumulate and grow in their interior, promoting the secretion of cellular active factors, thus improving cell physiology. Moreover, gels have high elasticity, excellent biocompatibility and degradability, making it an effective carrier for MSCs and their secretions. Gels can address the issue of rapid clearance of MSC secretions by tissues, enabling controlled and sustained release of these secretions. Hydrogels are made from various natural and synthetic polymers, such as hyaluronic acid, alginate, and gelatin. These polymers have distinct chemical and physical properties, giving hydrogels diverse characteristics and applications. By selecting different composites, suitable hydrogels can be designed. For example, the design of appropriate gel thermal stability, biocompatibility, mechanical strength, etc., can meet the internal delivery of cells and their secretions, regulate cell physiological activities and secretion release [76,77].

Lee, H. et al. functionalized hyaluronic acid (HA) as HA-SH containing thiol groups to cross-link it under physiological conditions to form a three-dimensional HA-SH hydrogel structure. In vitro experiments on incubation of HA-SH hydrogel mixed with MSCs and in vivo experiments on treating mouse AD model using HA-SH hydrogel carrying MSCs (HA-SH/MSCs) all found that HA-SH hydrogel could significantly increase the release of anti-inflammatory cytokine TSG-6 in MSCs, demonstrating its immunomodulatory effect. HA-SH/MSCs can reduce epidermal thickness and mast cell infiltration in AD mice. They also significantly downregulate the inflammatory cytokines IL-13, CCL11, and CCL24. Researchers have found that HA-SH itself has anti-inflammatory effects that help regulate inflammation. Furthermore, HA-SH hydrogel as a carrier effectively improved the survival and retention rate of MSCs in damaged tissues compared with the injection of MSCs alone [78].

3.4. Fusion nanovesicles

Hybrid membrane nanovesicles (HMNVs) are formed by the fusion of homologous and heterologous membrane materials from two different cell types, either naturally secreted or artificially synthesized. The synthesis method includes co-extrusion, freeze-thaw method, ultrasonic method, co-incubation, microfluidic and other physical methods, as well as chemical induction method and chimera strategy. HMNVs combine the superior properties of two different sources of nanovesicles to display more abundant biological functions. The optimization of HMNVs encapsulated

biomolecules or surface cell membrane components through gene editing or chemical modification can demonstrate promising applications in disease diagnosis, imaging, and treatment [79].

Plant-derived nanovesicles (PDNVs) share similarities with mammalian cell-derived EVs, possessing potential for promoting cell growth, migration, and differentiation into various tissues, as well as biological activities such as immune regulation, microbiota modulation, antioxidation, and anti-aging. Additionally, their unique structure provides an optimal platform for drug encapsulation [80]. Huang, R. et al. loaded the poorly soluble CX5461 (a specific rRNA synthesis inhibitor with immunosuppressive effects) into grapefruit-derived nanovesicles (GEVs) via electroporation. These were then fused with CCR6 gene-overexpressing MSC-derived nanovesicles (CCR6-NVs) to create fusion nanovesicles, FV@CX5461. FV@CX5461 can compete with immune cells to bind the chemokine CCL20 to exert anti-inflammatory effects and demonstrates significant immunosuppressive and antioxidative properties. It was found that miR159a in GEVs is retained in FV@CX5461, potentially exerting a cross-species target gene regulatory effect on human cells. Since activated immune cells and excessive proliferation of keratinocytes contribute to AD skin lesions, the researchers first conducted in vitro experiments to verify the function of FV@CX5461. The results indicate that FV@CX5461 inhibits reactive oxygen species and the expression of inflammatory factors in HaCaT cells, promotes macrophage polarization toward the M2 phenotype, and suppresses PBMC proliferation and the migration of CCR6-expressing T cells. Additionally, it affects the T cell receptor pathway and the JAK/STAT pathway, thereby inhibiting T cell proliferation, activation, and the production of inflammatory cytokines. Subsequently, FV@CX5461's therapeutic effects were observed in a mouse AD model, revealing that FV@CX5461 reduced skin inflammatory cytokines and the proportion of $CD4^+$ T cells, while increasing the proportion of Treg cells, thereby effectively treating AD [81]. HMNVs, as a novel technology product, retain the biological characteristics of two different nanovesicles, and appropriately processing before the fusion of the two nanovesicles can maximize the therapeutic effect of both as far as possible. After the fusion of nanovesicles, the biological effects are also combined. Compared to the original nanovesicles, HMNVs offer more advantages in treating immune inflammation.

Different engineering techniques yield MSCs and EVs with distinct features, all aimed at enhancing the efficacy, targeting, or intra-tissue retention of MSCs and EVs (Table 2). Appropriate methods can be selected based on treatment needs and objectives.

In summary, the current preclinical research indicates that natural and engineered MSCs and MSC-EVs can alleviate AD immune inflammation and repair the skin barrier. For natural MSCs and MSC-EVs, they can secrete bioactive substances that inhibit barrier damage caused by SA colonization, suppress neural cell activation, neuroimmune receptors, pruritus-related cytokines, and pruritus signaling pathways, thereby blocking the itch-scratch cycle. They also enhance the expression of barrier-protective genes, proteins, and lipids to facilitate barrier repair. Their regulation of immune inflammation occurs through direct actions or the secretion of active components such as IL-10, PGE2, TGF-β, EGF, and IDO, which modulate T cell proliferation, apoptosis, and differentiation, inhibit mast cell and macrophage inflammatory activation, reduce the infiltration of inflammatory cells into the skin, adjust cytokine levels, and weaken the signal activation of ERK, JAK/STAT, NF-κB and other pathways. These processes restore immune inflammation. For engineered MSCs and EVs, almost all engineering methods enhance the secretion of active regulatory components from MSCs. However, the substances secreted and the biological characteristics of MSCs and EVs differ depending on the engineering method used. Nevertheless, the immune regulatory functions of modified MSCs and EVs are enhanced, similarly reducing the activation of ERK, JAK/STAT, and NF-κB pathways (Fig. 2).

4. Advances in clinical research on MSCs and MSC-EVs for AD

A clinical trial investigated the safety and efficacy of human umbilical cord blood MSCs in treating moderate to severe AD over a 12-week period. The study recruited 34 adult patients, randomly assigning them to receive either low-dose (2.5×10^7 cell) or high-dose (5.0×10^7 cell) subcutaneous MSC injections. Among participants receiving low or high doses of MSCs, the proportion of those with more than a 50 % decrease in the eczema area and severity index (EASI) and the scoring atopic dermatitis index (SCORAD) was 33.3 % and 66.7 %, respectively, indicating a dose-dependent effect. At week 12, although the investigator's global assessment (IGA) showed less reduction compared to EASI and SCORAD scores, both dosing groups exhibited significant decreases compared to baseline IGA scores. MSCs at all doses reduced serum total IgE levels and blood eosinophil counts. No serious adverse events were reported. Most adverse events were local reactions at the injection site, such as nodule, bruising, erythema, or pain, and some cases of skin infections and gastrointestinal diseases, but all were transient and of mild severity [82]. In another clinical trial, the long-term efficacy and safety of intravenous injection of bone marrow-derived MSCs were evaluated in 5 AD patients. Results showed significant improvements in body surface area (BSA), EASI, SCORAD, and IGA scores approximately 16 weeks later. Eighty percent of these patients achieved a EASI 50 response after one or two courses of treatment. In addition, eosinophil counts and eosinophil cationic protein decreased, though not significantly. During the subsequent 16–86 weeks of follow-up, three participants maintained EASI 50 response for over 84 weeks, while two others experienced symptom exacerbation and used additional systemic medications, leading to discontinuation of the study. No severe adverse events, including local inflammatory reactions, severe allergic reactions, or vascular obstruction, were reported. Due to the small sample size, larger-scale clinical trials are needed to confirm long-term efficacy and safety [83]. Recently, a research team conducted a Phase I/II clinical trial to evaluate the safety and efficacy of human bone marrow-derived MSCs in adults with moderate to severe AD. In the Phase I trial, 20 subjects were randomly assigned to receive an intravenous infusion of either a high dose (1×10^6 cells/kg) or a low dose (5×10^5 cells/kg) of MSCs. Since no significant difference was observed between the two dose groups, the low dose was selected for the Phase II trial. The Phase II trial was a randomized, double-blind, placebo-controlled study involving 72 subjects, who received three weekly intravenous infusions of 5×10^5 cells/kg MSCs. At weeks 12 and 24, the EASI 50 and EASI 90 response rates were significantly higher in the MSC-treated group compared to the placebo group. Additionally, at weeks 16 and 24, the proportion of patients achieving IGA 0/1 was significantly greater in the MSC group than in the control group. Most adverse events in this trial were mild to moderate and resolved by the end of the study. The most commonly reported side effects included herpetic ophthalmitis, rash, and upper respiratory tract infections [84].

A previous study of 28 AD patients has shown that the cream containing human umbilical cord blood-derived MSCs culture medium (MSCs-CM) could improve the skin barrier, as evidenced by significant improvements in skin hydration and transepidermal water loss (TEWL) at both lesional and non-lesional sites [85]. Skin sensitivity and skin barrier function have been implicated in many skin diseases, including AD. Researchers explored the safety and

Table 2
Roles of engineered-MSCs and MSC-EVs in AD.

Classification of Engineering Strategies	Processing method	Effects of engineered-MSCs and MSC-EVs	Advantages	References
Inducing with inflammatory mediators	Ploy I:C primed	Modifying the gene expression profile of MSCs. Regulating Th2 and Th17 immunity. The protein content of EVs is regulated.	Improving the loading rate of active ingredients.	[65,68]
	IFN-γ primed	Altering the gene expression profile of MSCs. Regulating Th17 immunity. Increased expression of IDO. The transcriptional profile of iMSCs and the protein composition of EVs have significantly changed.	Improving the loading rate of active ingredients.	[65–67]
	Mast cell granule induction	Increased expression level of COX2.	Improving the loading rate of active ingredients.	[69]
Genetic manipulation	SOD3 transduction	Increased expression and secretion of SOD3.	Improving the loading rate of active ingredients.	[73,74]
	MiR-147a transduction	Increased expression of miR-147a.	Improving the loading rate of active ingredients.	[75]
Gel loading technology	HA-SH Hydrogel	Increased release of TSG-6, survival rate increases.	Increasing the retention of lesion site.	[78]
Fusion nanovesicles	CX5461 loaded into GEV,Chronic viral infection of GMSCs, Coextrusion facilitates the fusion of nanocapsules	Conferring immunomodulatory, anti-inflammatory and antioxidant functions, as well as the ability to target CCL20	Improving the targeting and active ingredient loading rate.	[81]

MSCs: mesenchymal stem cell; EVs: extracellular vesicles; AD: atopic dermatitis; IFN-γ: interferon-gamma; SOD3: superoxide dismutase 3, extracellular; HA-SH: hyaluronic acid-thiol; GEV: grapefruit-derived exosome-like nanovesicles; GMSCs: Gingiva-derived mesenchymal stem cells; Th: helper T; IDO: indoleamine 2,3-dioxygenase; COX2: cyclooxygenase-2; TSG-6: tumor necrosis factor-inducible gene 6 protein; CCL20: chemokine (C–C motif) ligand 20.

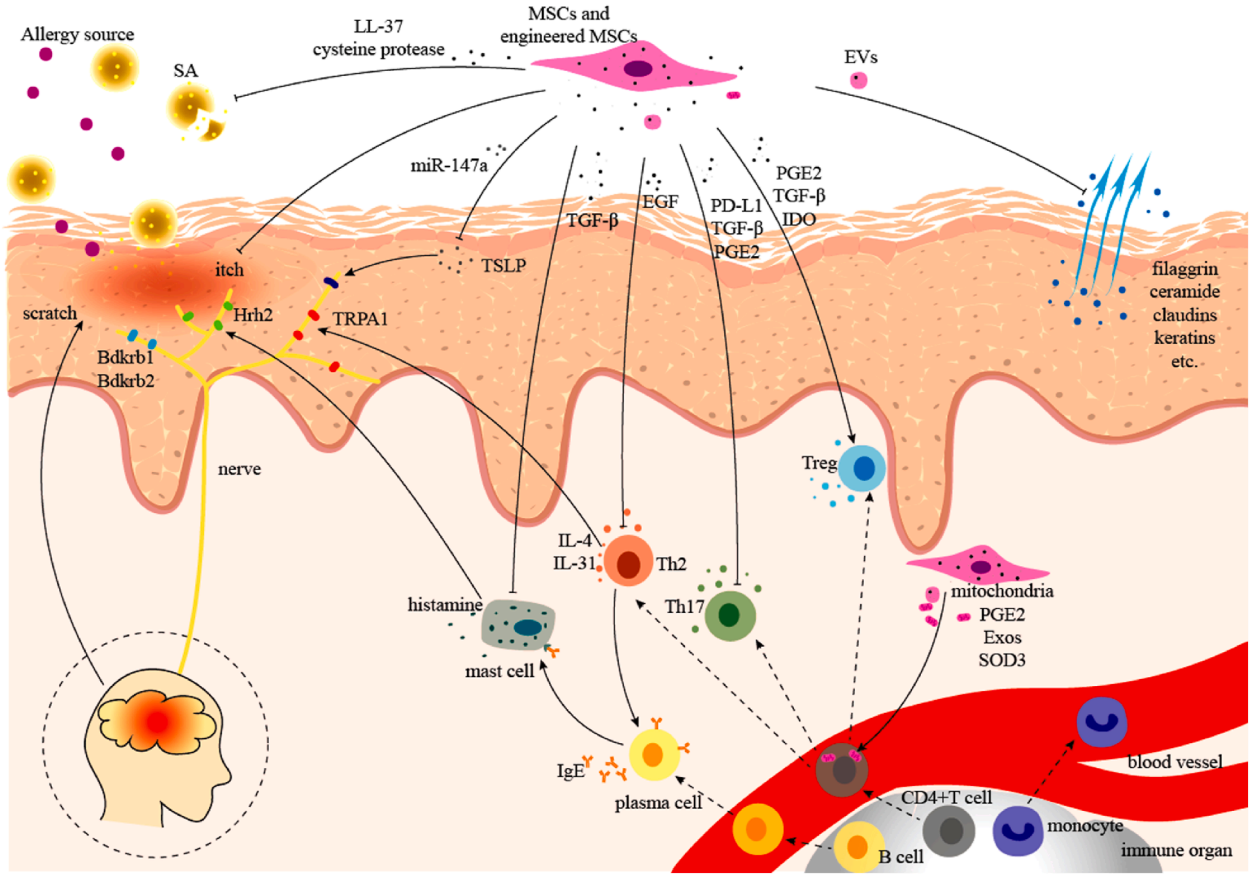

Fig. 2. Effects and molecular mechanisms of natural- and engineered-MSCs and MSC-EVs in regulating AD. SA: staphylococcus aureus; LL-37: antibacterial protein LL-37; MSCs: mesenchymal stem cell; miR-147a: microRNA-147a; TSLP: thymic stromal lymphopoietin; TGF-β: transforming growth factor-β; EGF: epidermal growth factor; PD-L1: programmed death-ligand 1; PGE2: prostaglandin E2; IDO: indoleamine 2,3-dioxygenase; IL: interleukin; EVs: Extracellular vesicles; TRPA1: transient receptor potential A1; Hrh2: histamine receptor H2; Bdkrb1/2: bradykinin receptor B1/2; Th: helper T; Treg: regulatory T; M1/2: macrophages M1/2; IgE: immunoglobulin E; Exos: exosomes; SOD3: superoxide dismutase 3,extracellular.

Table 3
Current status of clinical research on MSCs and MSC-EVs for the treatment of AD.

Number of participants	Source of MSCs/MSC-EVs	Administration route	Treatment duration	Therapeutic effects	Adverse reactions	References
34	Umbilical cord blood MSCs	Subcutaneous injection	12 weeks	Significant reduction in EASI and SCORAD scores; decreased serum IgE levels and peripheral blood eosinophil counts	Transient mild lesions, skin pain, infections, gastrointestinal disorders	[82]
5	Bone marrow MSCs	Intravenous injection	16 weeks	Significant improvement in BSA, EASI, SCORAD, and IGA scores	No severe adverse events	[83]
72	Bone marrow MSCs	Intravenous infusion	24 weeks	Significant improvement in EASI and IGA scores compared to control group	Herpetic keratitis, rash, and respiratory infections	[84]
28	Umbilical cord blood MSC-Exos	Topical emulsion	4 weeks	Significant improvement in skin hydration and TEWL	Not reported	[85]
22	Umbilical cord MSC-Exos	Topical liquid application	28 days	Significant decrease in dryness scores, objective and subjective symptoms; Significant decrease in improvement index and skin a* values.; Significant decrease in lactic acid tingling test score and significant decrease in skin sebum level	No adverse events	[86]

MSCs: mesenchymal stem cell; MSC-Exos: MSC-derived exosomes; EASI: eczema area and severity index; SCORAD: scoring atopic dermatitis index; IgE: Immunoglobulin E; BSA: body surface area; IGA: investigator's global assessment; TEWL: transepidermal water loss.

efficacy of topical treatment with MSC-Exos for sensitive skin. Twenty-two women diagnosed with sensitive skin (scoring $\geq$3 on a 5 % lactic acid sting test, experiencing repeated dryness, stinging, burning, itching, or other discomforts) were enrolled in the study. Patients apply 1 mL of MSC-Exos fluid derived from umbilical wharton glue twice daily to the face. Patient symptoms and improvement indices were assessed before product use and at day 7,14 and 28 after product use. Among the 20 patients who completed the follow-up, dryness scores, objective symptoms (including roughness, scaling, erythema), and subjective symptoms (including tightness, burning, or itching) significantly decreased. The improvement index and skin a* values (measuring product efficacy on sensitive skin) were markedly reduced. Lactic acid sting test scores decreased significantly compared to baseline, skin sebum levels were notably reduced, and the percentage of participants with a very satisfactory score exceeded 75 %. Although no significant differences were found in skin TEWL and hydration compared to baseline, a gradual decrease in TEWL and an increase in hydration were observed over time with continued use of the product [86]. MSCs and MSC-EVs have shown promise in improving AD symptoms and clinical scores in clinical studies, with optimistic response rates (Table 3). However, variations in MSCs and EVs administration methods across studies highlight the need for further research to validate and standardize their clinical applications.

5. Conclusion

AD usually presents as chronic and recurrent, requiring long-term treatment to alleviate clinical symptoms. Traditional anti-inflammatory drugs for treating AD are topical and systemic corticosteroids, immunosuppressants, and local calcineurin inhibitors [87]. Long-term use of these medications can result in adverse effects, including skin atrophy, liver and kidney damage, and an increased risk of infection [88]. Currently, several biological agents and janus kinase (JAK) inhibitors have been approved to treat AD, targeting specific inflammatory cytokine receptors and pathways. Local JAK inhibitors, phosphodiesterase-4 (PDE-4) inhibitors, and other novel topical drugs have emerged [89]. These treatments provide a relatively high response rate and long-term benefits, particularly for patients with moderately severe AD. However, these novel targeted therapies, when used alone, only address specific inflammatory factor receptors or signaling pathways (such as blocking IL-4 receptors, IL-13 receptors, IgE receptors, or the JAK/STAT pathway). The pathogenesis of AD involves numerous inflammatory factors and pathways. Given the complexity of the inflammatory response network, these new therapies cannot comprehensively resolve these issues [89–91].

In recent years, MSCs and MSC-EVs have attracted significant attention for their potential applications in the treatment of AD. Firstly, MSCs have been shown to promote the repair of damaged skin barriers by combating or reducing inflammation caused by infections, regulating the expression of barrier proteins and lipids, and secreting growth factors and cytokines [19,21,26,27,92,93]. Additionally, MSCs exert their immune-regulatory effects by suppressing the activity of inflammatory cells and the production of inflammatory mediators, and by promoting the generation of regulatory T cells [94,95], thus alleviating the abnormal immune responses observed in AD. MSCs interact with immune cells through cell-to-cell contact or by secreting bioactive molecules. Among these interactions, MSC-EVs are effective mediators of intercellular communication, which can deliver bioactive molecules to the target cells and regulate their functions [64]. EVs carry proteins, nucleic acids, and lipids, which contribute to their ability

to regulate immune responses and promote tissue repair in AD. Compared to MSCs, EVs have very low immunogenicity, higher concentrations of active components, efficient biological barrier penetration, do not accumulate in highly vascularized areas, and are easier to store and quality control [33,95]. To enhance therapeutic effects, researchers have started engineering MSCs and MSC-EVs, such as increasing the expression of specific therapeutic molecules through gene editing technologies, improving their biocompatibility and targeting capabilities through surface modification techniques, extending cell survival and function through gel loading, and activating MSCs using various pretreatment methods [56,64]. Currently, the experiments on engineered MSCs and MSC-EVs for AD treatment are still in the preliminary stages, with many issues yet to be explored: (1) More research is needed to confirm their safety and efficacy. (2) Maintaining the biological characteristics and functions of MSCs and MSC-EVs during large-scale engineered production is an urgent issue to address. (3) Developing unified quality control standards and regulatory frameworks in the future is also crucial for advancing the clinical application of engineered stem cell therapies.

From the perspective of the skin microbiome, the diversity of symbiotic microorganisms can maintain a normal skin microenvironment, with some microorganisms secreting SA growth inhibitors. Increasing skin microbiome diversity and reducing pathogenic SA colonization are considered promising therapeutic approaches [13,96–98]. The antimicrobial effects of MSCs and MSC-EVs are well-established, and it is worth exploring whether they can complement new AD drugs to achieve better antimicrobial treatment outcomes. Additionally, one study found that MSCs were more effective than the JAK inhibitor Oclacitinib in improving symptoms and enhancing clinical scores, significantly reducing epidermal thickness, mast cell infiltration and degranulation, and inflammation factor expression, and demonstrating stronger immunomodulatory effects. MSCs showed greater efficacy in local wound repair without side effects, indicating superior effectiveness [40]. MSCs and MSC-EVs may offer a more comprehensive therapeutic effect, impacting multiple pathological processes of AD. In contrast, biologics and small-molecule drugs target only a few key disease pathways, but their production processes are relatively mature, with strict quality control standards and easier large-scale production. Although MSCs, MSC-EVs and new drugs each have advantages in AD treatment, there are not simple antagonistic relationships between them. Future research may explore the synergistic effects between these treatments to provide more comprehensive and personalized treatment options. It is also important to note that some drugs combined with MSCs might reduce the efficacy of MSCs. Researchers have found that Pimecrolimus, a commonly used drug for AD, can block the therapeutic potential of MSCs when used in combination. The main mechanism is through the inhibition of the nuclear translocation of the COX2 transcription factor NFAT3 in MSCs, which downregulates the COX2-PGE2 axis, thereby suppressing COX2 expression and reducing PGE2 production, impacting the immunomodulatory function of MSCs [99]. This indicates that combination therapies are not simply additive, and standardized clinical combination protocols for MSCs and other drugs still have a long way to go.

Despite their vast potential, MSCs and MSC-EVs also have limitations that must be considered. MSCs-based therapies face challenges such as low cell survival rates, low engraftment rates, and potential tumorigenicity. Research has demonstrated that MSCs exhibit significant tumor tropism and can promote tumor growth in vivo. After prolonged exposure to tumor-conditioned medium, MSCs form a cancer-associated fibroblast (CAFs) -like phenotype and produce growth factors, cytokines, and chemokines to promote tumor progression. TNF-α -activated MSCs can promote tumor growth and tumor metastasis through the recruitment of $CXCR2^{+}$ neutrophils [95]. Both normal MSCs and cancer tissue-derived MSCs can direct T lymphocytes to specific regulatory phenotypes that may support immune evasion and tumor growth [100]. We had to consider the risk of MSCs leading to occurrence and accelerated tumor development under certain conditions. EV-based cell-free therapy can address the tumorigenic concerns associated with MSCs; however, the cargo capacity and efficacy of EVs vary depending on their source. Large-scale production and standardization continue to be major obstacles to clinical translation. Additionally, the lack of standardized protocols for the isolation, characterization, and management of MSCs and MSC-EVs further complicates their therapeutic application in AD.

In conclusion, current research highlights the therapeutic potential of MSCs and MSC-EVs in AD but also underscores the need to address their limitations and develop more effective strategies to harness their beneficial effects.

6. Summary and outlook

MSCs and MSC-EVs exhibit distinct abilities in promoting barrier repair and regulating immune responses in AD. The regenerative and immunomodulatory properties of MSCs and MSC-EVs provide a potential avenue for developing innovative treatments for AD. Currently, MSCs and MSC-EVs have undergone clinical trials; however, the limitations in large-scale and standardized production have, to some extent, restricted their further clinical applications. This highlights the necessity of addressing these challenges to fully realize their therapeutic potential. With advancements in the field of bioengineering, future research should focus on optimizing the properties of MSCs and MSC-EVs, overcoming their limitations, and establishing standardized protocols to maximize their efficacy and safety in the treatment of AD. Further exploration of the mechanisms underlying MSC- and MSC-EV-based therapies for AD, combined with a series of bioengineering approaches to facilitate their clinical application, holds promise for advancing new therapeutic strategies for AD and addressing the limitations of existing treatments.

Authors' contributions

TTR: Writing-Original Draft, Visualization, Data curation, Formal analysis, Writing-Review and Editing;

KH: Writing-Original Draft, Data curation, Writing-review and editing;

DHX: Funding acquisition, Writing-Review and Editing;

YXK: Data curation, Writing-Review and Editing;

SYJ: Data curation, Writing-Review and Editing;

JJC: Writing-Review and Editing;

YS: Writing-Review and Editing.

JZ: Conceptualization, Funding acquisition, Writing-Review and Editing.

ZHW: Conceptualization, Supervision, Funding acquisition, Writing-Review and Editing;

Each author have approved the submitted version.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Mortz CG, Andersen KE, Dellgren C, Barington T, Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. Allergy 2015;70(7):836–45. https://doi.org/10.1111/all.12619.
[2] Bylund S, Kobyletzki LB, Svalstedt M, Svensson A. Prevalence and incidence of atopic dermatitis: a systematic review. Acta Derm Venereol 2020;100(12):adv00160. https://doi.org/10.2340/00015555-3510.
[3] Tian J, Zhang D, Yang Y, Huang Y, Wang L, Yao X, et al. Global epidemiology of atopic dermatitis: a comprehensive systematic analysis and modelling study. Br J Dermatol 2023;190(1):55–61. https://doi.org/10.1093/bjd/ljad339.
[4] Duarte B, Mendes-Bastos P, Antunes J, Azevedo F, Gonçalo M, Henrique M, et al. The apolo study: a cross-sectional analysis of disease characteristics and patient burden in moderate-to-severe atopic dermatitis in Portugal. Dermatol Ther 2025. https://doi.org/10.1007/s13555-025-01347-9.
[5] Sroka-Tomaszewska J, Trzeciak M. Molecular mechanisms of atopic dermatitis pathogenesis. Int J Mol Sci 2021;22(8). https://doi.org/10.3390/ijms22084130.
[6] Maqsood M, Kang M, Wu X, Chen J, Teng L, Qiu L. Adult mesenchymal stem cells and their exosomes: sources, characteristics, and application in regenerative medicine. Life Sci 2020;256:118002. https://doi.org/10.1016/j.lfs.2020.118002.
[7] Margiana R, Markov A, Zekiy AO, Hamza MU, Al-Dabbagh KA, Al-Zubaidi SH, et al. Clinical application of mesenchymal stem cell in regenerative medicine: a narrative review. Stem Cell Res Ther 2022;13(1):366. https://doi.org/10.1186/s13287-022-03054-0.
[8] Kim KH, Blasco-Morente G, Cuende N, Arias-Santiago S. Mesenchymal stromal cells: properties and role in management of cutaneous diseases. J Eur Acad Dermatol Venereol 2017;31(3):414–23. https://doi.org/10.1111/jdv.13934.
[9] Harrell CR, Fellabaum C, Jovicic N, Djonov V, Arsenijevic N, Volarevic V. Molecular mechanisms responsible for therapeutic potential of mesenchymal stem cell-derived secretome. Cells 2019;8(5). https://doi.org/10.3390/cells8050467.
[10] Zhou T, Yuan Z, Weng J, Pei D, Du X, He C, et al. Challenges and advances in clinical applications of mesenchymal stromal cells. J Hematol Oncol 2021;14(1):24. https://doi.org/10.1186/s13045-021-01037-x.
[11] Yi E, Go J, Yun SH, Lee SE, Kwak J, Kim SW, et al. CEACAM1-engineered MSCs have a broad spectrum of immunomodulatory functions and therapeutic potential via cell-to-cell interaction. Biomaterials 2024;311:122667. https://doi.org/10.1016/j.biomaterials.2024.122667.
[12] Yin T, Liu Y, Ji W, Zhuang J, Chen X, Gong B, et al. Engineered mesenchymal stem cell-derived extracellular vesicles: a state-of-the-art multifunctional weapon against Alzheimer's disease. Theranostics 2023;13(4):1264–85. https://doi.org/10.7150/thno.81860.
[13] Demessant-Flavigny AL, Connétable S, Kerob D, Moreau M, Aguilar L, Wollenberg A. Skin microbiome dysbiosis and the role of Staphylococcus aureus in atopic dermatitis in adults and children: a narrative review. J Eur Acad Dermatol Venereol 2023;37(Suppl 5):3–17. https://doi.org/10.1111/jdv.19125.
[14] Geoghegan JA, Irvine AD, Foster TJ. Staphylococcus aureus and atopic dermatitis: a complex and evolving relationship. Trends Microbiol 2018;26(6):484–97. https://doi.org/10.1016/j.tim.2017.11.008.
[15] Seiti Yamada Yoshikawa F, Feitosa de Lima J, Notomi Sato M, Álefe Leuzzi Ramos Y, Aoki V, Leao Orfali R. Exploring the role of Staphylococcus aureus toxins in atopic dermatitis. Toxins 2019;11(6). https://doi.org/10.3390/toxins11060321.
[16] Yagi H, Chen AF, Hirsch D, Rothenberg AC, Tan J, Alexander PG, et al. Antimicrobial activity of mesenchymal stem cells against Staphylococcus aureus. Stem Cell Res Ther 2020;11(1):293. https://doi.org/10.1186/s13287-020-01807-3.
[17] Bujňáková D, Čuvalová A, Čížek M, Humenik F, Salzet M, Čížková D. Canine bone marrow mesenchymal stem cell conditioned media affect bacterial growth, biofilm-associated Staphylococcus aureus and AHL-dependent quorum sensing. Microorganisms 2020;8(10). https://doi.org/10.3390/microorganisms8101478.
[18] Marx C, Gardner S, Harman RM, Van de Walle GR. The mesenchymal stromal cell secretome impairs methicillin-resistant Staphylococcus aureus biofilms via cysteine protease activity in the equine model. Stem Cells Transl Med 2020;9(7):746–57. https://doi.org/10.1002/sctm.19-0333.
[19] Hua C, Liang Q, Chen S, Zhu J, Tang Y, Chen X, et al. Human umbilical cord mesenchymal stem cell treatment alleviates symptoms in an atopic dermatitis-like mouse model. Stem Cell Res Ther 2023;14(1):147. https://doi.org/10.1186/s13287-023-03365-w.
[20] Beck LA, Cork MJ, Amagai M, De Benedetto A, Kabashima K, Hamilton JD, et al. Type 2 inflammation contributes to skin barrier dysfunction in atopic dermatitis. JID Innov 2022;2(5):100131. https://doi.org/10.1016/j.xjidi.2022.100131.
[21] Shin KO, Ha DH, Kim JO, Crumrine DA, Meyer JM, Wakefield JS, et al. Exosomes from Human Adipose Tissue-Derived Mesenchymal Stem Cells Promote Epidermal Barrier Repair by Inducing de Novo Synthesis of Ceramides in Atopic Dermatitis. Cells 2020;9(3). https://doi.org/10.3390/cells9030680.
[22] Fei W, Wu J, Gao M, Wang Q, Zhao YY, Shan C, et al. Multilineage-differentiating stress-enduring cells alleviate atopic dermatitis-associated behaviors in mice. Stem Cell Res Ther 2021;12(1):606. https://doi.org/10.1186/s13287-021-02671-5.
[23] Margolis DJ. Atopic dermatitis: filaggrin and skin barrier dysfunction. Br J Dermatol 2022;186(3):396. https://doi.org/10.1111/bjd.20946.
[24] Pontikas A, Antonatos C, Evangelou E, Vasilopoulos Y. Candidate gene association studies in atopic dermatitis in participants of European and asian ancestry: a systematic review and meta-analysis. Genes 2023;14(7). https://doi.org/10.3390/genes14071456.
[25] Wang X, Wang Q, Yin P, Liang C, Zhao X, Wen D, et al. Secretome of human umbilical cord mesenchymal stem cell maintains skin homeostasis by regulating multiple skin physiological function. Cell Tissue Res 2023;391(1):111–25. https://doi.org/10.1007/s00441-022-03697-8.
[26] Kang SJ, Gu NY, Byeon JS, Hyun BH, Lee J, Yang DK. Immunomodulatory effects of canine mesenchymal stem cells in an experimental atopic dermatitis model. Front Vet Sci 2023;10:1201382. https://doi.org/10.3389/fvets.2023.1201382.
[27] Kim SY, Yoon TH, Na J, Yi SJ, Jin Y, Kim M, et al. Mesenchymal stem cells and extracellular vesicles derived from canine adipose tissue ameliorates inflammation, skin barrier function and pruritus by reducing JAK/STAT signaling in atopic dermatitis. Int J Mol Sci 2022;23(9). https://doi.org/10.3390/ijms23094868.
[28] de Oliveira Ramos F, Malard PF, Brunel Hdss, Paludo GR, de Castro MB, da Silva PHS, et al. Canine atopic dermatitis attenuated by mesenchymal stem cells. J Adv Vet Anim Res 2020;7(3):554–65. https://doi.org/10.5455/javar.2020.g453.
[29] Cho BS, Kim SB, Kim S, Rhee B, Yoon J, Lee JW. Canine mesenchymal-stem-cell-derived extracellular vesicles attenuate atopic dermatitis. Animals (Basel) 2023;13(13). https://doi.org/10.3390/ani13132215.
[30] Baker P, Huang C, Radi R, Moll SB, Jules E, Arbiser JL. Skin barrier function: the interplay of physical, chemical, and immunologic properties. Cells 2023;12(23). https://doi.org/10.3390/cells12232745.
[31] Yamaguchi HL, Yamaguchi Y, Peeva E. Role of innate immunity in allergic contact dermatitis: an update. Int J Mol Sci 2023;24(16). https://doi.org/10.3390/ijms241612975.
[32] Gittler JK, Shemer A, Suárez-Fariñas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol 2012;130(6):1344–54. https://doi.org/10.1016/j.jaci.2012.07.012.
[33] Peng YQ, Deng XH, Xu ZB, Wu ZC, Fu QL. Mesenchymal stromal cells and their small extracellular vesicles in allergic diseases: from immunomodulation to therapy. Eur J Immunol 2023;53(10):e2149510. https://doi.org/10.1002/eji.202149510.
[34] Xiong H, Yang J, Liu T, Liu G, Han Y, Dong X. Stem cells from human exfoliated deciduous teeth attenuate atopic dermatitis symptoms in mice through modulating immune balance and skin barrier function. Mediat Inflamm 2022;2022:6206883. https://doi.org/10.1155/2022/6206883.
[35] Song JY, Kang HJ, Ju HM, Park A, Park H, Hong JS, et al. Umbilical cord-derived mesenchymal stem cell extracts ameliorate atopic dermatitis in mice by reducing the T cell responses. Sci Rep 2019;9(1):6623. https://doi.org/10.1038/s41598-019-42964-7.
[36] Cho BS, Kim JO, Ha DH, Yi YW. Exosomes derived from human adipose tissue-derived mesenchymal stem cells alleviate atopic dermatitis. Stem Cell Res Ther 2018;9(1):187. https://doi.org/10.1186/s13287-018-0939-5.
[37] Guan J, Li Y, Lu F, Feng J. Adipose-derived stem cells ameliorate atopic dermatitis by suppressing the IL-17 expression of Th17 cells in an ovalbumin-induced mouse model. Stem Cell Res Ther 2022;13(1):98. https://doi.org/10.1186/s13287-022-02774-7.
[38] Park HH, Lee S, Yu Y, Yoo SM, Baek SY, Jung N, et al. TGF-β secreted by human umbilical cord blood-derived mesenchymal stem cells ameliorates atopic dermatitis by inhibiting secretion of TNF-α and IgE. Stem Cell 2020;38(7):904–16. https://doi.org/10.1002/stem.3183.
[39] Kim M, Lee SH, Kim Y, Kwon Y, Park Y, Lee HK, et al. Human adipose tissue-derived mesenchymal stem cells attenuate atopic dermatitis by regulating the expression of MIP-2, miR-122a-SOCS1 Axis, and Th1/Th2 responses. Front Pharmacol 2018;9:1175. https://doi.org/10.3389/fphar.2018.01175.
[40] Kim MS, Kong D, Han M, Roh K, Koo H, Lee S, et al. Canine amniotic membrane-derived mesenchymal stem cells ameliorate atopic dermatitis through regeneration and immunomodulation. Vet Res Commun 2023;47(4):2055–70. https://doi.org/10.1007/s11259-023-10155-5.

[41] Jung H, Son GM, Lee JJ, Park HS. Therapeutic effects of tonsil-derived mesenchymal stem cells in an atopic dermatitis mouse model. In Vivo. (Athens) 2021;35(2):845–57. https://doi.org/10.21873/invivo.12325.
[42] Zibandeh N, Genc D, Ozgen Z, Duran Y, Goker K, Baris S, et al. Mesenchymal stem cells derived from human dental follicle modulate the aberrant immune response in atopic dermatitis. Immunotherapy 2021;13(10):825–40. https://doi.org/10.2217/imt-2020-0257.
[43] Jung N, Kong T, Yu Y, Park H, Lee E, Yoo S, et al. Immunomodulatory effect of epidermal growth factor secreted by human umbilical cord blood-derived mesenchymal stem cells on atopic dermatitis. Int J Stem Cells 2022;15(3): 311–23. https://doi.org/10.15283/ijsc21173.
[44] Zhai Z, Cui T, Chen J, Mao X, Zhang T. Advancements in engineered mesenchymal stem cell exosomes for chronic lung disease treatment. J Transl Med 2023;21(1):895. https://doi.org/10.1186/s12967-023-04729-9.
[45] Zhou Z, Liu D. Mesenchymal stem cell-seeded porous tantalum-based biomaterial: a promising choice for promoting bone regeneration. Colloids Surf B Biointerfaces 2022;215:112491. https://doi.org/10.1016/j.colsurfb.2022.112491.
[46] Ji ST, Kim H, Yun J, Chung JS, Kwon SM. Promising therapeutic strategies for mesenchymal stem cell-based cardiovascular regeneration: from cell priming to tissue engineering. Stem Cell Int 2017;2017:3945403. https://doi.org/10.1155/2017/3945403.
[47] de Abreu RC, Fernandes H, da Costa Martins PA, Sahoo S, Emanueli C, Ferreira L. Native and bioengineered extracellular vesicles for cardiovascular therapeutics. Nat Rev Cardiol 2020;17(11):685–97. https://doi.org/10.1038/s41569-020-0389-5.
[48] Sun Z, Zhang J, Li J, Li M, Ge J, Wu P, et al. Roles of mesenchymal stem cell-derived exosomes in cancer development and targeted therapy. Stem Cell Int 2021;2021:9962194. https://doi.org/10.1155/2021/9962194.
[49] Ma X, Liu B, Fan L, Liu Y, Zhao Y, Ren T, et al. Native and engineered exosomes for inflammatory disease. Nano Res 2023;16(5):6991–7006. https://doi.org/10.1007/s12274-022-5275-5.
[50] Han H, Chen BT, Liu Y, Wang Y, Xing L, Wang H, et al. Engineered stem cell-based strategy: a new paradigm of next-generation stem cell product in regenerative medicine. J Contr Release 2024;365:981–1003. https://doi.org/10.1016/j.jconrel.2023.12.024.
[51] Keshavarz Shahbaz S, Mansourabadi AH, Jafari D. Genetically engineered mesenchymal stromal cells as a new trend for treatment of severe acute graft-versus-host disease. Clin Exp Immunol 2022;208(1):12–24. https://doi.org/10.1093/cei/uxac016.
[52] Li M, Hu X, Liu X, Zhao L, Zhao W, Li Y, et al. 3D bioprinted piezoelectric hydrogel synergized with LIPUS to promote bone regeneration. Mater Today Bio 2025;31:101604. https://doi.org/10.1016/j.mtbio.2025.101604.
[53] Li W, Shi X, Zhang D, Hu J, Zhao S, Ye S, et al. Adipose derived mesenchymal stem cell-seeded regenerated silk fibroin scaffolds reverse liver fibrosis in mice. J Mater Chem B 2025. https://doi.org/10.1039/d5tb00275c.
[54] Yuan J, Li M, He X, Hou Q, Fu X, Hao J. A thermally stable bioactive chitosan scaffold with pH-responsive exosome adsorption and release function promotes wound healing. Int J Biol Macromol 2025;306(Pt 3):141552. https://doi.org/10.1016/j.ijbiomac.2025.141552.
[55] Deng M, Xie P, Xue H, Chen Q, Zhou Y, Ming J, et al. Decellularized tissue matrices hydrogels functionalized with extracellular vesicles promote macrophage reprogramming and neural stem cell differentiation for spinal cord injury repair. J Nanobiotechnol 2025;23(1):139. https://doi.org/10.1186/s12951-025-03152-0.
[56] Zhu X, Ma D, Yang B, An Q, Zhao J, Gao X, et al. Research progress of engineered mesenchymal stem cells and their derived exosomes and their application in autoimmune/inflammatory diseases. Stem Cell Res Ther 2023;14(1):71. https://doi.org/10.1186/s13287-023-03295-7.
[57] English K, Barry FP, Field-Corbett CP, Mahon BP. IFN-gamma and TNF-alpha differentially regulate immunomodulation by murine mesenchymal stem cells. Immunol Lett 2007;110(2):91–100. https://doi.org/10.1016/j.imlet.2007.04.001.
[58] Krampera M, Cosmi L, Angeli R, Pasini A, Liotta F, Andreini A, et al. Role for interferon-gamma in the immunomodulatory activity of human bone marrow mesenchymal stem cells. Stem Cell 2006;24(2):386–98. https://doi.org/10.1634/stemcells.2005-0008.
[59] Prasanna SJ, Gopalakrishnan D, Shankar SR, Vasandan AB. Pro-inflammatory cytokines, IFNgamma and TNFalpha, influence immune properties of human bone marrow and Wharton jelly mesenchymal stem cells differentially. PLoS One 2010;5(2):e9016. https://doi.org/10.1371/journal.pone.0009016.
[60] Mondal J, Pillarisetti S, Junnuthula V, Saha M, Hwang SR, Park IK, et al. Hybrid exosomes, exosome-like nanovesicles and engineered exosomes for therapeutic applications. J Contr Release 2023;353:1127–49. https://doi.org/10.1016/j.jconrel.2022.12.027.
[61] Chen SY, Chen YL, Li PC, Cheng TS, Chu YS, Shen YS, et al. Engineered extracellular vesicles carrying let-7a-5p for alleviating inflammation in acute lung injury. J Biomed Sci 2024;31(1):30. https://doi.org/10.1186/s12929-024-01019-4.
[62] Chu Y, Jiang Z, Gong Z, Ji X, Zhu M, Shang Q, et al. PML-mediated nuclear loosening permits immunomodulation of mesenchymal stem/stromal cells under inflammatory conditions. Cell Prolif 2024;57(4):e13566. https://doi.org/10.1111/cpr.13566.
[63] Hackel A, Vollmer S, Bruderek K, Lang S, Brandau S. Immunological priming of mesenchymal stromal/stem cells and their extracellular vesicles augments their therapeutic benefits in experimental graft-versus-host disease via engagement of PD-1 ligands. Front Immunol 2023;14: 1078551. https://doi.org/10.3389/fimmu.2023.1078551.
[64] Song N, Scholtemeijer M, Shah K. Mesenchymal stem cell immunomodulation: mechanisms and therapeutic potential. Trends Pharmacol Sci 2020;41(9):653–64. https://doi.org/10.1016/j.tips.2020.06.009.
[65] Park A, Park H, Yoon J, Kang D, Kang MH, Park YY, et al. Priming with Toll-like receptor 3 agonist or interferon-gamma enhances the therapeutic effects of human mesenchymal stem cells in a murine model of atopic dermatitis. Stem Cell Res Ther 2019;10(1):66. https://doi.org/10.1186/s13287-019-1164-6.
[66] Yoon J, Lee SK, Park A, Lee J, Jung I, Song KB, et al. Exosome from IFN-γ-Primed induced pluripotent stem cell-derived mesenchymal stem cells improved skin inflammation and barrier function. Int J Mol Sci 2023;24(14). https://doi.org/10.3390/ijms241411635.
[67] Kim J, Lee SK, Jung M, Jeong SY, You H, Won JY, et al. Extracellular vesicles from IFN-γ-primed mesenchymal stem cells repress atopic dermatitis in mice. J Nanobiotechnol 2022;20(1):526. https://doi.org/10.1186/s12951-022-01728-8.
[68] Pierce LM, Kurata WE. Priming with toll-like receptor 3 agonist poly(I:C) enhances content of innate immune defense proteins but not MicroRNAs in human mesenchymal stem cell-derived extracellular vesicles. Front Cell Dev Biol 2021;9:676356. https://doi.org/10.3389/fcell.2021.676356.
[69] Lee BC, Kim JJ, Lee JY, Kang I, Shin N, Lee SE, et al. Disease-specific primed human adult stem cells effectively ameliorate experimental atopic dermatitis in mice. Theranostics 2019;9(12):3608–21. https://doi.org/10.7150/thno.32945.
[70] Wong JKU, Mehta A, Vũ TT, Yeo GC. Cellular modifications and biomaterial design to improve mesenchymal stem cell transplantation. Biomater Sci 2023;11(14):4752–73. https://doi.org/10.1039/d3bm00376k.
[71] Hazrati A, Malekpour K, Soudi S, Hashemi SM. CRISPR/Cas9-engineered mesenchymal stromal/stem cells and their extracellular vesicles: a new approach to overcoming cell therapy limitations. Biomed Pharmacother 2022;156:113943. https://doi.org/10.1016/j.biopha.2022.113943.
[72] Li M, Jiang Y, Hou Q, Zhao Y, Zhong L, Fu X. Potential pre-activation strategies for improving therapeutic efficacy of mesenchymal stem cells: current status and future prospects. Stem Cell Res Ther 2022;13(1):146. https://doi.org/10.1186/s13287-022-02822-2.
[73] Sah SK, Agrahari G, Nguyen CT, Kim YS, Kang KS, Kim TY. Enhanced therapeutic effects of human mesenchymal stem cells transduced with superoxide dismutase 3 in a murine atopic dermatitis-like skin inflammation model. Allergy 2018;73(12):2364–76. https://doi.org/10.1111/all.13594.
[74] Yang JW, Seo Y, Shin TH, Ahn JS, Oh SJ, Shin YY, et al. Extracellular vesicles from SOD3-transduced stem cells exhibit improved immunomodulatory abilities in the murine dermatitis model. Antioxidants 2020;9(11). https://doi.org/10.3390/antiox9111165.
[75] Shi C, Pei S, Ding Y, Tao C, Zhu Y, Peng Y, et al. Exosomes with overexpressed miR 147a suppress angiogenesis and infammatory injury in an experimental model of atopic dermatitis. Sci Rep 2023;13(1):8904. https://doi.org/10.1038/s41598-023-34418-y.
[76] Arifka M, Wilar G, Elamin KM, Wathoni N. Polymeric hydrogels as mesenchymal stem cell secretome delivery system in biomedical applications. Polymers 2022;14(6). https://doi.org/10.3390/polym14061218.
[77] Wang X, Young DJ, Wu YL, Loh XJ. Thermogelling 3D systems towards stem cell-based tissue regeneration therapies. Molecules 2018;23(3). https://doi.org/10.3390/molecules23030553.
[78] Lee H, Lee TW, Chandrasekharan A, Sung SE, Yim SG, Kim S, et al. Injectable self-crosslinkable thiolated hyaluronic acid for stem cell therapy of atopic dermatitis. ACS Biomater Sci Eng 2022;8(4):1613–22. https://doi.org/10.1021/acsbiomaterials.1c01374.
[79] Sun M, Yang J, Fan Y, Zhang Y, Sun J, Hu M, et al. Beyond extracellular vesicles: hybrid membrane nanovesicles as emerging advanced tools for biomedical applications. Adv Sci (Weinh) 2023;10(32):e2303617. https://doi.org/10.1002/advs.202303617.
[80] Chen X, Xing X, Lin S, Huang L, He L, Zou Y, et al. Plant-derived nanovesicles: harnessing nature's power for tissue protection and repair. J Nanobiotechnol 2023;21(1):445. https://doi.org/10.1186/s12951-023-02193-7.
[81] Huang R, Jia B, Su D, Li M, Xu Z, He C, et al. Plant exosomes fused with engineered mesenchymal stem cell-derived nanovesicles for synergistic therapy of autoimmune skin disorders. J Extracell Vesicles 2023;12(10): e12361. https://doi.org/10.1002/jev2.12361.
[82] Kim HS, Lee JH, Roh KH, Jun HJ, Kang KS, Kim TY. Clinical trial of human umbilical cord blood-derived stem cells for the treatment of moderate-to-severe atopic dermatitis: phase I/IIa studies. Stem Cell 2017;35(1):248–55. https://doi.org/10.1002/stem.2401.
[83] Shin HT, Lee SH, Yoon HS, Heo JH, Lee SB, Byun JW, et al. Long-term efficacy and safety of intravenous injection of clonal mesenchymal stem cells derived from bone marrow in five adults with moderate to severe atopic dermatitis. J Dermatol 2021;48(8):1236–42. https://doi.org/10.1111/1346-8138.15928.
[84] Seo HM, Lew BL, Lee YW, Son SW, Park CO, Park YL, et al. Phase 1/2 trials of human bone marrow-derived clonal mesenchymal stem cells for treatment of adults with moderate to severe atopic dermatitis. J Allergy Clin Immunol 2024. https://doi.org/10.1016/j.jaci.2024.06.013.

[85] Kim YJ, Ahn HJ, Lee SH, Lee MH, Kang KS. Effects of conditioned media from human umbilical cord blood-derived mesenchymal stem cells in the skin immune response. Biomed Pharmacother 2020;131:110789. https://doi.org/10.1016/j.biopha.2020.110789.
[86] Ye C, Zhang Y, Su Z, Wu S, Li Y, Yi J, et al. hMSC exosomes as a novel treatment for female sensitive skin: an in vivo study. Front Bioeng Biotechnol 2022;10:1053679. https://doi.org/10.3389/fbioe.2022.1053679.
[87] Wollenberg A, Werfel T, Ring J, Ott H, Gieler U. Atopic dermatitis in children and adults—diagnosis and treatment. Dtsch Arztebl Int 2023;120(13):224–34. https://doi.org/10.3238/arztebl.m2023.0011.
[88] Yim HJ, Jean T, Ong PY. Comparison of old and new systemic treatments for moderate to severe atopic dermatitis. Curr Allergy Asthma Rep 2024;24(5):289–301. https://doi.org/10.1007/s11882-024-01145-x.
[89] Guttman-Yassky E, Renert-Yuval Y, Brunner PM. Atopic dermatitis. Lancet 2025;405(10478):583–96. https://doi.org/10.1016/s0140-6736(24)02519-4.
[90] Facheris P, Jeffery J, Del Duca E, Guttman-Yassky E. The translational revolution in atopic dermatitis: the paradigm shift from pathogenesis to treatment. Cell Mol Immunol 2023;20(5):448–74. https://doi.org/10.1038/s41423-023-00992-4.
[91] Müller S, Maintz L, Bieber T. Treatment of atopic dermatitis: recently approved drugs and advanced clinical development programs. Allergy 2024. https://doi.org/10.1111/all.16009.
[92] Li X, Zhang D, Yu Y, Wang L, Zhao M. Umbilical cord-derived mesenchymal stem cell secretome promotes skin regeneration and rejuvenation: from mechanism to therapeutics. Cell Prolif 2023:e13586. https://doi.org/10.1111/cpr.13586.
[93] Mohanan MM, Shetty R, Bang-Berthelsen CH, Mudnakudu-Nagaraju KK. Role of mesenchymal stem cells and short chain fatty acids in allergy: a prophylactic therapy for future. Immunol Lett 2023;260:1–10. https://doi.org/10.1016/j.imlet.2023.06.002.
[94] Kim EY, Kim HS, Hong KS, Chung HM, Park SP, Noh G. Mesenchymal stem/stromal cell therapy in atopic dermatitis and chronic urticaria: immunological and clinical viewpoints. Stem Cell Res Ther 2021;12(1):539. https://doi.org/10.1186/s13287-021-02583-4.
[95] Weiss ARR, Dahlke MH. Immunomodulation by mesenchymal stem cells (MSCs): mechanisms of action of living, apoptotic, and dead MSCs. Front Immunol 2019;10:1191. https://doi.org/10.3389/fimmu.2019.01191.
[96] Rauer L, Reiger M, Bhattacharyya M, Brunner PM, Krueger JG, Guttman-Yassky E, et al. Skin microbiome and its association with host cofactors in determining atopic dermatitis severity. J Eur Acad Dermatol Venereol 2023;37(4):772–82. https://doi.org/10.1111/jdv.18776.
[97] Clausen ML, Agner T, Lilje B, Edslev SM, Johannesen TB, Andersen PS. Association of disease severity with skin microbiome and filaggrin gene mutations in adult atopic dermatitis. JAMA Dermatol 2018;154(3):293–300. https://doi.org/10.1001/jamadermatol.2017.5440.
[98] Dahal A, Chang WC, Almasri C, Johansson E, Hurd M, Velasquez V, et al. Temporal relationships between Staphylococcus aureus colonization, filaggrin expression, and pediatric atopic dermatitis. Allergy 2023. https://doi.org/10.1111/all.15871.
[99] Shin N, Jung N, Lee SE, Kong D, Kim NG, Kook MG, et al. Pimecrolimus interferes the therapeutic efficacy of human mesenchymal stem cells in atopic dermatitis by regulating NFAT-COX2 signaling. Stem Cell Res Ther 2021;12(1):482. https://doi.org/10.1186/s13287-021-02547-8.
[100] Fakhimi M, Talei AR, Ghaderi A, Habibagahi M, Razmkhah M. Helios, CD73 and CD39 induction in regulatory T cells exposed to adipose derived mesenchymal stem cells. Cell J 2020;22(2):236–44. https://doi.org/10.22074/cellj.2020.6313.