

New Approaches to Dermatological Conditions Employing Mesenchymal Stem Cell Therapies

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Review Article

Volume 3 Issue 3

Received Date: December 21, 2018

Published Date: December 31, 2018

DOI: 10.23880/cdoaj-16000167

Abstract

Mesenchymal stem cells (MSCs) are multipotent stem cells with the capacity to differentiate in vitro into diverse cell lineages and secrete different bioactive molecules with trophic, paracrine and immunomodulatory functions. On the other hand, skin inflammation may be a sign of allergic, autoimmune, or infectious conditions and it is observed in several diseases such as atopic dermatitis, cutaneous graft versus host disease, cutaneous lupus erythematosus, psoriasis and systemic sclerosis.

Traditional therapies for these skin diseases are not completely effective and have potential systemic adverse events. Consequently, new safer therapies need to be developed, being MSCs a value alternative. Due to the lack of knowledge on MSCs mode of action, animal models of disease help to discern their mechanism of immunoregulation and improve their safety after their application.

The literature supports that MSCs act by a paracrine via by using anti-inflammatory cytokines targeting specifically those cells involved in the inflammation of immune-regulated diseases. Consequently, MSCs reduce the excessive immune responses and protect the adjacent tissues.

Keywords: Atopic dermatitis; Cutaneous graft versus host disease; Cutaneous lupus erythematosus; Mesenchymal stem cell; Psoriasis; Systemic sclerosis

Introduction

Skin inflammation may be a sign of allergic, autoimmune, or infectious conditions. Atopic dermatitis (AD), contact dermatitis, and urticaria (hives) are examples of allergic skin conditions whilst psoriasis and acne are considered primarily inflammatory in nature [1]. AD and psoriasis have increased their prevalence in

industrialized countries due to the higher level of contamination [2], which resulted in a considerable psychosocial and economic burden for patients and their families [3-5].

AD is a common, clinically defined skin disease frequently associated with allergic rhinitis, asthma, and immunoglobulin E (IgE)-mediated food reactions [6]. The

traditional treatment for AD is based in topical anti-inflammatory agents (corticosteroids), that provide a short-term benefit but long-term remission is difficult to achieve [7].

Psoriasis is a lifelong, chronic, and immune-mediated systemic disease with preferential skin involvement. It is characterized by excessive growth and aberrant differentiation of keratinocytes through the activation of the cellular immune system, with T cells, dendritic cells and various immune-related cytokines and chemokines implicated in pathogenesis. Topical corticosteroids is the mainstay of treatment for psoriasis due to their immunosuppressive, anti-inflammatory and antiproliferative properties [8].

Although corticosteroids are the traditional therapy for these skin diseases, they have cutaneous adverse effects such as atrophy, striae and/or telangiectases, and also potential systemic adverse events. Consequently, long-term utilization is not recommended [9] and alternative and safer therapies are being applied.

Mesenchymal stem cells (MSC) have been exploited for their immunomodulatory properties in the treatment of a number of immune-based disorders [10], and different works in recent years have shown their possible use in dermatological diseases. That is why we will focus this review on the main characteristics of these cells and their possible mechanism of action in specific dermatological pathologies.

Mesenchymal Stem Cells

Sources of MSCs

MSCs were originally isolated from the bone marrow [11], but later they have been obtained from nearly all tissues of the body, including adipose tissue [12,13], umbilical cord blood [14], umbilical cord Wharton's jelly [15,16], allanto-amniotic membranes [17], synovia [18], periost [13], skeletal muscle [13], teeth [19], placenta [20] or endometrium [21]. All of them were sources of MSCs, as determined by morphology, adherence to plastic, trilineage differentiation, and detection of stem cell surface markers with immunofluorescent and flow cytometric analyses.

The two more abundant sources for MSCs are foetal umbilical cord matrix (Wharton's jelly) and adult adipose tissue [15]. Although both sources show potential for their application in biomedicine, the number of scientific publications based on the use of adipose-tissue derived MSCs (5469 publications in PubMed, accessed December 2018 the 26th) overpass those using Wharton's jelly MSCs (712 publications in PubMed, accessed December 2018 the 26th). Consequently, and because they are the main objective of the authors research, this review is mainly focussed on adipose tissue derived MSCs. The stem cells derived from adipose tissue are similar to bone marrow-derived MSCs in morphology and phenotype, but show some differences [22]. Adipose tissue collection is less traumatic and the presence of MSCs in this tissue is higher than bone marrow. Consequently, adipose tissue MSCs are a promising source for regenerative medicine (Figure 1).

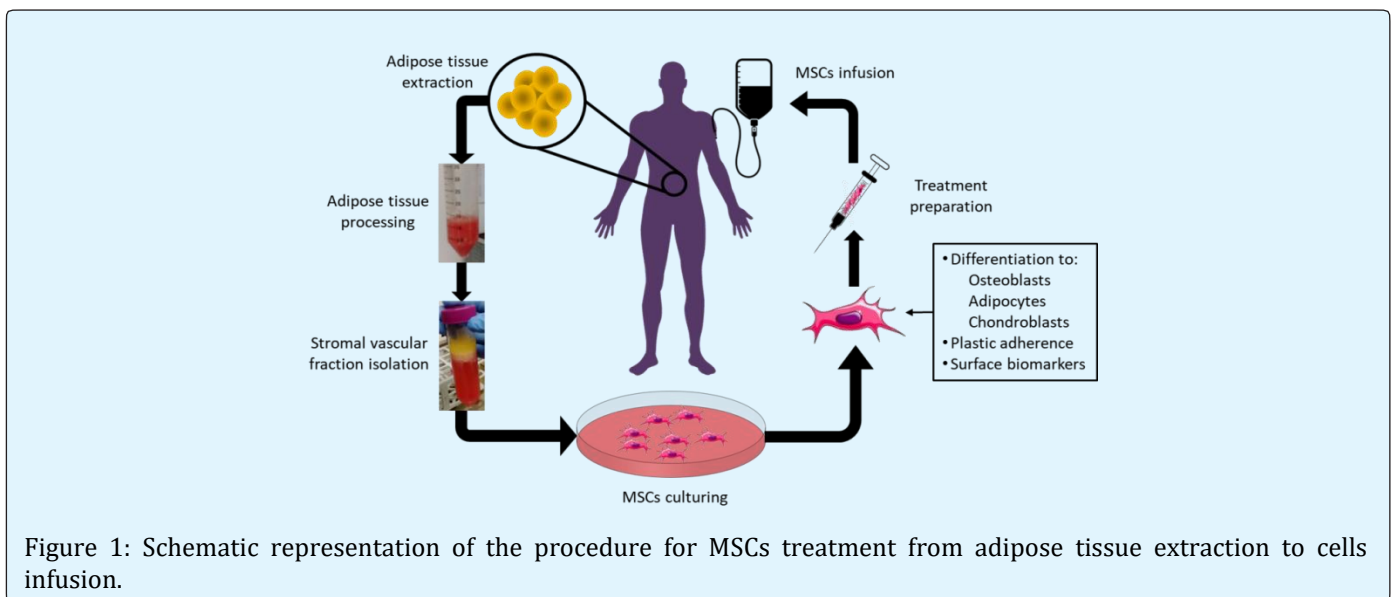


Figure 1: Schematic representation of the procedure for MSCs treatment from adipose tissue extraction to cells infusion.

Characterization of MSCs

The International Society for Cellular Therapy (ISCT) established the minimal criteria to define human mesenchymal stem cells (MSCs) in order to allow the comparison of results among different studies: (i) MSCs must be plastic-adherent when maintained in standard culture conditions; (ii) MSCs must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR surface molecules; (iii) MSCs must differentiate into osteoblasts, adipocytes and chondroblasts *in vitro* [23,24].

General Mode of Action

Despite the capacity of MSCs to differentiate, growing evidence suggests that disease-modifying activity of MSCs is due to different products secreted by the cells in response to environmental niche stimuli [25,26] (Figure 2). This paracrine signalling mechanism by MSCs might be more important than differentiation in stimulating repair responses [27] and makes allogeneic MSCs a suitable therapy for many diseases, due to the possibility of infusion without a substantial risk of immune rejection. Differentiation to specialized cell types, would change MSCs phenotype making them prone to be detected and deleted by the host immune system. Since paracrine mechanism is active in a stemness state, it is not affected by the host immune system.

MSCs exhibit immunosuppressive effects on MHC-mismatched lymphocytes proliferation and these cells can also inhibit naive, memory and activated T cells, B cells, natural killer cells and dendritic cells [28,29].

MSCs have a trophic, anti-inflammatory and immunosuppressive action, by modulating T and B cells and inducing the expression of anti-inflammatory factors, and among them transforming growth factor (TGF)- β 1 [30].

TGF- β is widely expressed in a variety of tissues and local production of TGF- β is a potent mechanism of immune suppression in a variety of contexts. MSC production of TGF- β has been demonstrated in MSCs derived from numerous tissues including adipose [31], being the essential contribution of TGF- β the suppression of T cell proliferation [32].

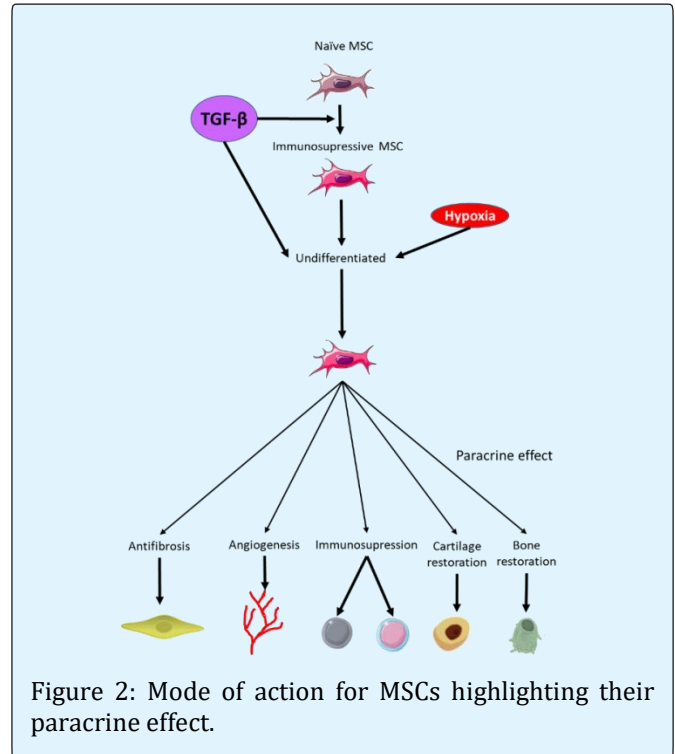


Figure 2: Mode of action for MSCs highlighting their paracrine effect.

Allogeneic vs Autologous MSCs Use

MSCs express low levels of major histocompatibility complex class I (MHC-I) but lack expression of MHC-II surface molecules. Their low immunogenicity and their immunomodulatory potential allow their allogeneic use, which makes them a promising new treatment for severe refractory autoimmune diseases [28,33-37].

Although the majority of clinical trials listed on www.clinicaltrials.gov test the efficacy in humans of autologous MSCs (more than 300), the number of clinical trials testing allogeneic MSCs efficacy has increased reaching more than 200 studies.

Therapeutic Use of MSCs in Skin Diseases

There are currently many registered clinical trials (<https://clinicaltrials.gov/>) about the therapeutic use of the MSCs in different skin diseases (Table 1). This is a proof of their potential as cell therapy in dermatologic conditions.

ClinicalTrials.gov Identifier	Intervention	Phase	Condition
NCT02888704	BM-derived adult human MSC	Phase 1	Atopic Dermatitis
NCT03252340	BM-derived adult human MSCs	Not Applicable	Atopic Dermatitis
NCT03765957	Umbilical cord blood-derived MSCs	Early phase 1	Psoriasis
NCT03745417	Umbilical cord-derived MSCs	Phase 1/Phase 2	Psoriasis
NCT02491658	Umbilical cord-derived MSCs	Phase 1/Phase 2	Psoriasis Vulgaris
NCT03265613	Adipose-derived multipotent MSCs	Phase 1/Phase 2	Psoriasis
NCT03392311	Adipose-derived multipotent MSCs	Phase 1/Phase 2	Psoriasis
NCT03424629	Low-dose umbilical cord-derived MSCs	Phase 1	Moderate and Severe Plaque Psoriasis
	High-dose umbilical cord derived MSCs		
NCT02918123	Allogeneic human umbilical cord blood-derived MSCs	Phase 1	Psoriasis
NCT01765634	BM-derived MSCs	Phase 2	Acute GvHD
NCT01765660	BM-derived MSCs	Phase 2	Chronic GvHD
NCT01956903	BM-derived allogeneic MSCs	Phase 1/Phase 2	Chronic GvHD
NCT00972660	BM-derived MSCs	Phase 2	GvHD
NCT01526850	BM-derived MSCs	Phase 2/Phase 3	Chronic GvHD
NCT01222039	Adipose-derived allogeneic MSCs	Phase 1/Phase 2	GvHD
NCT00366145	BM-derived MSCs	Phase 3	GvHD
NCT00314483	MSCs infusion (MSCs origin not specified)	Phase 1/Phase 2	GvHD
NCT01941394	BM-derived MSCs	Phase 2	GvHD
NCT00447460	BM-derived MSCs	Phase 1/Phase 2	GvHD
NCT03219801	Umbilical cord-derived MSCs	Early phase 1	SLE
NCT03171194	Low-dose umbilical cord-derived MSCs	Phase 1	SLE
NCT03562065	Umbilical cord-derived MSCs	Phase 1/Phase 2	Lupus Erythematosus
NCT02633163	Low-dose umbilical cord-derived MSCs	Phase 2	SLE
	High-dose umbilical cord-derived MSCs		
NCT00698191	BM-derived allogeneic MSCs	Phase 1/Phase 2	Refractory SLE
NCT01741857	Human umbilical cord-derived MSCs	Phase 1/Phase 2	SLE
NCT03673748	BM-derived MSCs	Phase 2	Lupus Erythematosus
NCT02213705	Allogeneic MSCs (MSCs origin not specified)	Phase 1/Phase 2	Systemic Scleroderma
NCT00962923	Umbilical cord-derived allogeneic MSCs	Phase 1/Phase 2	Systemic Sclerosis
NCT02975960	Autologous stromal vascular fraction (adipose tissue)	Not Applicable	Systemic Sclerosis
NCT03211793	BM-derived MSCs	Phase 1/Phase 2	Systemic Sclerosis

Table 1: Registered clinical trials testing MSCs on dermatological conditions.

BM: Bone marrow; GvHD: Graft-versus-host disease; SLE: Systemic lupus erythematosus; MSCs: Mesenchymal stem (or stromal) cells.

Atopic Dermatitis

MSCs have been extensively studied as a cellular therapy for different pathological conditions using the dog as an animal model [34,37-41]. There are currently many studies in both, animals and human beings, which demonstrate the efficacy of MSCs in atopic dermatitis [42,43]. Our research group showed that systemic

administration of allogeneic MSCs appeared to be a simple therapy with positive outcome in the remission of clinical signs for canine AD refractory to conventional medications, for at least six months and with no adverse events [44].

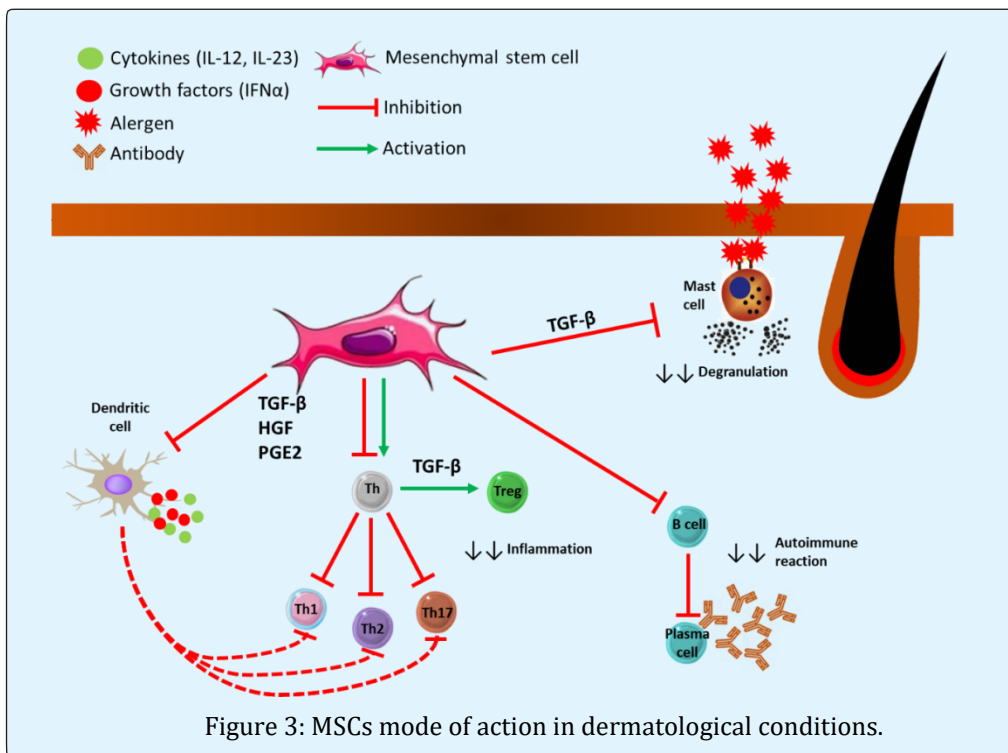
Allogeneic use of MSCs is an alternative to autologous when limiting factors such as age, medications and

concomitant diseases, may have an impact on the quality and immunomodulatory capacity of autologous therapy [45].

Recently, human MSCs derived from different tissues affected by AD showed immunomodulatory profile differences compared with healthy subjects, evidencing that MSCs could be involved in the AD pathogenesis [46] as it has been described in other immune-mediated diseases [47-49]. This would support the idea of an allogeneic MSCs therapy in AD [42].

Considering that the dog develops AD naturally with cutaneous clinical characteristics similar to the human beings, despite some differences, [50-53] dogs might serve as a partial model for human AD therapy with cell-based regenerative strategies.

Different *in vivo* studies evidenced that systemically infused MSCs homing to injured and inflamed tissues resulted in a positive therapeutic effect [43,54-56]. In AD, MSCs migrate to skin lesions through draining lymph nodes [43] and decrease physiological migration of interstitial dendritic cells from skin to lymph nodes. At the same time, MSCs decrease cell infiltration in the skin lesion reducing generation of effector T cells [43]. Dendritic cells are the most potent type of antigen-presenting cells and play crucial roles in the initiation and control of the adaptive immune responses [57]. In addition, some MSCs may remain in secondary lymphoid organs to block the migration of effector T cells to the inflamed region [43,57] (Figure 3).



Psoriasis

Human psoriasis, in contrast to AD, is characterized by the lack of a naturally occurring disorder in animals [58], making difficult to test new biological therapies effect on the disease. Nevertheless, animal models of psoriasis have helped to find out the biological functions of inflammatory mediators, adaptive immune mechanisms, keratinocytes, and endothelial cells.

Dendritic cells (DCs) and T cell-mediated immune responses are key actors in the psoriasis development being Th1 and Th17 subsets the primary effector cells [59]. DCs produce interferon α (IFN- α) and interleukins (IL-12, IL-23) that drive the differentiation of Th1 and Th17 cells, leading to the onset of psoriasis.

MSCs from patients with psoriasis showed impaired anti-inflammatory function against Th cell subsets [60],

suggesting that allogeneic MSC therapy could be beneficial in treating psoriasis. Previous preclinical studies demonstrated that MSCs efficiently attenuates skin inflammation in mice via suppression of Th1, Th2 and Th17 differentiation and up-regulating Treg population [61] (Figure 3).

Cutaneous Graft Versus Host Disease (GvHD)

Chronic graft-versus-host disease (GvHD) is the major cause of morbidity and mortality in those patients that received allogeneic hematopoietic cell transplantation. In this disease, T cells transferred from donor recognize host HLA molecules as non-self and generate an immune response [62]. Current immunosuppressive drugs are not effective to treat chronic GvHD and there is a significant impediment to progress in treating chronic GvHD due to the lack of existing animal models.

T cells can differentiate into Th1, Th2 and Th17 subsets in response to the environment cytokines. The different T cells subsets play a role in GvHD development and recent animal models research have explained how Th1 cells are major effector cells in acute GvHD, although Th2 cells and IL-22-producing CD4+ T cells are also actors in this condition. Th17 and Treg cells and also B cells might contribute to the development of the disease [63]. MSCs can inhibit the proliferation and differentiation of T lymphocytes through various mechanisms, including secretion of soluble mediators such as hepatocyte growth factor (HGF), transforming growth factor β 1 (TGF- β 1) and prostaglandin E2 (PGE2) [64,65] (Figure 3).

Prochymal® (remestemcel-L) is the first stem cell therapy approved by Canada for GvHD. It is an allogeneic stem therapy based on bone marrow derived MSCs that demonstrated a statistically important improvement in survival, with the largest benefit of survival being noted in those with the most severe forms of GvHD [66].

Cutaneous Lupus Erythematosus

Lupus erythematosus is an autoimmune chronic inflammatory disease that can affect every organ. It triggers among others the cutaneous lupus erythematosus when the skin is predominantly affected. In this skin condition, specific antibodies are produced and cause damage to the skin resulting in the appearance of a rash. Complex cascades of native skin cells, such as endothelial cells, keratinocytes, and immune cells, especially Th1 cells, neutrophils and polyclonal B cells, are known to be implicated in cutaneous inflammation [67].

Mutated mice have been widely used as experimental animal models of lupus erythematosus to explore the therapeutic potential of MSCs, showing a down-regulated B cell activation and maturation through soluble mediators [68] (Figure 3).

In humans, MSC-based therapies have shown to trigger remission in patients with refractory systemic lupus erythematosus including skin manifestations [69].

Systemic Sclerosis

Systemic sclerosis is an autoimmune disorder where healthy tissue is destroyed by the own immune system. Systemic sclerosis is characterized by changes in the texture and appearance of the skin due to increased collagen production [70]. The immunological responses in patients with systemic sclerosis are predominated by Th2 cells and relevant cytokines like IL-4 and IL-13, which contributes to the formation of pro-fibrotic microenvironment [71]. Due to the different features and complexity of pathogenesis, currently there are no satisfactory therapeutic approaches for systemic sclerosis that keeps higher rates of morbidity and mortality [72].

MSCs show anti-fibrotic, anti-oxidant and immunomodulatory capabilities for skin lesions as well as lung injuries in murine models of disease [73]. MSCs were able to mediate T-cell apoptosis, trigger macrophages to produce TGF- β 1 and finally up-regulate Treg cells population [74] (Figure 3).

Despite that the animal models did not reproduce perfectly the human disease condition, the results are enough to expect clinical benefit of MSC transplantation in patients with systemic sclerosis. In fact, transplantation of MSCs triggered a significant improvement in tightening of the skin without complications, thus suggesting they are a potentially valuable skin therapy in systemic sclerosis [75].

Conclusion

Research in stem cell-based therapies is increasing thus promising a great impact of this cell-based treatment on the medicine of the 21st century. Current studies on the use of MSCs are not only exponentially increasing but also broadening their target conditions, so they can be applied to various skin diseases. Anyhow, most of the works are focused on the potential of MSCs to treat immunomodulated skin diseases through their paracrine effect.

MSCs can be obtained from different tissue sources, but adipose tissue-derived MSCs have some advantages such as: (1) their abundance in donors and (2) their convenient isolation by less invasive and traumatic methods.

Normally, in research for drugs and other cell therapies there is a comprehensive understanding of the therapeutic mechanism before their clinical application. Nevertheless, MSCs have been successfully applied despite a limited understanding of their *in vivo* function under normal physiological conditions. Given that the current understanding of MSCs mode of action is still limited, the use of animal models of disease will help to discern not only their mechanism of immunoregulation but also improve their safety and reduce the adverse events after their application.

MSCs act by a paracrine via by using anti-inflammatory cytokines targeting specifically those cells involved in the inflammation of immune-regulated diseases. Consequently, MSCs reduce the excessive immune responses and protect the adjacent tissues.

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