BIOCELL
2022 46(11): 2363-2367

Tech Science Press

Mesenchymal stem cells and cell-free preparations for treating atopic dermatitis

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Key words: Atopic dermatitis, Conditioned medium, Dermatology, Mesenchymal stem cells, Stem cells

Abstract: Atopic dermatitis (AD) is a chronic cutaneous inflammatory disease caused by an interaction between genetic, immune and epidermal barrier factors. Several treatments can be used to treat this disease but there are patients that do not respond to actual drugs. So, there is a need to develop effective therapies for AD. Mesenchymal stem cells (MSCs) are non-hematopoietic multipotent adult progenitor cells with immunomodulatory power and self-regenerating capacity to repair tissue damage, so they could be a potential effective treatment for AD. MSCs-Conditioned Medium (CM) and MSCs-exosomes are cell-free preparation with molecules secreted by stem cells that could be also beneficial for AD. This viewpoint reviews the actual development of MSCs, MSCs-CM and MSCs-exosomes for treating patients with AD.

Introduction

There is a need to develop effective drugs for treating atopic dermatitis (AD). Mesenchymal stem cells (MSCs) are non-hematopoietic multipotent adult progenitor cells with immunomodulatory potential and self-regenerating capacity to restore tissue damage. MSCs-Conditioned Medium (CM) and MSCs-exosomes are cell-free preparation that contains molecules secreted by stem cells and have similar therapeutic potential than MSCs. This viewpoint reviews the actual development of MSCs, MSCs-CM and MSCs-exosomes for treating patients with AD in clinical settings.

Systematic Description

Human mesenchymal stem cells (MSCs) are non-hematopoietic multipotent adult progenitor cells that can be isolated from several sources, including adipose tissue (AT-MSCs), umbilical cord blood (UC-MSCs), bone marrow (BM-MSCs) and skin (Sierra-Sanchez *et al.*, 2021). The beneficial effect of MSCs is not only in the cell component but also in its secretome, due to its abundant resource of paracrine factors. The secretome include the molecules secreted by stem cells, containing proteins, microRNA, growth factors, antioxidants, proteasomes and exosomes (Montero-Vilchez *et al.*, 2021). MSCs secretome has one free fraction- called Conditioned Media (CM), and other encapsulated into extracellular vesicles–called exosomes (Quinones-Vico *et al.*, 2021). It has been described that cell to cell interaction or a long-term remaining in the body can be the strong point in efficacy or safety, but cell-free preparations could have several advantages over cell therapy, as their manufacturing process is easier and more economic and there is no risk of adverse events associated with cell, including rejection, tumors, thrombosis, ossification or calcification (Bogatcheva and Coleman, 2019). Nevertheless, it is still difficult to define the composition of the secretome, there are inconsistencies about cell-free preparation, the quantities needed are about 10–25 times higher than directly administered live cells and there could be instability and short half-life of some proteins (Ahangar *et al.*, 2020). Despite all these facts, MSCs, CM-MSCs and MSCs-exosomes are a promising therapeutic option for several skin conditions due to their potential to proliferate and repair tissue damage and to modulate immune responses (Kim *et al.*, 2017). They have been mainly used in ulcers, hair restoration, skin rejuvenation and inflammatory skin diseases (Montero-Vilchez *et al.*, 2021; Quinones-Vico *et al.*, 2021; Sierra-Sanchez *et al.*, 2021).

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Received: 12 January 2022; Accepted: 11 April 2022

Doi: 10.32604/biocell.2022.021399

Atopic dermatitis (AD) is a chronic cutaneous inflammatory disease characterized by pruritic and recurrent eczematous lesions (Wollenberg *et al.*, 2020). It is one of the most prevalent (Bylund *et al.*, 2020) and most expensive cutaneous disease (Sacotte and Silverberg, 2018). Its etiopathogenesis is multifactorial and includes genetic factors, immune dysregulation, epidermal barrier dysfunction, and gut dysbiosis (Luger *et al.*, 2021). Topical corticosteroids are the basic treatment for AD, but patients with severe disease need systemic immunosuppressants, including cyclosporin or methotrexate, or biologic therapies, such as dupilumab, tralokinumab and JAK inhibitors (Wollenberg *et al.*, 2020). Long-term use of immunosuppressants may cause side-effects, including nephrotoxicity, hematological alterations or gastrointestinal problems, and multiple administrations of these drugs are needed to achieve effectiveness. Moreover, there are patients that do not reach a clinical response with these treatments (Simpson *et al.*, 2016). Therefore, there is still a need to develop safe and effective therapies for AD.

MSCs, CM-MSCs and MSCs-exosomes could be a promising treatment for AD patients. Their main advantages compared to traditional treatment could be their longer-term effect with a capacity to restore the immune system and the possibility to avoid traditional drugs side events (Shin *et al.*, 2020). MSCs and cell free preparations could be effective for AD due to their ability to regulate innate and acquired immune responses and their capacity of homing and repairing areas of inflammation and tissue damage (Balato and Caiazzo, 2017; Fig. 1). The imbalance between type 2 helper T cell (Th2) and type 1 helper T cell (Th1) plays a key role in the pathogenesis of AD. This disease is mainly characterized by excessive Th2 mediated inflammatory responses, but other subsets of helper T cells, including Th1, Th17, and Th22 might also be involved in its pathogenesis. Preclinical studies have shown that different types of MSCs have immunomodulatory effects on lymphocyte function, suppress T-cell proliferation, reduce the number of CD4+ and CD8+ T cells in the spleen, lymph and skin, and reduce cytokine production, including Th2 cytokines (IL-4, IL-5 and IL-13) and other proinflammatory cytokines such as TNF-α, TGF-β or IFN-γ (Sierra-Sanchez *et al.*, 2021). MSCs derived from skin of AD patients also overexpress Th1/Th17 cytokines, emphasizing the role of the Th17 pathway in the chronic phase of AD (Orciani *et al.*, 2017). Moreover, MSCs inhibit B cell proliferation and maturation, decrease Ig E levels and inhibit mast cell degranulation and histamine and prostaglandin E2 level (Daltro *et al.*, 2020). Moreover, the impact of MSCs on epidermal barrier function in animal models have been shown by a reduced transepidermal water loss (TEWL) and epidermal thickness in the areas treated with MSCs (Sierra-Sanchez *et al.*, 2021). It should be also considered that MSCs therapeutic effects could be disturb by conventional AD treatments, such as calcineurin inhibitors that decrease the production of prostaglandin E2, one of the most critical immunomodulatory factors for MSCs treatment (Shin *et al.*, 2021).

MSCs-CM derived from murine adipose tissue and injected subcutaneously decrease AD severity in murine

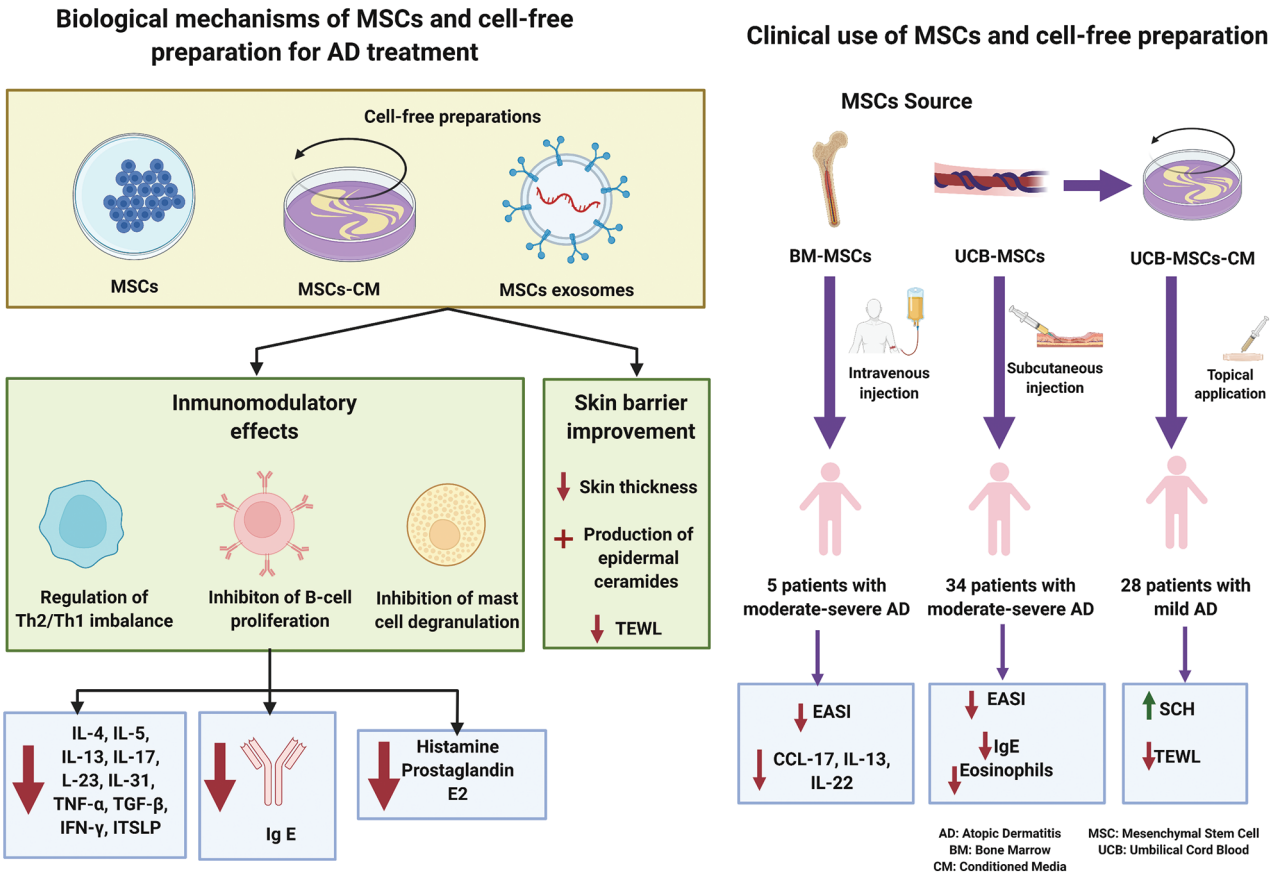

FIGURE 1. Summarize of biological mechanism and clinical use of mesenchymal stem cell and their cell-free preparations for treating atopic dermatitis.

TABLE 1

Studies reported using mesenchymal stem cell and their conditioned medium for treating atopic dermatitis

	MSC source	Dose regimen and route of administration	Number of participants	Age (years)/ Sex	Follow-up (weeks)	Baseline AD severity	Final AD severity	Percentage of patients reaching EASI50	Other outcomes	Adverse events
		Two doses of 2.5 × 10^7 cells subcutaneously injected	17	29.07 ± 2.03 64.29% male	12	EASI: 20.54 ± 3.97 SCORAD: 61.17 ± 4.11 IGA: 3.79 ± 0.16 NRS for pruritus: 7 ± 0.54	EASI decreased 25.81 ± 11.27% SCORAD decreased 28.04 ± 6.20% IGA decreased 18.69 ± 5.03% NRS for pruritus decreased: 33.47 ± 11.15%	36% (5/14)	Ig E and eosinophil counts decreased	No severe adverse events. Total rate of adverse events: 12% (2/17) Skin infection: 6% (1/17)
Kim *et al.* (2017)	Human umbilical cord	Two doses of 5 × 10^7 cells subcutaneously injected	17	28.08 ± 1.07 63.64% male	12	EASI: 19.60 ± 2.30 SCORAD: 65.46 ± 3.37 IGA: 3.91 ± 0.21 NRS for pruritus: 6.18 ± 0.69	EASI decreased 55.02 ± 5.83% SCORAD decreased 49.97 ± 4.33% IGA decreased 33.03 ± 6.61% NRS for pruritus decreased: 57.55 ± 7.41%	55% (6/11)		No severe adverse events. Total rate of adverse events: 56% (9/16) General disorders and injection related side events: 31% (5/17) Gastrointestinal disorders: 6% (1/17) Skin infection: 6% (1/17)
Shin *et al.* (2021)	Human bone marrow	1.0 × 10^6 cells/kg intravenously administrated 3 times every 2 weeks at 2–4.5 mL/min infusion rate for 4 weeks.	5	23 years (range, 20–29). 60% male	16	EASI: 31.5 (range 15.5-40) SCORAD: 66.2 (range 51–76.1) IGA: 3.8 (range 3–4)	EASI decreased 15.88 (49.59% reduction) SCORAD decreased 39.95 (39.66% reduction) IGA decreased 3.2 (15.79 reduction)	80% (4/5)	CCL-17, IL-13 and IL-22 decreased. Total IgE in the undiluted serum did not reduce. IgE measured by diluting the serum decreased in patients 1 and 2	No severe adverse events
Kim *et al.* (2020)	Human umbilical cord	MSCs-CM containing cream bases were applied twice a day to patients' lesion and non-lesion skin	28	24.68 ± 4.32 53.57% male	4	NS	NS	NS	SCH increased by 15.67 AU and 14.49 AU both on eczematous lesions and non-involved skin, respectively. TEWL decreased by 15.09 and 3.08 $g{\cdot}h^{-1}{\cdot}m^{-2}$ both on eczematous lesions and non-involved skin, respectively	No adverse events

Notes: AD, Atopic Dermatitis; AU, Arbitrary Units; CM, Conditioned Media; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; MSC, Mesenchymal Stem Cell; NS, Not Specified; SCORAD, Severity Scoring for Atopic Dermatitis.

model, skin thickness, mast cell infiltration, Th2 expression, Ig E levels and IL-4 (Park *et al.*, 2019). Furthermore, MSCs-exosomes decrease the production of Th2 cytokines (including IL-4, IL-5, IL-13, IL-23 and IL-31) and others pro-inflammatory cytokines (such as IL-17, TNF-α, IFN-γ and TSLP) in a dose-dependent manner, stimulate the production of epidermal ceramides and activate genes associated with keratinocyte differentiation, improving epidermal barrier function (Quinones-Vico *et al.*, 2021).

The clinical use of MSC and MSCs-CM has been reported in few studies (Table 1). Two studies have evaluated the effect of MSCs derived from human umbilical cord blood (Kim *et al.*, 2017) and human bone marrow (Shin *et al.*, 2021) on patients with moderate to severe AD with persistent symptoms that had not previously responded to conventional therapies. Thirty-four patients with moderate to severe AD received two doses of UC-MSCs subcutaneously injected. Patients were assigned to receive a low dose of MSCs (2.5 × 107 cells) or a high dose (5.0 × 107 cells). After 12-weeks follow-up, 36% of the patients treated with a low dose of UC-MSCs and 55% of the patients treated with a high dose reached a clinical respond, assessed by a decreased higher than 50% in the Eczema Area and Severity Index (EASI)-50 (Kim *et al.*, 2017). Ig E and eosinophil counts also decreased after the treatment (Kim *et al.*, 2017). Moreover, BM-MSCs injected intravenously three times every 2 weeks were tested in five patients with moderate to severe AD. 80% of the participants reached EASI-50 after one or two cycles of treatment and was maintained. CCL-17, IL-13, and IL-22 decreased in these patients, but Ig E was not reduced after 16 weeks follow-up (Shin *et al.*, 2021). In this study two patients maintained long-term efficacy (84 weeks follow-up) without systemic steroids and immunomodulators, and increased levels of IL-17, so the authors suggested that MSCs therapy could be a therapeutic option for moderate to severe AD with high IL-17 levels (Shin *et al.*, 2021). No serious adverse events were reported in these studies (Kim *et al.*, 2017; Shin *et al.*, 2021). The adverse events were transient and mild and mainly related to injection site responses (Kim *et al.*, 2017). Another clinical trial has been completed evaluating the effect of one intravenous injection of AT-MSCs (NCT02888704), but the results have not been posted. There are also ongoing clinical trials testing UC-MSCs subcutaneously injected (NCT05004324), BM-MSCs intravenously injected (NCT04179760) and AT-MSCs intravenously injected (NCT04137562). The routes of administration evaluated are subcutaneous and intravenous injections. Subcutaneous injections could be safer, due to a lower rate of side events such as pulmonary embolism (Kim *et al.*, 2021), and more effective to reduce gross and histological signatures of AD (Kim *et al.*, 2017).

Regarding cell-free preparations, one study evaluated the effects of MSCs-CM, derived from human umbilical cord blood, for treating patients with mild AD. Twenty-eight patients with AD were treated with MSCs-CM in cream base for 4 weeks. MSCs-CM was applied on both eczematous lesions and non-involved skin twice a day. After treatment, stratum corneum hydration increased while transepidermal water loss decreased both on eczematous lesions and non-involved skin, reflecting skin barrier improvement (Kim *et al.*, 2020). No study about the use of MSCs-exosomes in human has been reported yet.

Conclusion

In conclusion, MSCs, MSCs-CM and exosomes seem promising therapy for AD. It is difficult to know what therapy could be more effective at such early stages. Cell-free preparations could have advantages over cell therapy as risks related to cell therapies may be avoided. Nevertheless, there are no clinical trials about CM and exosomes use in AD. Cell free preparations should be further investigated for treating AD and clinical trials comparing MSCs, MSCs-CM and exosomes should be conducted. More studies regarding the ideal source of MSCs and the route of administration should also be carried out.

Availability of Data and Materials: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contribution: This statement should make clear the contribution of all authors. An author name can appear multiple times, and each author name must appear at least once. It can be described in the following manner: The authors confirm contribution to the paper as follows: study conception and design: TMV; data collection: TMV, MSD, CMV, ASS; analysis and interpretation of results: TMV and SAS; draft manuscript preparation: TMV and SAS. All authors reviewed the results and approved the final version of the manuscript.

Ethics Approval: Not applicable.

Funding Statement: The authors received no specific funding for this study.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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