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REVIEW

Therapeutic Potential and Mechanisms of Mesenchymal Stem Cell and Mesenchymal Stem Cell-Derived Extracellular Vesicles in Atopic Dermatitis

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Abstract: Atopic dermatitis (AD) is a chronic and inflammatory skin disease with intense itchiness that is highly prevalent worldwide.The pathogenesis of AD is complex and closely related to genetic factors, immunopathogenic factors, environmental factors, and skin infections. Mesenchymal stem cells (MSCs) are non-hematopoietic progenitor cells derived from the mesenchymal stroma. They have anti-inflammatory, anti-apoptotic, and regenerative properties. Numerous studies demonstrate that MSCs can play a therapeutic role in AD by regulating various immune cells, maintaining immune homeostasis, and promoting the repair of damaged tissues. The key mediators for their biological functions are extracellular vesicles (MSC-Evs) and soluble cytokines derived from MSCs. The safety and efficacy of MSCs have been demonstrated in clinical Phase I / IIa trials for AD. This paper provides a comprehensive review of the pathogenesis of AD and the currently published studies on the function of MSCs and MSC-Evs in AD, primarily including the pathogenesis and the immunomodulatory impacts of MSCs and MSC-Evs, along with advancements in clinical studies. It provides insights for comprehending AD pathogenesis and investigating treatments based on MSCs.

Keywords: atopic dermatitis, mesenchymal stem cells, Th2-associated immunity, extracellular vesicle

Introduction

Atopic dermatitis (AD) is a skin disease that is chronic and inflammatory. It causes intense itching, redness, and flaking of the skin, and tends to relapse over time. The disease is highly prevalent globally, especially in affluent nations, with 20% of children and 10% of adults afflicted by it. This places a considerable burden on human health and social healthcare.[1,2] AD's intricate pathogenesis primarily involves genetic elements, epidermal barrier defects, immunopathogenic aspects, and environmental factors.[3] Dysregulated T and B cells and the induced Th2-associated immunity play crucial roles in AD. Although more therapeutic agents are now available on the market, traditional therapies such as oral antihistamines, topical cortisol, and calcium-modulated phosphatase inhibitors are only effective in patients with mild to moderate AD. For patients with severe AD, Janus kinase inhibitors and IL-4R alpha receptor blockers are effective in improving dermatitis and itching, but they also carry the risk of serious adverse effects, such as immunosuppression and infections. Moreover, they are expensive and prone to relapse after discontinuation.[4,5] Therefore, exploring effective therapeutic strategies for AD is of great importance.

Mesenchymal stem cells (MSCs) are a group of pluripotent progenitor cells that can be found in most tissues. They have the ability to self-renew and diversify, and they also possess low immunogenicity and high immunomodulatory

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properties. MSCs commonly express membrane molecules, such as CD73 and CD90, while not expressing CD14, CD34, CD45, and HLA-DR. The lack of expression of immunostimulatory molecules makes MSCs immunocompatible.[6] MSCs can be derived from various tissues like bone marrow, adipose tissue, umbilical cord, periodontal tissue, umbilical cord blood, and placenta.[7] However, different tissue-derived MSCs vary in their differentiation ability and immunomodulatory capacity. Among them, adipose tissue-derived MSCs (Ad-MSCs), bone marrow-derived MSCs (BM-MSCs), and umbilical cord-derived MSCs (UC-MSCs) are commonly used in stem cell therapy research due to their high proliferation rate and immunosuppressive ability,[8–10] MSCs can modulate the innate and adaptive immune systems by altering macrophage immune phenotype, promoting anti-inflammatory cytokine production, inhibiting natural killer (NK) cell growth and cytokine release, and suppressing the growth and differentiation of T and B cells.[11] Increasing evidence suggests that MSCs are critical in regulating inflammation and autoimmunity in AD.

MSC exerts its therapeutic effects on AD through cellular interactions and paracrine communication in vivo. Extracellular vesicles (Evs) are the primary paracrine factors produced by MSCs. MSC-Evs, characterized by excellent biocompatibility, stability, and permeability, exhibit critical biological activity similar to MSCs. Evs can be classified into small Evs (sEvs) and medium/large Evs (m/lEvs) based on their size. sEvs are nanosized vesicles with a diameter range of 200 nm or less, which express transmembrane protein molecular markers like CD9, CD63, and CD81.[12–14] sEvs encapsulate a variety of bioactive components such as lipids, RNAs, and proteins, which act as important communication factors between cells. By transferring these bioactive components to target organs or tissues, Evs can effectively regulate the functions of target cells through complex signaling pathways.[15,16] Evs secreted by MSCs from different tissue sources have similar biological functions and play an important role in AD by regulating inflammatory and immune responses, angiogenesis, and promoting tissue repair.[17] A previous study confirmed significant recovery of rash wounds and lower levels of scarring in MSC-Evs-treated AD model mice compared to controls.[18] Compared to MSCs, MSC-Evs have obvious advantages such as easy production and preservation, large-scale preparation, and low immunogenicity.[19] Therefore, MSC-Evs become a promising and beneficial strategy for the treatment of AD.

This comprehensive review clarifies the pathogenesis of AD, along with the immunoregulatory effects and mechanisms of MSCs and MSC-Evs in AD. Additionally, the latest progress in both preclinical and clinical research is also summarized. By synthesizing these insights, this review not only provides an updated understanding of the role of MSCs and MSC-Evs in controlling AD but also furnishes valuable perspectives for the exploration of new treatment strategies for AD patients.

The Pathogenesis of AD

Skin Barrier Defects in AD

The Role of Genetic Factors in AD and Their Effect on Skin Barrier Function

Numerous epidemiological and genetic association studies have emphasized the genetic susceptibility of AD, pinpointing 31 distinct chromosomal loci housing genes susceptible to AD.[20] Genes responsible for epithelial structural and functional proteins are the most important susceptible genes among them. Mutations in these susceptible genes can impair the skin barrier, consisting of epithelial cells, intercellular connections, and skin lipids.

Filaggrin (FLG), a key molecule in the stratum corneum, forms a robust physical barrier against water loss and foreign invasion.[21] When FLG is decreased, natural moisturizing factors are compromised, leading to increased skin water loss and dryness.[22] Variations in the FLG gene lead to a decrease in its expression, impairing the skin barrier function and promoting subclinical inflammation of the epidermis. Additionally, these variations can disrupt the normal differentiation of keratinocyte terminals, altering the aggregation process of keratinocytes and leading to abnormalities.[23] The intercellular connections of epithelial cells, including tight junctions, intermediate junctions, and desmosomes, are crucial in maintaining barrier integrity. In AD patients, reduced expression of adhesion protein CLDN1 in tight junctions has been observed, resulting in defects in these tight junctions.[24] This impairment makes the skin more susceptible to bacteria colonization and allergen irritation.

AD-susceptible gene loci are closely associated with immune disorders. Extensive genome-wide association studies (GWAS) have been carried out across populations from multiple countries to identify the key susceptibility loci

associated with AD. These studies have pinpointed various cytokines and their receptors, including IL-4, IL-13, thymic stromal lymphopoietin (TSLP), IL-1, IL-18, IL-33, TNF receptor-associated factor (TRAF6), IL-1RL1, IL-18R1, IL-18RAP, and nerve growth factor receptor (NGFR).[25] These findings have highlighted the intricate interaction among genetic factors, skin barrier function, and immune responses in AD progression.

Role of Environmental Factors in AD and Their Effects on Skin Barrier Function

Various environmental factors can significantly impact skin barrier function in individuals suffering from AD. Research in clinical settings has highlighted the role of the living environment, air quality, UV exposure, and regional climate changes in the pathogenesis of AD. Living in urban environments with low UV exposure or residing in arid regions correlates with a heightened incidence of AD. Airborne allergens like dust mites, pollen, and pet dander can trigger or worsen AD symptoms,[26] particularly when the skin barrier is damaged.[27] In addition, common industrial pollutants and traffic exhaust emissions contribute to the occurrence of AD. It has been demonstrated that airborne formaldehyde increases transepidermal water loss (TEWL) and alters skin pH, while Benzene, along with several other substances, can increase the production of IL-4 and promote Th2 polarization.[28,29] Furthermore, In cold and dry climates, the skin's protective barrier function may decrease. The skin barrier defects lead to broken intercellular junctions, heightened protease activity, enhanced permeability of the epidermis, infiltrating antigens, and pro-inflammatory cytokine activation.[30] This makes allergens or microorganisms more likely to breach the skin's stratum corneum, increasing TEWL in AD skin and promoting sensitization and infection. Therefore, environmental factors are important risk factors for AD, such as dry climate, pollution, high allergens, low temperature, and low UV exposure. The environmental factors exacerbate the impaired skin barrier function, resulting in an increased generation of pro-inflammatory cytokines and heightened mast cell reactivity in the skin.

Immunoregulatory Disorders in AD

The immune disorders in AD are primarily attributed to the disproportion between Th1 and Th2 immune reactions, marked by a predominant Th2-type immune reaction accompanied by elevated levels of Th2 cytokines, activation of B-cells and IgE release, followed by the activation of mast cells, resulting in their degranulation. Meanwhile, secretion of IL-22 and IL-17 by Th 22 and Th 17 cells was also found to impair the skin barrier and promote AD progression.

Currently, AD has two different views on its pathogenesis. Some experts believe that immune abnormalities are the main factor leading to an inflammatory response and secondary skin barrier disruption. On the other hand, others think that skin barrier dysfunction is the initial factor that causes immune dysfunction and eventually leads to the development of AD.[31] Regardless of which hypothesis is considered the initiating factor, the phenotype and chronic nature of AD are primarily associated with immune abnormalities. In addition to the immune response, the two hypotheses provide valuable perspectives on understanding the intricate interaction between skin barrier function and immune dysregulation in AD. Whether immune dysfunction or skin barrier dysfunction takes precedence in the disease's onset, the resulting phenotype and chronicity underscore the central role of immune abnormalities in AD.

Role of the Th2-Associated Immunity in the Pathogenesis of AD

The skin encounters various stimuli, including allergens, microorganisms, and physical injuries triggering innate immune responses. Upon stimulation by these factors, epithelial cells secrete proinflammatory cytokines like IL-25, TSLP, and IL-33. Such cytokines activate type 2 innate lymphocytes (ILC-2), leading to the secretion of type 2 cytokines like IL-5 and IL-13, which in turn promote a Th2-type inflammatory reaction.[32] Inflammatory mediators of IL-25, TSLP, and IL-33 also directly stimulate Th2 cells, promoting Th2 immune response.[33] Dermal cells and DCs attract Th2 cells and eosinophils by secretion of chemokines like CCL17, CCL18, and CCL22, which amplify the Th2 response.[34] Langerhans cells (LCs) and dermal dendritic cells (DDCs) ensnare and present antigens to naive T cells, steering their transformation into Th2 cells.

Th2 cells secrete the cytokines IL-4 and IL-13, which exert pro-inflammatory effects by binding to IL-4Rα expressed on diverse immune cells (Figure 1). For instance, they prompt B cells to undergo IgE class switching and secretion, regulate eosinophils and mast cell behavior,[35] and prompt mast cells to release inflammatory mediators, inciting allergic reactions. Moreover, IL-4 and IL-13 inhibit the mobilization of human b-defensin-3 (HBD-3) in skin keratinocytes (KCs)

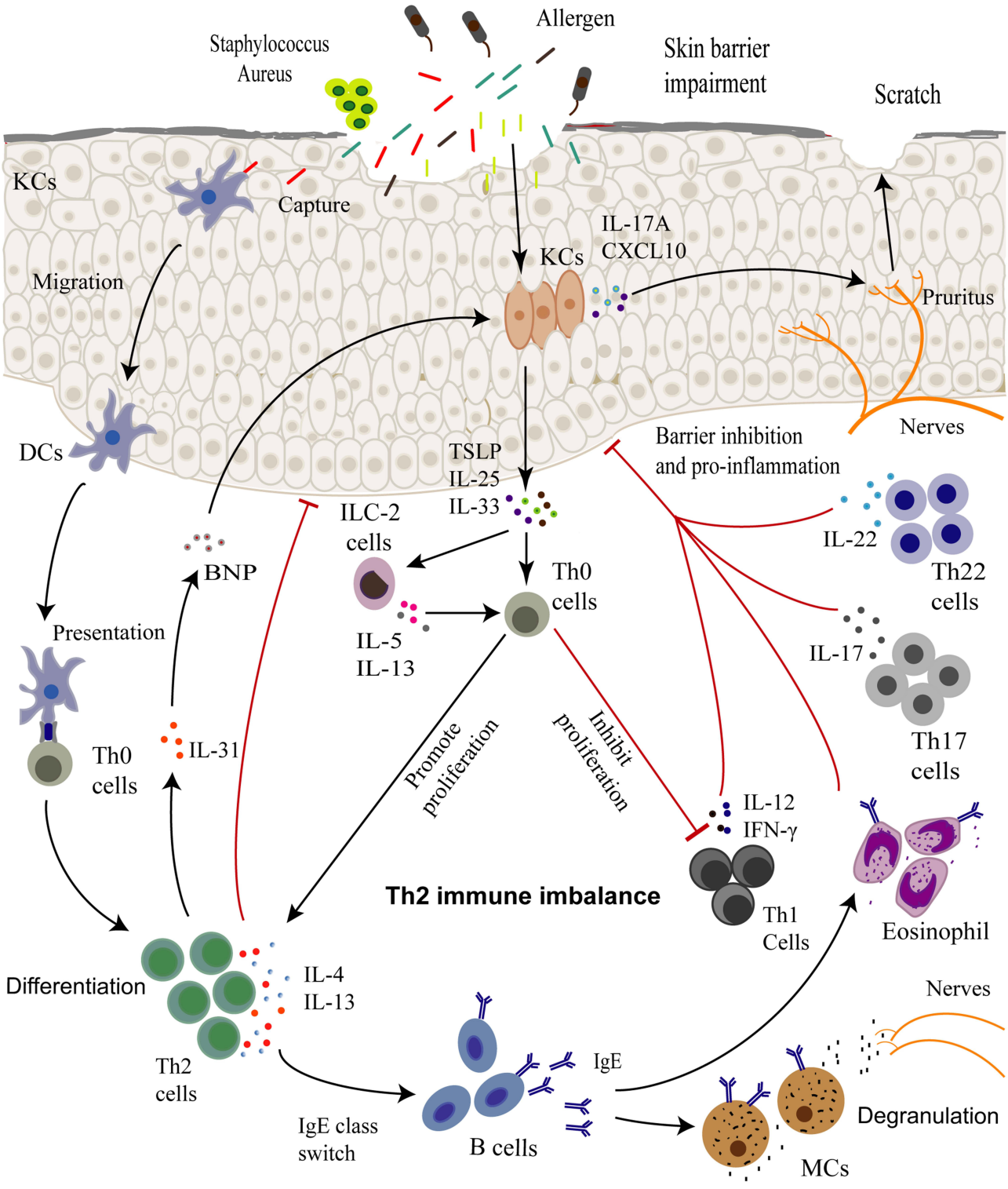

Figure 1 Mechanisms of AD pathology and immune dysregulation.Immune imbalance is an important pathogenic factor in AD. When the skin barrier function is weakened, allergens can enter the body and be processed by APC cells (such as DCs). These cells then present the allergens to Th0 cells, which differentiate into Th2 cells. Th2 cytokines, such as IL-4, IL-5, and IL-13, promote the differentiation of Th2 cells, leading to an imbalance between Th1 and Th2 immune responses. IL-4 and IL-13 exacerbate skin barrier damage and induce pruritus by promoting B-cell maturation and IgE class switch, promoting eosinophil and mast cell degranulation, and cooperating with cytokines such as IL-22, IL-17, IFN-γ, and IL-31. Regulation of Th1/Th2 balance, differentiation, and polarization of Th17 cells plays a key role in treating AD.

Abbreviations: KCs, keratinocytes; APC, Antigen-presenting cells; DCs, Dendritic cells; Th0 cells, T helper 0 cells; Th1 cells, T helper 1 cells; Th2 cells, T helper 2 cells; Th17 cells, T helper 17 cells; Th22 cells, T helper 22 cells; IgE, Immunoglobulin E; TSLP, thymic stromal lymphopoietin; ILC-2, type 2 innate lymphocytes; IL-4, interleukin 4; IL-5, interleukin 5; IL-12, interleukin 12; IL-13, interleukin 13; IL-17, interleukin 17; IL-17A, interleukin 17A; IL-22, interleukin 22; IL-25, interleukin 25; IL-31, interleukin 31; IL-33, interleukin 33; CXCL10, Chemokine (C-X-C motif) ligand 10; IFN-γ, interferon gamma; MCs:mast cells; BNP:brain natriuretic peptide.

cells, making AD patients more susceptible to Staphylococcus aureus infection.[36] Furthermore, IL-4 and IL-13 can also suppress the synthesis of epidermal barrier proteins and KC differentiation, contributing to barrier deterioration.[37] Reduced expression of loricrin and involucrin driven by IL-4 and IL-13 further exacerbates the skin barrier damage.[38] The compromised barrier function results in skin dryness, elevated levels of nerve growth factor (NGF), coupled with a decrease in the expression of signal protein 3A (Sema3A), leading to extended sensory nerve fibers in the epidermis, and heightened skin sensitivity. Weakened barrier function allows direct stimulation of intraepidermal nerve fibers (IENFs) by mechanical and chemical stimuli, triggering increased sensitivity and itching.[39] In acute AD lesions, Th2 cells release large amounts of itch-related cytokine IL-31, which is associated with disease severity. IL-31 promotes the secretion of brain natriuretic peptide (BNP), which indirectly promotes the secretion of IL-17A and CXCL10 through stimulation of KC, thereby inducing itching in AD.[40] Transition from Th2 to Th1 dominance is an important factor in chronic disease progression. During the chronic phase of AD, the Th1 cell response prevails, marked by an increased generation of IL-12 and IFN-γ. These Th1 cells secrete various proteinases and free radicals that contribute to epidermal barrier damage, tissue repair, and fibrosis.

Role of Th22/Th17 in the Pathogenesis of AD

Th22 and Th17 cells secrete IL-22 and IL-17, contributing to impairing the skin barrier and the progression of AD. In AD patients, IL-22 shows elevated levels in the affected skin, influencing both epidermal hyperplasia and the weakening of barriers.[41] Its effects include inhibiting epidermal differentiation, promoting KC cell migration, and enhancing the activation of genes that promote inflammation in KCs.[42] Early clinical trials with the anti-IL-22 antibody ILV-094 have demonstrated promising results in AD treatment, emphasizing IL-22's crucial function in the development of AD.[41] The levels of IL-17 were elevated in the damaged skin of AD patients in contrast to healthy individuals.[43] Through the pathway of IL-17R-Act1-TRAF4-MEKK3-ERK5, IL-17 enhances the proliferation of the epidermis.[44] Activation of the P38/ERK MAPK signaling pathway by IL-17 diminishes the expression of FLG and involucrin, while significantly boosting the secretion of stem cell factor (SCF) of KCs.[45] SCF plays a crucial role as a growth factor for mast cells, enhancing their ability to proliferate.[46] Nonetheless, the precise disease-causing functions of Th17 and Th22 cells in AD need to be further investigated to validate their implications.

Other Factors Contributing to the Pathogenesis of AD

Multiple factors play a role in the development of AD, encompassing age, geographical differences, ethnic and racial disparities, smoking, psychological factors, and skin infections.[2] The prevalence and clinical characteristics of AD varies with age. Children have a higher prevalence with more than 90% experiencing mild to moderate symptoms.[47] Infants often manifest as oozing eczema around the eyelids, ears, and wrists, while adults commonly exhibit erythroderma and lichenification.[48] Distinct immune profiles and skin barrier abnormalities are observed among Asian and European populations. Molecular analysis of AD patients of African American and European American descent reveals significant phenotypic differences. African Americans exhibit a sixfold higher mutation rate of FLG compared to European Americans, while FLG mutations are rare in South African and Ethiopian populations.[49] AD patients frequently experience sleep disorders, anxiety, depression, and other psychological illnesses. Compared to healthy individuals, AD patients exhibit a notably increased occurrence of these ailments, suggesting potential associations between AD development and psychological orders.[50] Infection by Staphylococcus aureus (S. aureus) is also crucial in the progression of AD. *S. aureus* can trigger Th2 cytokines by secreting proteinases, activate mast cells through exotoxins, and upregulate T cells via superantigen-mediated mechanisms.[51] Furthermore, studies have found that in AD animal models, the levels of damage-associated molecular pattern (DAMP) molecules are significantly increased, including S100A9 and S100A8.[52] DAMP molecules, released after tissue or cell injury, stress, or hypoxia, prompt immune responses through Toll-like receptors. Elevated S100A8/A9 expression exacerbates immune-induced damage, and there is a positive correlation between protein concentration and skin barrier dysfunction severity.[53]

Taken together, AD is characterized by defective skin barrier function and immune dysregulation, influenced by various factors such as genetic susceptibility, age-related changes, racial differences, environmental issues, and psychological disorders. Genetic abnormalities in skin structural and functional protein expression lead to a compromised skin

barrier function. Environmental factors like pollution, dry climate, high allergens, and skin infections can cause or worsen the decline in skin barrier function and activate immune responses such as Th2, Th1, and Th22/Th17, leading to dermatitis symptoms and further impairment of the skin barrier function. Understanding the complex interactions between these factors is crucial for developing effective treatments for AD. Although genetic and hereditary issues currently lack effective solutions, implementing daily skin protection and modulating immune dysregulation are promising treatment strategies. However, immune dysregulation in AD is complex, and most drugs used in clinical treatment target a single causative molecule. This presents challenges in effectively treating patients with multiple pathogenic factors, resulting in varying clinical outcomes. Therefore, MSCs with strong immunomodulatory effects have significant advantages in treating AD.

Therapeutic Mechanisms of MSCs and MSC-Evs in AD

Growing research indicates that MSCs and MSC-Evs serve as new strategies for the treatment of AD.[54] These vesicles exhibit efficacy by orchestrating multiple mechanisms, involving the regulation of T and B cell functions, modulation of mast cell (MC) activation and degranulation, mitigation of skin lesions, and facilitation of epidermal repair (Table 1, Figure 2). MSCs primarily control immune cell function via direct intercellular communication and paracrine methods, thereby actively engaging in the regulation of AD development and progression. MSC-Evs is the classic paracrine way for MSCs to confer immunomodulatory effects.

Effects of MSCs and MSC-Evs on T Cells

Dysfunction of T cells (especially $CD4^+$ T cells) is a critical factor in AD, resulting in an imbalance between Th1 and Th2 cells. Strategies targeting T-cell dysregulation hold promise for AD treatment. Following exposures to allergens or antigens, skin APC cells capture and present antigens, leading to Th2 cell activation. MSCs are found to hinder T-cell and APC interaction through non-homologous mechanisms. IL-10 produced by MSCs inhibits DC maturation, cytokine production, and antigen presentation,[68,69] thereby inhibiting lymphocyte recruitment and T-cell activation. Emerging evidence has implicated the critical effects of MSCs on autoimmunity (Figure 2). When MSCs and T cells are co-cultured in vitro, MSCs suppress the proliferation of T cells by releasing TGF-β1 and hepatocyte growth factor (HGF).[70] Besides, MSCs inhibit the growth of activated T cells during the G0/G1 phase through direct cell-to-cell contact.[71] Indoleamine 2.3-dioxygenase (IDO) consumes tryptophan in the local microenvironment, leading to tryptophan starvation in T cells and induction of endoplasmic reticulum stress in cells. MSCs can produce high levels of IDO in inflammatory responses, resulting in the inhibition of T-cell activation and proliferation.[72] Furthermore, there is growing evidence that MSC-Evs plays a critical role in influencing T-cell differentiation and function in infectious and autoimmune diseases[73–75] (Figure 2). Evs is an important vehicle for protecting bioactive molecules and delivering them to the appropriate targets. MicroRNAs derived from MSC-Evs play a role in signal transduction, regulation of immune response, tissue regeneration and repair, and other biological functions. For example, miR-125a-3p can inhibit the differentiation of effector T-cells, miR-146a down-regulates the NF-kB signaling pathway, and miR-21-5p, miR-142-3p, miR-223-3p, miR126-3p inhibit the maturation of dendritic cells.[76] It also promotes regulatory T cell (Treg) polarization, maintains Th17/Treg immune homeostasis, and prevents excessive inflammation and aberrant immune activation.[74] MSC-Evs can be transported by the bloodstream and other body fluids, interacting with cells in paracrine and endocrine ways. Thus, MSCs can secrete Evs to simultaneously and remotely regulate a variety of cellular functions.[77]

Growing research has supported the crucial function of MSC and MSC-Evs or MSC extracts (MSC-Exs) in the onset and progression of AD. In an experiment, injecting UC-MSCs or UC-MSC-Exs under the skin significantly improved dermatitis symptoms and decreased the expression of cytokines such as TNF-α, IFN-γ, IL-17, and IL-13 in the affected skin of AD mice, and found that the efficacy of UC-MSC- Exs was superior to UC-MSCs. To investigate the specific mechanism behind this therapeutic effect, researchers conducted an in vitro experiment where they observed that UC-MSC-Exs inhibited T-cell activation and expression of inflammatory cytokines. They found that these effects were mediated through the inhibition of the NF-κB pathway[55](Table 1, Figure 2), which explains how MSC-Exs can alleviate AD symptoms.[55] However, further studies are necessary to identify the target molecules that play specific roles in MSC-Exs. In a previous study, researchers discovered that macrophage inflammatory protein 2 (MIP-2) was

Table 1 The Biological Effects and Mechanisms of MSCs and MSC-Evs in AD

Source	MSC/ MSC-Evs	Target Cells	Mechanism	Outcomes/Effects	Ref.
Human umbilical cord	MSC-Exs	T cells	Downregulation of IFN-γ and IL-17 in T cells; inhibition of T cell activation	Significantly decreased clinical symptom score, serum IgE level, and histological dermatitis score	[55]
Human adipose tissue	MSCs	T cells	Suppressed expression of MIP-2; inhibited miR-122a-5p-SOCS1 axis; Th1/Th2 regulation	Reduced clinical symptoms; reduced number of degranulated mast cells; decreased IgE levels, histamine release, and PGE2	[56]
Human adipose tissue	MSCs	T cells	Downregulation of IL-4R expression; suppressed Th2 inflammation; regulation of PD-L1, TGF-β and PGE2; inhibition of Th17 cells activation and IL-17 expression	Ameliorated ova-induced AD symptoms	[57]
Mice bone marrow	MSCs	B cells	Inhibition of Blimp-1 expression; inhibition of the terminal differentiation of B cells	Regulation of B cell differentiation	[58]
Human adipose tissue	MSCs	B cells	Inhibition of COX-2 signaling pathway; reduced maturation and proliferation of B cells; increased TGF-β secretion	Alleviating AD symptoms; regulating B cell function	[59]
Human umbilical cord	MSCs	B cells	Increased level of TGF-β; inhibition of B cell maturation and IgE secretion	Improved symptoms in AD mice	[60]
Human tonsils	MSC-Evs	Mast cells	Regulation of inflammation in mast cells; targeting of miRNAs in Evs	Inhibiting the activation and proliferation of mast cells	[61]
Human umbilical cord	MSCs	Mast cells	Regulation PGE2 via NOD2-RIP2-COX-2 signaling pathway; affecting TGF-β1 via IL-4-STAT6 signaling pathway; inhibiting the degranulation of mast cells	Significantly improved the symptoms of AD; reducing the clinical severity and epidermal hyperplasia in mice	[62]
Human bone marrow	MSCs	HUVECs	Increased expression of VEGF and Ang2; promoting angiogenesis	Promoting wound healing	[63]
The Wharton's jelly tissue	MSCs	HUVECs	Upregulation of VEGF, EGF, bFGF, and KDR expression; promoting neoangiogenesis	Alleviating radiation-induced skin injury in rats	[64]
Human cord blood	MSCs	Keratinocytes	Promoting the differentiation into keratinocytes	Improving wound healing of skin defects in mice	[65]
Human cord blood	MSC-Evs	HSFs and HMECs	Induction of PTEN and SPRY1 of PI3K/Akt and ERK1/2 pathway activation by miR-21-3p	Accelerating re-epithelialization; reducing scar width; promoting fibroblast proliferation, migration, and angiogenesis; promoting skin wound healing	[66]
Human umbilical cord	MSC-Evs	HaCAT and DFL	Activation of the AKT pathway; inhibition of skin cell apoptosis; activation of Wnt4/β-catenin and AKT signaling	Promoting skin repair in second-degree burn injury	[67]

Abbreviations: AD, Atopic dermatitis; MSCs, mesenchymal stem cells; HUVECs, Human umbilical vein endothelial cells; HSFs, Human skin fibroblasts; HMECs, Human microvascular endothelial cells; HaCAT, human immortalized keratinocytes; DFL, Dermal fibroblasts; TGF-β1 Transforming growth factor-βl; IFN-γ, Interferon gamma; IL-17, interleukin 17; MIP-2, macrophage inflammatory protein 2; SOCS1, suppressor of cytokine signaling 1; Mast cells, Mast cells; Th1, T helper 1; Th2, T helper 2; IL-4R, Interleukin-4 Receptors; PD-L1, Programmed Death-Ligand 1; PGE2, Prostaglandin 2; Th17 cells, T helper 17 cells; COX-2, cyclooxygenase-2; miRNA, MicroRNA; NOD2, Nucleotide-binding oligomerization domain 2; RIP2, receptor-interacting protein 2; COX-2, Cyclooxygenase-2; IL-4, Interleukin-4; VEGF, Vascular Endothelial Growth Factor; Ang2, Angiopoietin-2; EGF, Epidermal Growth Factor; bFGF, basic fibroblast growth factor; KDR, Vascular Endothelial Growth Factor Receptor; BMSCs, bone marrow mesenchymal stem cells; UC-MSCs, umbilical cord mesenchymal stem cells; MSC-Exs; MSC extracts; AdMSCs, Adipose mesenchymal stem cell; ova, ovalbumin; hAT-MSCs, Human adipose tissue mesenchymal stem cell; hub-MSCs, Human umbilical cord mesenchymal stem cells; IgE, Immunoglobulin E; T-MSC-Evs, tonsils mesenchymal stem cell extracellular vesicles; PTEN, phosphatase and tensin homolog; SPRY1, sprouty homolog 1; PI3K/Akt pathway, Phosphatidylinositol 3-kinase protein kinase b pathway; ERK1/2 pathway, extracellular regulated protein kinases pathway; Akt pathway, protein kinase b pathway; Wnt4/β-catenin, Wnt4/β-catenin Pathway.

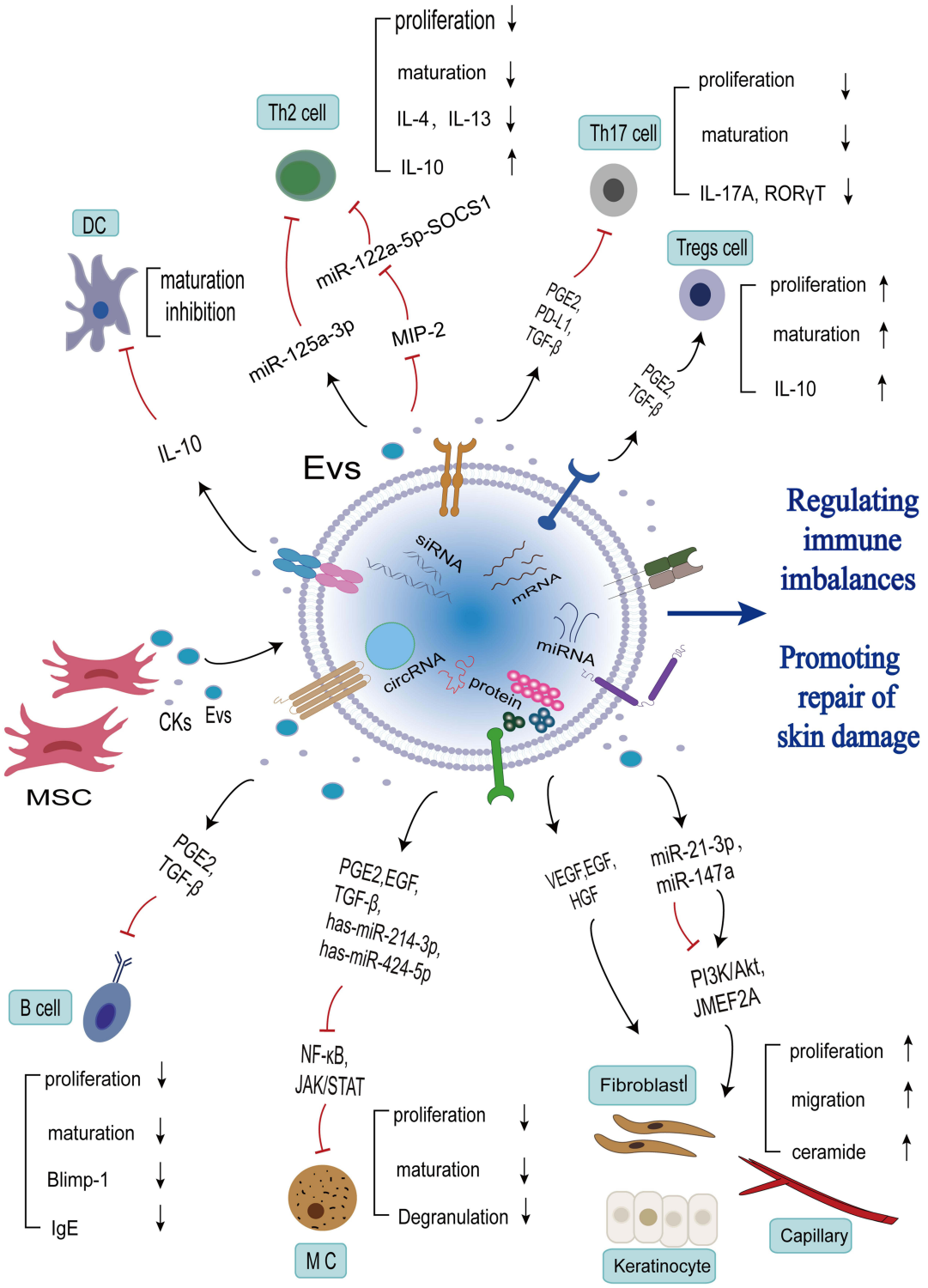

Figure 2 Role and mechanisms of MSCs/MSC-Evs in the regulation of AD.MSCs can regulate the immune system by releasing Evs and soluble cytokines. The secretion of IL-10 by MSCs inhibits dendritic cell proliferation and differentiation. PGE2 and TGF-β inhibit the proliferation, activation, and IgE production of Th17 cells and B cells while promoting the proliferation, maturation, and production of IL-10 by Tregs cells. Additionally, PGE2, TGF-β, EGF, has-miR-214-3p, has-miR-424-5p, and other intra-Evs miRNAs inhibit mast cell maturation and degranulation. VEGF, EGF, and HGF promote the proliferation of fibroblasts and vascular endothelial cells, while Evs miRNAs miR-125a-3p inhibit Th2 cell proliferation and activation. Moreover, miR-147a and miR-21-3p activate the PI3K/Akt pathway and inhibit MEF2A and VEGFA, promoting the proliferation of keratinocytes and vascular endothelial cells and ultimately facilitating the healing of skin lesions.

Abbreviations: Evs, Extracellular vesicles; CKs, cytokines; *DCs, Dendritic cells*; Th2 cells, T helper 2 cells; Th17 cells, T helper 17 cells; MCs:mast cells; Tregs cells: Regulatory T cells; VEGF, Vascular Endothelial Growth Factor; EGF, Epidermal Growth Factor; TGF-β1 Transforming growth factor-β; HGF, Hepatocyte Growth Factor; PGE2, Prostaglandin 2; MIP-2, macrophage inflammatory protein 2; IL-4, interleukin 4; IL-10, interleukin 10; IL-13, interleukin 13; IL-17A, interleukin 17A; PI3K/Akt, Phosphatidylinositol 3-kinase protein kinase b pathway; NF-κB, NF-κB signaling pathway; JAK/STAT, JAK/STAT signaling pathway.

elevated in the serum of AD mice and activated the miR-122a-5p-SOCS1 axis.[56] SOCS1 plays a crucial role in AD by promoting the expression of Th1/Th2 inflammatory factors and inhibiting the expression of IL-10. Ad-MSCs down-regulated the expression of cytokines such as MIP-2 and IL-5, affected the miR-122a-5p-SOCS1 axis and Th1/Th2 response, and effectively ameliorated the symptoms of AD mice, which may be mediated by the secretion of MCP1, CCL5, and other cytokines by Ad-MSCs.[56] These results suggest that MSCs as a novel and effective therapeutic strategy for AD.

Previous studies have shown that Th17 cells play a role in the progression of AD.[78] Elevated levels of IL-17 have been found to inhibit the synthesis of FLG in KCs and promote th2-associated inflammation, leading to skin barrier dysfunction.[79] Guan Jy et al used transcriptome sequencing technology and found that the IL-17 signaling pathway was highly enriched in the skin tissues of AD mice and Ad-MSCs-treated AD mice. The application of Ad-MSCs treatment down-regulated the expression of Th17-related factors and IL-4R in the skin tissues of AD mice, which significantly reduced skin inflammation in AD mice.[57] In an in vitro experiment, co-cultured Ad-MSCs were found to up-regulate the expression of prostaglandin E2 (PGE2), PD-L1, and TGF-β, and inhibit the expression of differentiation-associated transcription factors IL-17A and RORγT by Th17 cells. This suggests that Ad-MSCs may inhibit the proliferation and differentiation of T cells through the secretion of soluble factors or Evs.[57] Additionally, another study found that canine amniotic membrane-derived MSCs (cAM-MSCs) treated with pro-inflammatory cytokines up-regulated the expression of immunomodulatory factors such as TGF-β1 and IDO1. This inhibited the activation of natural T cells and effector T cells in paracrine ways and alleviated canine AD symptoms.[80] Treg cells are responsible for maintaining immune balance and play an important role in regulating immune responses. A study conducted by Kang SJ found that the number of Treg cells in the blood PBMCs of canines with AD was lower than those in the control group. However, after the treatment with AT-MSCs, the number of Tregs cells increased significantly, which confirms that MSCs have an immunomodulatory effect on AD by promoting the proliferation of Tregs cells.[81] Another study also showed that MSCs can increase Tregs cells' proliferation rate by activating the TGF-β and PGE2 pathways.[82]

MSCs regulate T cell activation and proliferation by secreting immunomodulatory factors, Evs are indispensable transport vectors. A recent study has shown that injecting Evs derived from canine adipose-derived mesenchymal stem cells (cASC-Evs) can significantly improve the symptoms of dermatitis in mice with AD. The study analyzed the microRNAs present in the Evs and found that let-7a, let-7b, miR-21, let-7f, miR-125b, miR-24, and miR-29a were highly expressed and associated with the JAK-STAT signaling pathway. This suggests that the therapeutic effects of MSCs-Evs may be achieved through the inhibition of the JAK-STAT signaling pathway by microRNAs.[83] Kim and Lee also conducted similar experiments and found that MSCs-Evs inhibited the IL-31R-JAK-STAT signaling pathway, leading to the amelioration of pruritus.[84] These findings suggest that MSCs-Evs are important mediators of MSCs' biological functions and may serve as a therapeutic alternative to MSCs in the future.

To summarize, T-cell dysfunction is a significant factor in AD development. MSCs and MSC-Evs treat AD by inhibiting the proliferation, differentiation, and activation of Th2 and Th17 cells, promoting the proliferation of Treg cells, and maintaining Th17/Treg immune homeostasis. TGF-β1, HGF, IDO, PGE2, and microRNA within MSC-Evs are the main effector molecules that treat AD by inhibiting signaling pathways, such as JAK-STAT and NF-kB. However, there is a need for further studies on the specific mechanisms by which MSC-Evs content affects molecular signaling pathways within target cells. Future exploration of target molecules within MSC-Evs and studies on the mechanism of action are expected to identify therapeutic targets and innovative therapeutic strategies.

Effects of MSCs and MSC-Evs on B Cells and IgE Production

B cells orchestrate humoral immunity and antigen presentation.[85] In AD, heightened Th2 cytokine secretion activates B cells, resulting in an excessive production of IgE.[86] IgE binds to allergens and Fc receptors on mast cells, triggering the degranulation of these cells and the release of inflammatory factors. In addition, IgE promotes the development of AD via reacting with self-antigens, positively correlated with the severity of AD.[87,88] In a mouse AD model study, it was found that B cell antigen presentation predominantly induces Th2 cell activation and increased generation of IL-4,

surpassing levels induced by conventional APCs.[89] Rituximab, an anti-CD20 drug, effectively eliminates B cells in AD, curbing T-cell activation, IL-5, and IL-13 production.[90] Consequently, Th2-type inflammation and B-cell activation are crucial in the development of AD.

MSCs exhibit potent immunosuppressive effects on B cells, which could be beneficial in treating AD by inhibiting B cell proliferation and differentiation[58,91](Table 1). It has been found that MSCs downregulate Blimp-1 gene expression, impeding B cells differentiation into plasma cells, and selectively inhibiting B cell proliferation and differentiation into IgM-producing cells. Additionally, MSCs not merely hinder the growth and division of B cells, but also suppress IgE production through cell-cell contact. Lee BC et al have explored the impact of MSCs on AD at different dosages.[59] In a dose-dependent manner, both low and high doses of human adipose tissue-derived MSCs (hA-T-MSCs) effectively reduce serum IgE levels in AD mice, with higher doses significantly mitigating IgE levels, epidermal hyperplasia, and the amount of degranulated MC in skin tissue.[59] In order to study the mechanism involved, they conducted co-culture experiments of hA-T-MSCs and B cells and found that hA-T-MSCs significantly suppressed the growth of B cells. This suppression could be reversed by blocking the COX-2 signaling pathway with celecoxib, which indicates that this pathway plays a role in MSC-mediated immunosuppression.[59] Subsequently, the research group treated UC-MSCs with celecoxib and observed a reversal of mast cell degranulation and a return to normal levels of B-cell maturation markers and IgE expression,[92] thus validating this hypothesis. PGE2, a crucial immunomodulatory factor secreted by MSCs, is synthesized by the COX-2 pathway, and blocking this pathway reduces the production of PGE2. Nari Shin et al found that UC-MSCs administered alone were more effective in treating AD mice than those co-administered with pimecrolimus because pimecrolimus inhibited the COX2-PGE2 axis and decreased the production of PGE2. This verified the important role of PGE2 in the immunomodulation of MSCs.[93] However, the specific mechanism regarding the suppressive effect of PGE2 on immune cells is still unclear, and further studies are needed to explore this in the future.

TGF-β is a crucial cytokine in regulating allergic diseases. Park H et al discovered that when TGF-β was knocked down in MSCs, the inhibitory effects of hUCB-MSCs on B-cell activation and IgE production were reduced. They hypothesized that MSCs inhibit B-cell activation and IgE production by TGF-β signaling.[83] In subsequent experiments, the researchers found that MSCs can inhibit STAT3 and ERK signaling pathways in mast cells by secreting TGF-β. This inhibition prevented mast cell secretion of histamine, TNF-α, and degranulation. These findings confirmed the essential immunomodulatory role of TGF-β in treating AD with MSCs.[60] Overall, MSCs can inhibit B cell maturation, differentiation, and IgE production, and this effect may be mediated through TGF-β and COX-2/PGE2 signaling pathways. Blocking IgE production can prevent mast cell activation, degranulation, and the development of allergic co-morbidities in AD.[94] These mechanisms highlight the potential therapeutic function of MSCs in AD (Table 1, Figure 1). However, it is unclear whether TGF-β and PGE2 function as soluble factors or in EVs and the role of MSC-Evs in regulating B-cell-mediated immunity in AD needs more research. Further studies are necessary to explain the mechanism of action of MSC-Evs in the future.

Effects of MSCs and MSC-Evs on Mast Cells

Mast cells play pivotal roles in allergic diseases, contributing to antigen presentation, leukocyte recruitment, and adaptive immune responses.[95,96] Mast cells significantly increase in the lesional skin of mice with AD.[97] During the progression of AD, a substantial production of IgE occurs in the body. IgE binds FcεRI receptors on mast cells, resulting in the clumping of FcεRI, its cross-linking occurs, which triggers the degranulation of mast cells.[98,99] Mast cells degranulation results in histamine secretion, which binds to histamine receptors on peripheral nerves and causes itching symptoms. In addition, MRGPRX2 and various cationic ligands can activate mast cells to exert degranulation in an IgE-independent manner.[100] Significantly, mast cells exhibit functions that are both pro-inflammatory and anti-inflammatory. By generating IL-4 and IL-13, they facilitate Th2-type inflammation,[101] while also inhibiting skin inflammation by producing IL-2 and activating Tregs.[102] Therefore, regulating mast cells in AD is crucial for symptom alleviation and disease outcome improvement.

Several research findings indicate that MSCs can inhibit the growth and degranulation of mast cells. Administering ASCs and ASC-derived extracellular vesicles (ASC-Evs) to AD mice results in a notable reduction of mast cell invasion in their skin,[103,104] highlighting the substantial suppression of mast cell proliferation by MSCs. To understand how MSCs suppress mast cell proliferation at the molecular level, Tonsil-derived MSC-Evs (T-MSC-Evs) are used to intervene in IMQ-stimulated mast cells.[61] The results showed that T-MSC-Evs significantly inhibited mast cell proliferation, and

activation, and effectively reduced TLR7-mediated inflammatory responses in mast cells. Evs miRNA sequencing revealed that has-miR-214-3p, has-miR-424-5p, and has-miR-302c-3p were significantly elevated. It was hypothesized that these miRNAs might effectively inhibit mast cell proliferation and activation by targeting pro-inflammatory genes such as M-CSF, TIMP2, and MIP-1a.[61] Furthermore, co-culturing human mast cells (LAD2 cells) with hUCB-MSCs in vitro significantly reduced β-hexokinase secretion. Depletion of epidermal growth factor (EGF) in hUCB-MSCs attenuated this effect, suggesting that hUCB-MSCs can inhibit the degranulation of activated mast cells by secreting EGF.[105] EGF was also found to promote keratinocyte migration and inhibit pro-inflammatory cytokine production, thereby promoting wound healing in AD.[105]

Previous research has indicated that MSCs can effectively suppress allergic inflammatory responses by producing PGE2. When MSCs are treated with muramyl dipeptide(MDP) that has immunoadjuvant activity, it activate NOD2 receptors to upregulate PGE2.[62] mdp-treated MSCs (MDP-MSCs) inhibit mast cell degranulation by producing PGE2 and TGF-β1 through the NOD2-RIP2-COX-2 signaling pathway.[62] Furthermore, a study by Lin TY et al found that extracellular vesicles from human umbilical cord mesenchymal stem cells (UC-MSC-Evs) inhibit mast cell degranulation and reduce the production of pro-inflammatory factors by inhibiting the NF-kB and STAT5 signaling pathways.[106] In another study, CASC-Evs alleviated pruritus in AD mice by inhibiting STAT phosphorylation. However, both studies lacked further exploration of the bioactive components within Evs.[104]

Taking these findings together, we have concluded that MSCs and MSC-Evs can inhibit the proliferation and activation of mast cells. This is due to the production and release of EGF, TGF-β1, and PGE2, as well as miRNAs within Evs, and the inhibition of NF-kB and JAK/STAT signaling pathways within mast cells. We hypothesized that MSCs may inhibit the activation of pro-inflammatory signaling pathways in mast cells via cytokines in a paracrine or Evs way, and miRNA-targeted inhibition of pro-inflammatory genes exerts immunosuppressive effects on mast cells. However, it's essential to note conflicting reports suggesting that MSCs may also promote MC proliferation, playing a positive role in wound healing.[107,108] Further investigations are required to comprehensively understand how MSCs influence mast cells in AD.

MSCs and MSC-Evs Reduce Skin Lesions and Promote Epidermal Repair

A large number of studies have found the pro-epidermal repair properties of MSCs. MSCs promote wound healing by regulating vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang1).[63] Intervention with MSC-Evs in AD mice accelerated skin wound healing and improved epidermal barrier function by promoting angiogenesis, stimulating epidermal ceramide production, and inhibiting inflammatory cell infiltration.[18,109] Furthermore, conditioned medium for MSCs (MSC-CM) was found to significantly alleviate the symptoms of AD dermatitis by promoting cell proliferation and wound healing through down-regulation of IL-4 and IgE levels and up-regulation of key angiogenic genes such as VEGF and EGF.[64,110] The transplantation of UC-MSCs into wound tissues has shown their capacity to differentiate into HaCat cells, underscoring the potential for allogeneic therapy with differentiation potential.[65] Yin Hu et al studied miRNAs in extracellular vesicles derived from umbilical cord blood (UCB-Evs) and discovered that miR-21-3p had the highest expression. They conducted further experiments and found that UCB-Evs were taken up by fibroblasts and endothelial cells, leading to miR-21-3p activation of the PI3K/Akt and ERK1/2 pathways, which promoted fibroblast proliferation and migration. Besides, UCB-Evs inhibited PTEN and SPRY1 to promote angiogenesis, which helped skin wound healing. In a separate study,[66] Shi CL et al observed that miR-147a expression in the serum of mice with AD was down-regulated. However, overexpression of miR-147a in keratinocytes significantly increased resistance to TNF-α/IFN-γ-induced apoptosis. In further experiments, they applied AT-MSC-Ev overexpressing miR-147a to effectively ameliorate TNF-α/IFN-γ-mediated damage to HaCaT cells and HUVEC and found that this effect was generated by miR-147a binding to and downregulating the expression of MEF2A and VEGFA in the target cell.[111]

The rapid repair of AD eczema lesions is not only associated with angiogenesis, fibroblast proliferation, and migration, inflammation inhibition but also increased skin cell migration and proliferation. MSCs and the produced components significantly increase the multiplication of KCs and fibroblast cells, primarily by the regulation of growth factors like VEGF and HGF.[112] In addition, It has been discovered that Wnt4 is highly expressed in HUC-MSC-Evs. After Wnt4 is transferred to target cells via Evs, it promotes the proliferation and migration of epidermal cells through

activation of the β-catenin signaling pathway, resulting in the promotion of wound healing.[67] This mechanism of action is also associated with the activation of the AKT signaling pathway. Moreover, MSC-Evs enhances epidermal ceramide synthesis, which is essential for the bilayer structure of the SG-SC interface, improving skin barrier function.[113] In summary, the mechanisms underlying the epidermal repair capacity of MSCs include the promotion of angiogenesis, inhibition of inflammation, increased proliferation and migration of KCs and fibroblasts, and enhancement of epidermal ceramide synthesis, with VEGF, EGF, HGF, and MSC-Evs miRNAs playing a crucial bioregulatory role. In conclusion, the therapeutic effects of MSCs mainly involve regulating multiple immune cells, maintaining immune homeostasis in vivo, and promoting damaged tissue repair. Understanding the immunoregulatory mechanisms of MSCs not only explains the therapeutic principles and mechanisms of MSCs in AD but also provides potential targets and therapeutic ideas for further clinical treatment.

Clinical Trials for MSCs Treatment of AD

Preclinical studies focusing on the treatment of AD with MSCs have consistently demonstrated positive efficacy (Table 2). However, the count of clinical studies conducted in this field is relatively limited, with only 2 published clinical trials and 1 case report in AD patients. During the I/IIa phase of a two-stage study, 34 adults with moderate to severe AD were randomly split into two categories, each receiving subcutaneous injections of either low (2.5×10^7) or high-dose (5.0×10^7) hUCB-MSCs.[114] The results have revealed the degree of symptomatic improvement in AD was positively related to the dose of MSCs administered, with the high-dose group showing a greater rate of improvement than the low-dose group. Furthermore, serum IgE level and blood eosinophil number are significantly downregulated after hUCB-MSCs treatment. Another trial, which included 5 adults with moderate to severe AD, received intravenous MSC treatment (1.0×10^6/kg) over 4 weeks, succeeded by a 12-week monitoring phase and a 38-week extended safety observation period.[115] The inflammatory mediators of IL-22, IL-13, CCL-17, CCL-22, and IgE are notably reduced after MSC treatment without severe adverse reactions. Furthermore, Park KY et al' study has reported that facial redness lesions are significantly improved in two severe AD patients treated with MSC-exosomes for 6 weeks,[116] suggesting the critical role of MSC-exosomes in AD treatment. Accordingly, current clinical trial data on the treatment of AD with MSCs has suggested benefits and safety. However, the available research is limited. To establish the standardized cell therapy based on MSCs, more future studies with larger patient cohorts and high quality should be carried out, facilitating the widespread application of MSC therapy in AD treatment.

Discussion and Perspectives

In summary, AD has become a significant public health problem due to its high incidence, long duration, and easy recurrence, resulting in a heavy disease burden, great mental pressure for patients, and significant demands on medical resources. The pathogenesis of AD is complex, and traditional drug therapy has limitations, highlighting the need for innovative therapeutic approaches. Although existing drugs can relieve AD skin inflammation and itching symptoms, they often fail to prevent the recurrence of the disease. Long-term use of drugs can bring adverse reactions and drug resistance. Currently, new treatments for AD, including drugs that are still in the clinical trial stage, include IL-4Rα receptor antagonists, Janus kinase inhibitors, IL-31Rα blockers, and IL-22 and Th17/IL-23 monoclonal antibodies.[117] One of the most notable drugs is Dupilumab, the first IL-4Rα receptor antagonist used in clinical treatment, which has shown promising results in treating patients with moderate-to-severe AD. However, some patients do not respond well to Dupilumab treatment, and relapse upon discontinuing the drug is common.[118,119] Although Janus Kinase Inhibitors improve symptoms in patients with poor efficacy of Dupilumab therapy, their inhibitory effect on the JAK/STAT pathway makes patients more susceptible to herpes, respiratory tract infections, and other adverse events.[120] In clinical trials of new biologics for AD treatment, IL-31Rα blockers have been shown to effectively improve dermatitis symptoms in patients with moderate-to-severe AD, and IL-22 monoclonal antibodies have been successful in treating patients with high baseline levels of IL-22. Unfortunately, Th17/IL-23 monoclonal antibodies did not achieve satisfactory results.[117] These findings suggest that AD's pathogenesis is complex, with multiple inflammatory factors playing pathogenic roles in the body. Moreover, the clinical variability of individuals is extensive, and a single treatment often fails to improve the patient's condition.

Table 2 The Clinical Experiments Estimating the Efficacy of MSC Treatment and AD Outcomes

Phase	MSC/ MSC-EV Source	Enrollment Criteria	Period	Therapy	Dose	Frequency	Follow-Up Indicators	Clinical Outcomes	Ref.
I/IIa	Umbilical cord	34 patients with moderate to severe AD (7 in stage 1 and 27 in stage 2a) SCORAD Score> 20, age 20 and 60 years, persistent symptoms (6 months)	Phase 1:4 weeks; Phase 2a: 12 weeks. To evaluate the safety of hUCB-MSCs in moderate to severe AD	Hypodermic injection	Low dose: 2.5^10^7 MSC; High dose: 5.0^10^7 MSC	Once a week	EASI, IGA, and SCORAD scores; Serum IgE levels and the number of eosinophils	Achieved EASI-50 remission in 55% of high-dose patients and 36% of low-dose patients; decreased total serum IgE levels and blood eosinophil count	[114]
–	Bone marrow	5 patients with moderate to severe AD with a SCORAD score> 20); Ages ranged from 20 to 60 years, persistent symptoms (6 months)	16 weeks (4 weeks of treatment, 12 weeks of follow-up)	Intravenous injection	1.0^10^6 cells/kg.	Every 2 weeks 3 times	EAS I, IGA, and SCORAD scores; serum levels of CCL-17, CCL-22, IL-13, IL-18, IL-22, and IgE	EASI-50 mitigation: S001 first cycle; S002 two cycles; S003 and S004 second cycle; S005 none; decreased CCL-17, IL-13, and IL-22; S001 and S002 IgE decreased significantly	[115]
–	Adipose tissue	Two AD patients with refractory DFR	6 weeks	Electropore transdermal administration	1mL ASCEs	Once a week	Whether the facial erythema lesions	Significantly improved facial erythema lesion	[116]

Abbreviations: hUCB-MSC, Human umbilical cord mesenchymal stem cells; AD, Atopic dermatitis; EASI, eczema area, and severity index; IGA, Investigator Global Assessment; SCORAD, SCORing Atopic Dermatitis; CCL-17, C-C motif chemokine ligand 17; CCL-22, C-C motif chemokine ligand 22; IL-13, Interleukin-13; IL-18, Interleukin-18; IL-22, Interleukin-22; IgE, Immunoglobulin E; ASCEs, Adipose tissue-derived mesenchymal stem cell (MSC)-derived exosome.

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The therapeutic role of MSCs in AD has been demonstrated in preclinical studies. MSCs inhibit the release of various inflammatory factors and help maintain a healthy immune balance. MSCs are hypoimmunogenic, meaning they are barely rejected by the immune system and are safe in clinical trials. However, there are functional differences between MSCs from different tissue sources. Further studies comparing the efficacy and safety of different MSCs are needed to determine the optimal therapeutic regimen for clinical application. MSC-Evs offer advantages such as easy production, convenient storage, and large-scale preparation, all prerequisites for future clinical applications. Although positive results have been observed in preclinical studies and limited clinical trials, MSC-Evs still face challenges such as expensive production costs and limited production capacity. Finding ways to increase production capacity and reduce production costs has become a critical concern.

Currently, induced mesenchymal stem cells (iMSCs) generated from induced pluripotent stem cells (iPSCs) have been extensively studied. It has been found that iMSCs exhibit mesenchymal stem cell-like characteristics, can be easily obtained from iPSCs, and possess the ability to proliferate indefinitely. Several studies have shown that iMSC extracellular vesicles (iMSC-Evs) are effective in alleviating dermatitis symptoms in AD mice. This indicates that iMSCs could be an ideal source for producing bulk Evs in the future.[84,121,122] However, clinical trials of MSCs for AD treatment are relatively limited. The mode of administration, effective therapeutic dose, and frequency of treatment of MSCs are still unclear. Most preclinical experiments have used subcutaneous injections as a therapeutic method. However, in severe AD cases with extensive skin rashes, subcutaneous injections of MSCs into multiple points of lesional skin can increase the pain and therapeutic risk for patients. Although intravenous injection is simpler and easier to standardize, MSCs injected into the body tend to be retained in tissues such as the lungs and liver, resulting in insufficient therapeutic efficacy and affecting local blood microcirculation.

It is essential to select appropriate therapeutic methods and clarify the therapeutic advantages of MSC-Evs for the future clinical application of MSCs. Simultaneously, it is crucial to establish a robust research and development and quality control system for MSCs to address the issue of MSCs heterogeneity, such as MSCs from different tissue sources or MSCs isolated from the same tissue, which still carry the risk of unstable immunomodulation in clinical trials. Additionally, conducting more extensive clinical trials is necessary to validate the safety and effectiveness of treatments involving MSCs and MSC-Evs.

This review summarizes and reflects on the pathogenesis of AD, therapeutic approaches, therapeutic mechanisms of MSCs, and clinical issues to be addressed. It has great potential to address the challenges posed by AD and to enhance the overall management of this complex dermatological condition.

Data Sharing Statement

The data supporting this review are from previously reported studies and datasets, which have been cited. The processed data are available from Donghua Xu upon request.

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Author Contributions

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

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Disclosure

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