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Immunomodulatory interactions between mesenchymal stromal/stem cells and immune cells in psoriasis: therapeutic potential and challenges

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Abstract

Psoriasis is defined as a persistent autoimmune disease characterized by the appearance of psoriatic lesions on the surface of the skin. Currently, various approaches including chemicals, corticosteroids, phototherapy, and biological agents are being proposed and implemented to improve psoriatic lesions by modulating immune system activity or metabolic processes, often with unintended consequences and side effects. Currently, mesenchymal stromal/stem cells (MSCs) have attracted considerable interest among researchers due to their ability to modulate immune responses and their ease of application, representing a promising strategy for alleviating clinical symptoms in the treatment of allergic reactions, autoimmune diseases, cancer, and more. This study will investigate how MSCs interact with immune system cells involved in psoriasis development, such as neutrophils, keratinocytes, dendritic cells (DC), and T cell subtypes, for potential therapeutic use in psoriasis management. In this case, several immunomodulatory mechanisms are involved, including expression of chemokines, pro-inflammatory cytokines, matrix metalloproteinase and other factors involved in cell proliferation and neutrophil extracellular trap (NET) formation are among the effects of MSCs on keratinocytes and neutrophils. keratinocytes and neutrophils as pro-inflammatory cells involved in psoriasis pathogenesis and pathogenesis and progression of psoriasis. On the other hand, MSCs interact with DCs and various subsets of T cells, including Th1, Th2, Th17 and Tregs, to generate tolerogenic DCs and increase the differentiation of Tregs and modulate the Th17/Treg towards a regulatory state through overexpression of anti-inflammatory and immunomodulatory and immunomodulatory cytokines, including IL-10 and transforming growth Factor beta (TGF-β). Finally, we will focus on the challenges and obstacles in psoriasis treatment using MSCs, including limitations in the case of using MSCs from different sources and side effects that may be encountered by whole cell therapy strategies, which are attracting attention towards the implication of cell-free regimens such as using MSC-derived secretome or extracellular vesicles and exosomes to provide similar therapeutic outcomes without presumed side effects.

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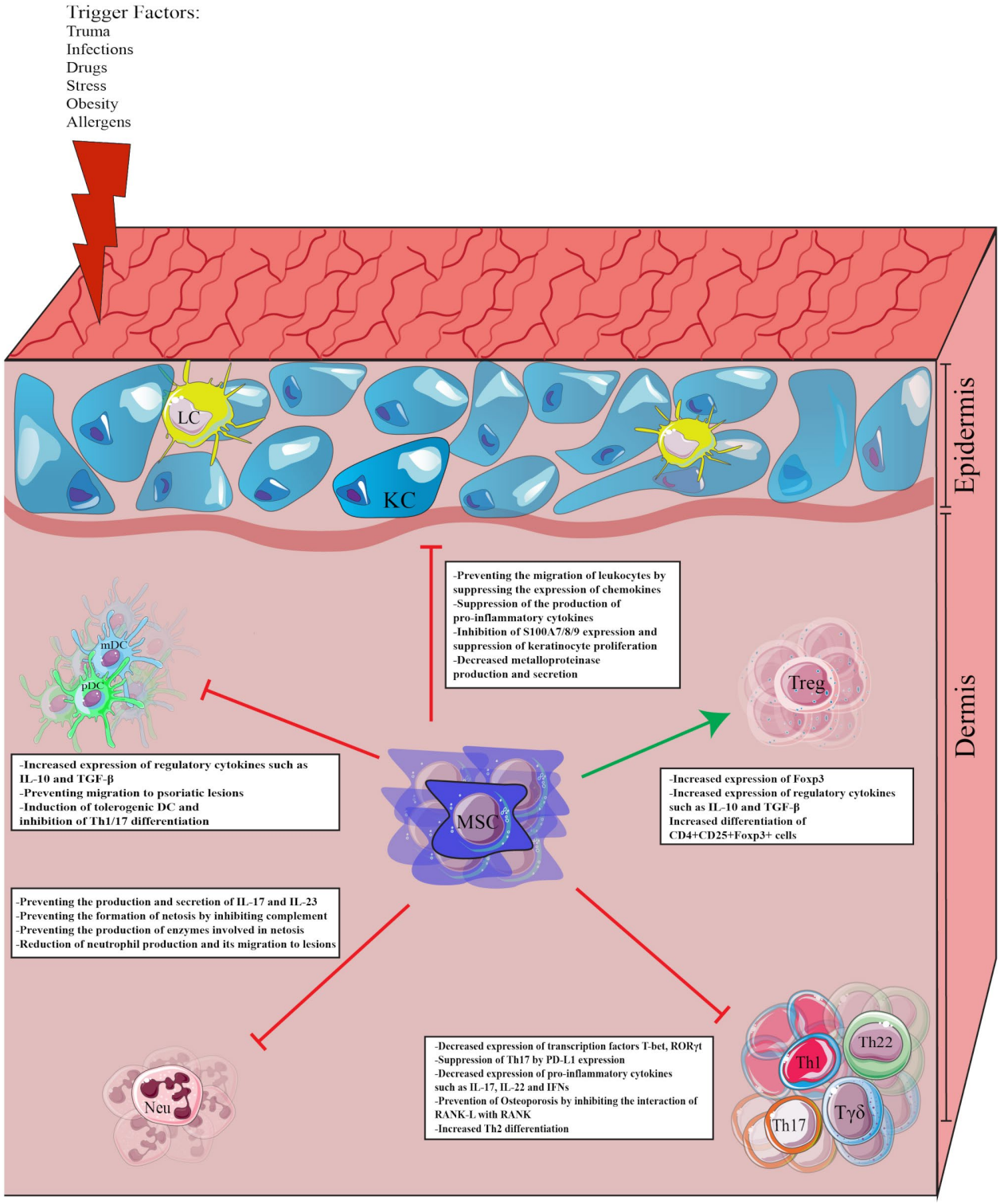
Graphical abstract



Keywords Mesenchymal stromal/stem cell, Psoriasis, Inflammation, Immune cells

Introduction

The World Health Organization (WHO) classifies

psoriasis as a non-communicable disease (NCD) and, to the best of our knowledge, the genetic makeup of the host and its immune system are closely related to psoriasis. Undoubtedly, in addition to these two concerns, lifestyle, antibiotic use, drug abuse, and other related environmental elements may contribute significantly to the development of this condition [1, 2]. The disease has a similar prevalence in both sexes, but is more common in adults with an estimated prevalence of 0.51–11.43% than in children with 0–1.37% [3–5]. Of the various forms identified, chronic plaque-type psoriasis has been the most studied, perhaps because of its effect on joint health and quality of life [6]. In addition to the manifestation of scaling, redness and thickening of the skin layer, the initiation and intensification of inflammation in arthritis also leads to joint deterioration and deformity, rendering patients immobile [7, 8]. In addition, the presence of psoriasis may increase the incidence of comorbidities such as cardiovascular disease (CVD), skin malignancies, diabetes mellitus, depression, and so on [9].

Several factors that may contribute to the onset of psoriasis have been extensively studied [10]. Stress, medications, microbes, pollutants, allergies, obesity, smoking, alcoholism, dysbiosis of the skin flora, and other factors can all cause a condition to flare-ups [10, 11]. It damages keratinocytes, which are epithelial cells, and releases molecules known to cause damage, such as self-nucleotides [12]. Damaged keratinocytes release pro-inflammatory cytokines that attracts effector lymphocytes, memory cells, neutrophils, monocytes, interleukin (IL)-15, IL-18, IL-19, IL-20, IL-33, CXCL10, CCL5, and CCL20, among other inflammatory cells, to the injured tissue [12, 13]. Mast cells, also known as tissue ghost cells, play a critical role in the escalation of the inflammation by producing IL-17, IL-22, and interferon-gamma (IFN-γ) [13–15]. Alternatively, self-nucleotides attached to antimicrobial peptides (AMP) released by keratinocytes, such as cathelicidin, bind to pattern recognition receptors (PRR) such as TLR7/9 and activate plasmacytoid dendritic cells (pDC) [16]. Monocyte-derived dendritic cells (moDC) can be stimulated by activated plasmacytoid dendritic cells through the production of interferon-alpha/beta (IFN-α/β) [17]. Primary helper T cells (Th) are polarized into Th1 and Th17 by monocytic dendritic cells through the secretion of IFN-γ, IL-23, IL-12, and tumor necrosis factor-alpha (TNF-α) [13]. By releasing pro-inflammatory mediators such as IL-1β, IL-6, IL-8, IL-12, IL-18, IL-21, IL-22, TNF-α, and IFN-γ, Th1 and Th17 increase inflammation at the site of injury [18, 19]. However, CD8 + T lymphocytes activated by plasmacytoid dendritic cells exacerbate inflammation by producing IL-17 [20]. By secreting IFN-γ and TNF-α, other CD8 + T effector cells enhance the activity of classical macrophages (MQ) at the site of injury [21]. Given the key role of the immune system in the pathogenesis of psoriasis, treatments that regulate immune function and inhibit immune-mediated processes have been used to improve psoriatic lesions.

Many common topical medications that have long been used to treat mild to severe forms of psoriasis are currently in use. These medications, such as dithranol (anthralin), calcineurin inhibitors, vitamin D analogs, keratolytics, retinoids, and corticosteroids are used for various purposes in the treatment of psoriasis, including reducing inflammation, slowing down skin cell growth, and relieving symptoms [22]. Phototherapy or application of ultraviolet (UV) light, including UVA and UVB, and biologic drugs, including brodalumab, secukinumab, etanercept, infliximab, ustekinumab, adalimumab, and ixekizumab are used to neutralize and suppress the secretion of TNF-α, IL-12/IL-23p40, and IL-23/IL-17 in order to treat moderate to severe psoriasis [22–24]. The Food and Drug Administration (FDA) has also approved tofacitinib as a Janus kinase (JAK) inhibitor for the treatment of psoriasis and rheumatoid arthritis (RA), indicating its efficacy in targeting specific pathways involved in these diseases [25].

Cell therapy has become one of the novel techniques that have attracted the interest of researchers, given the depth of studies conducted in the field of contemporary therapeutic strategies [26]. A population of multipotent, plastic, adherent, and self-renewing stromal cells (defined by high expression of markers such as CD105, CD90, and CD73), with low or absent expression of HLA-DR, CD45, CD34, CD14 or CD11b, and CD79a or CD19) predominates in tissues of mesenchymal origin and is responsible for the regeneration of these tissues, now referred to as mesenchymal stem/stromal cells (MSC) [27, 28]. MSCs are widely used in cell therapy because of their easy isolation, ability to differentiate into different cell types (such as adipocytes, chondrocytes, and osteocytes in vitro), ability to regulate the immune system by interacting with immune system cells, ability to migrate to injury sites, and secretion of biological molecules including cytokines and growth factors and extracellular vesicles (EV) [29, 30]. Recently, scientists have been able to isolate MSCs from bone marrow and other tissues like skin, adipose tissue, dental pulp, menstrual blood, amniotic fluid, Wharton's jelly of the umbilical cord, and umbilical blood and use them for therapeutic applications [31]. Given the therapeutic potential of MSCs in regulating the innate and acquired immune system, this review was undertaken to investigate the therapeutic approaches of MSCs and their mechanisms in regulating the active immune system in psoriatic lesions.

Immunomodulatory properties of MSCs (Fig. 1)

Several lines of evidence showed that MSCs are effective in the treatment of autoimmune disorders because of their anti-inflammatory features [32]. MSCs have the ability to inhibit the cell cycle, exert direct suppression of cells, and secrete molecules that inhibit the immune system [33]. Hepatocyte growth factor (HGF), prostaglandin E2 (PGE2), indoleamine 1, 3-dioxygenase (IDO), nitric oxide (NO), transforming growth factor-beta 1 (TGF-β1), and IL-10 are recognized immunomodulators that are synthesized and secreted by MSCs [34, 35]. In addition, the immunomodulatory functions of MSCs extend to regulation of antigen presentation by DCs and MQs, inhibition of type I interferon secretion by pDCs, prevention of expansion and polarization of Th17/Th1 lymphocytes and their cytokine secretion, inhibition of cytotoxic capacity of natural killer (NK) and CD8 + T cells, and suppression of autoantibody production by B lymphocytes [36, 37]. In addition, MSCs possess the capability to arrest the cell cycle in T lymphocytes [38, 39]. This effect was examined in the study by Li et al., in which it was found that the IDO released by hUCB-MSCs plays a crucial role in this process. IDO functions by consuming tryptophan, a cytokine that is indispensable for the survival of T lymphocytes, and converting it into kynurenine. This process leads to the inhibition and arrest of the cell cycle, specifically in the S phase, within T lymphocytes. Furthermore, hUCB-MSCs have been observed to augment apoptosis in T lymphocytes by increasing the expression of caspase 3, a hallmark of apoptosis, and decreasing the expression of Bcl-2, an anti-apoptotic protein, and CDK4, a cell cycle regulator [40]. Also, MSC-derived exosome function has been demonstrated to involve the induction of T lymphocyte cell cycle arrest, a process that is characterized by an increase in p27kip1 protein and a concomitant decrease in Cdk2 protein [41].

The immunomodulatory effect of MSCs can be modified by the microenvironment and the cytokines in it, according to research [42]. Reduction of anti-inflammatory activity and production of inflammatory mediators, including inducible nitric oxide synthase (iNOS), microRNA-155 (miR-155) (which is involved in inflammation and glucose metabolism in psoriasis lesions), vascular endothelial growth factor (VEGF), cadherin 13 (CDH13), basic fibroblast growth factor (bFGF), angiopoietin (Ang), hypoxia-inducible factor 1-alpha (HIF-1α), and consequently, angiogenesis, acanthosis, and an increase in the recruitment and activation of innate and adaptive immune responses have been observed when pro-inflammatory factors, including TNF-α, IL-1β, and IFN-γ, are administered to MSCs [42, 43].

Compared to MSCs isolated from the control group, a study by A. Campanati et al. demonstrated that MSCs isolated from psoriasis patients had higher concentration of inflammatory mediators, such as IFN-γ, IL-17(F/C/RA), IL-23 A, IL-8, and IL-6, as well as chemokines involved in the recruitment of more leukocytes to psoriasis lesions, such as CXCL-9 and CXCL-10 [44]. In

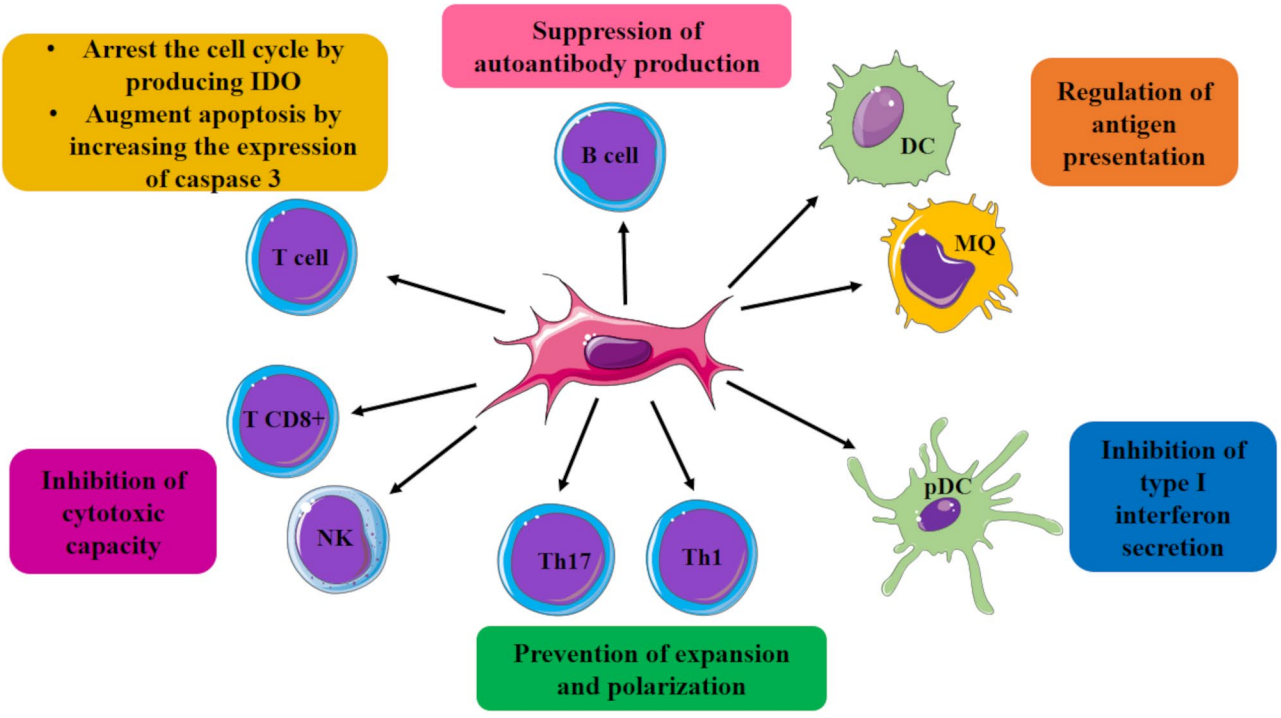


Fig. 1 Immunomodulatory properties of MSCs

this regard, studies have shown that MSCs isolated from psoriatic lesions (P-MSCs) exhibit distinct functional properties compared to those of conventional MSCs, characterized by secretion of pro-inflammatory factors and enzymes like glucose transporter (GLUT), hexokinase 2 (HK2), and VEGF [45]. In addition, a reduction in secreted frizzled related protein 2 (SFRP2) expression and a subsequent increase in Wingless-related integration site (Wnt) signaling cascades promotes the proliferation and differentiation of immune system cells and their migration to skin lesions [45]. Furthermore, another study by Orciani and colleagues showed that MSCs from psoriatic lesions had significantly elevated levels of VEGF and NO compared to those derived from healthy individuals with atopic dermatitis [46]. This increase in VEGF and NO led to a marked increase in angiogenesis and inflammation within the psoriatic lesions. In contrast to untreated MSCs, the study by Campanati and his colleagues showed that the treatment of MSCs with adalimumab and etanercept (two TNF-α inhibitors) decreased the expression of VEGF, iNOS and NO in them, indicating the importance of the microenvironment surrounding MSCs in the nature of their response [47]. In contrast, Zhao et al. separated MSCs from normal healthy individuals (N-MSC) and P-MSC, which were then subjected to further analysis. The results showed that both P- and N-MSCs led to a reduction in the expression of the T-box transcription factor (t-bet), which is associated with the differentiation of Th1 and cytotoxic T lymphocytes (CTL), and RoR-γt, which is associated with Th17 polarization [48]. Notably, N-MSCs showed greater suppression of pro-inflammatory molecule production and T-cell proliferation and specialization compared to P-MSCs [48].

Given the multiple roles of MSCs and their dependence on their microenvironment, further research is needed to elucidate the intricacies of this phenomenon.

Interaction of MSCs and immune cells in psoriasis (Table 1)

A literature search was conducted across various databases including Scopus, PubMed, Web of Science, and Google Scholar using relevant keywords including psoriasis, mesenchymal stromal/stem cell (MSC), immune cell, keratinocyte, neutrophil, monocyte/macrophage, dendritic cell, T cell, and B cell to gather articles which assessed the effects of MSC on the treatment of psoriasis and its interactions with immune cells in various in vitro and in vivo studies. (Fig. 2)

MSC and neutrophil

The phenomenon of neutrophil extracellular trap (NET) formation or NETosis in neutrophils has been observed to induce IFN-α production by pDC, thrombosis by platelets, autoantibody production by B lymphocytes, and activation of T lymphocytes [49]. This may contribute to the exacerbation of autoimmune disorders including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, RA, systemic lupus erythematosus (SLE), and antiphospholipid syndrome (APS) [50, 51]. In addition, neutrophils, the firs cells to migrate to damaged regions, exert a pivotal influence on the progression of inflammation due to their ability to produce pro-inflammatory cytokines [52]. Furthermore, studies in psoriasis patients have shown that IL-17, a cytokine produced by neutrophils, is a critical mediator in the psoriasis pathogenesis [53].

In a study conducted by Zhang et al. in a murine model of psoriasis, MSC-derived exosomes demonstrated the ability to decrease concentration of key mediators, such as IL-17 and IL-23, within psoriatic lesions [54]. In addition, the activity of the terminal pathway of the complement system (C5-9), which is considered to be a crucial inducer of NETosis, is suppressed by these exosomes and by CD59, preventing the formation of NETs and the secretion of IL-17 by neutrophils, thereby ameliorating psoriatic lesions [54]. Also, in this regard, Lai et al. showed that MSC-derived exosomes, by inhibiting the formation of C5-9 through the CD59 molecule, inhibited the production of IL-17 by neutrophils and, as a result, improved psoriatic lesions [55]. In the study conducted by Chen et al., the administration of MSCs was observed to result in a reduction in the number of CD11b + Ly6G + neutrophils and a concomitant decrease in the expression of NETs [56]. They also observed a reduction in the expression of neutrophilic enzymes, such as myeloperoxidase (MPO) and cathelin-related antimicrobial peptide (CRAMP), as well as IL-17 [56]. Consequently, the function of neutrophils was found to be regulated. The formation of NET by neutrophils has been shown to activate pDC and produce type 1 interferon, which ultimately exacerbates autoimmune diseases [57]. These findings suggest that the administration of MSCs can effectively alleviate inflammation and tissue damage in psoriatic lesions by inhibiting neutrophil chemotaxis, preventing IL-17 secretion, and suppressing NETosis. In this regard, in the study by Y, Ding et al., MSCs pretreated with IFN-γ and TNF-α showed more significant improvement in psoriatic lesions compared to MSCs in the imiquimod (IMQ)-induced mouse model [58]. Specifically, epidermal thickness, clinical symptoms, and spleen evaluation (cell count, volume, and mass) showed more significant improvement in the group receiving pre-treated MSCs in comparison with the group received MSCs and IMQ group [58]. Furthermore, this study demonstrated that pretreated MSCs, through tumor necrosis factor-inducible gene-6 (TSG-6), decreased the relative expression of CXCL1 (a key chemokine in neutrophil

Table 1 Summary of studies on the immunomodulating effects of MSCs on psoriasis

MSC source	Type of cases	Administration route	Main findings	ref
MSC-derived exosomes	Mouse model	Topical application	Concentration of key mediators, such as IL-17 and IL-23 (↓) Formation of NETs by C5b-9 formation (↓) Function of neutrophils (↓)	[54]
MSC-derived exosomes	Mouse model	Intraperitoneal injection and Topical application	Formation of C5-9 And NETs (↓) Production of IL-17 by neutrophils (↓)	[55]
hUC-MSC	Mouse model	Tail vein Injection	Number of CD11b + Ly6G + neutrophils (↓) Formation of NETs (↓) Expression of neutrophilic enzymes (like MPO and CRAMP) Level of keratin 16 (K16) (↓) Level of S100A7, S100A8, and S100A9 (↓) Levels of pro-inflammatory factors (↓) Expression of IL-10 (↑) and IL-17 (↓) Number of Th2 (↑)	[56]
hUC-MSC pretreated with IFN-γ and TNF-α	Mouse model	Subcutaneous Injection	Improvement in clinical symptoms, and spleen evaluation decreased the relative expression of CXCL1 (neutrophils migration (↓)) and inhibited STAT1 phosphorylation in keratinocytes (Healing of psoriatic lesions (↑))	[58]
hUC-MSCs	Mouse model	Tail vein Injection	TNF-α concentration in culture medium (↓) Matrix metalloproteinase (MMP)-13 (↓)	[64]
hUC-MSCs	Mouse model and cell culture	Subcutaneous injection	Level of pro-inflammatory cytokines (↓) Expression of IL-10 and IDO in DCs (↑) Differentiation of Th0 into Th1, Th2, and Th17 cells (↓) Migration and implantation of CD11c+, CD11b+, and CD4 + cells (↓) Treg differentiation (↑)	[69]
T-MSC	Mouse model	Tail vein Injection	Th17 differentiation (via PD-1/PD-L1 interaction) (↓) Volume, mass, and number of splenocytes (↓) PASI score (↓) Expression of IL-17, IL-22, IL-23, TNF-α, IFN-γ, K6, K16, and CCL20 genes (↓) Expression of PD-1 in T lymphocytes (↑)	[72]
Small EVs derived from IFN-γ-activated hUCB-MSCs	Mouse model and cell culture	Intradermal injection	Th17 exhaustion (↑) Th2 differentiation (↑) Inflammatory mediators including IL-17 A, IFN-γ, IL-6, and TNF-α (↓) PASI score (↓) Activity of the miR-210 molecule (plays a role in the differentiation of Th1/Th17) (↓)	[73]
BM-MSCs and AD-MSCs	Mouse model	Intravenous injection	PASI score (↓) Number of CD3 + cells (↓) Expression of S100A9/7 and CCL17 (↓)	[75]
hE-MSC	Mouse model	Subcutaneous injection	Th1 and Th17 secretome (such as TNF-α, IFN-γ, IFN-α, IL-27, IL-17 A and IL-23) (↓) Improvement in clinical symptoms (↑)	[76]
T-MSCs	Mouse model and cell culture	Intravenous injection	Level of osteoprotegerin (OPG) (↑) and (RANK)/RANKL interaction between Th17 and osteoclast (↓) PASI score (↓)	[77]
MSCs and SOD3-induced MSCs	Mouse model	Subcutaneous injection	Psoriatic epidermal thickness (↓) Mass and number of spleen and lymph nodes cells (↓) Number and proliferation of T lymphocytes, neutrophils, and DC (↓) and number of Treg (↑) Inhibitory molecules such as IL-10, TGF-β, and Foxp3 (↑) Decrease in IL-17, IL-22, IL-6, and IL-23, and transcription factors such as STAT1, STAT3, JAK1, RoR-γt (↓) Activation of NF-κB, MAPK (↓) cAMP and PKA/CREB (↑) and anti-inflammatory phenotype (↑)	[80]
G-MSC	Mouse model	Tail vein Injection	PASI score (↓) Number of CD3 + CD25 + T lymphocytes (↑) and CD3 + CD17 + T lymphocytes (↓) Concentration of IL-6, IL-17 A, IL-17 F, IL-21, and TNF-α (↓) and concentration of IL-10	[87]

Table 1 (continued)

MSC source	Type of cases	Administration route	Main findings	ref
hUCB-MSCs	Phase 1/2a (17 patients)	Intravenous injection	Population of CD3 + CD4 + CD25 + CD127-/low Tregs and CD3 + CD8 + CCR7 + CD45RA- memory T cells (↑) PASI, PGA and BSA score (↓) neutrophil count (↓) IgG titer (↓) BUN levels (↓)	[88]
DPSC and HGF-DPSC	Mouse model and cell culture	?	Number of Th1 and Th17 cells (↓) and Treg (↑) CK6 and CK17 (↓) pro-inflammatory factors such as IFN-γ, TNF-α, and IL-17 A (↓) IL-10 expression (↑) expression of T-bet, RoR-γt, IL-17 A, IL-17 F, and IL-23 (↓) and FOXP3 (↑)	[89]
dermal MSCs	Cell culture	-	Expression of the TGF-β receptor (↑) Ratio of Tregs to Th17 cells (↑)	[90]

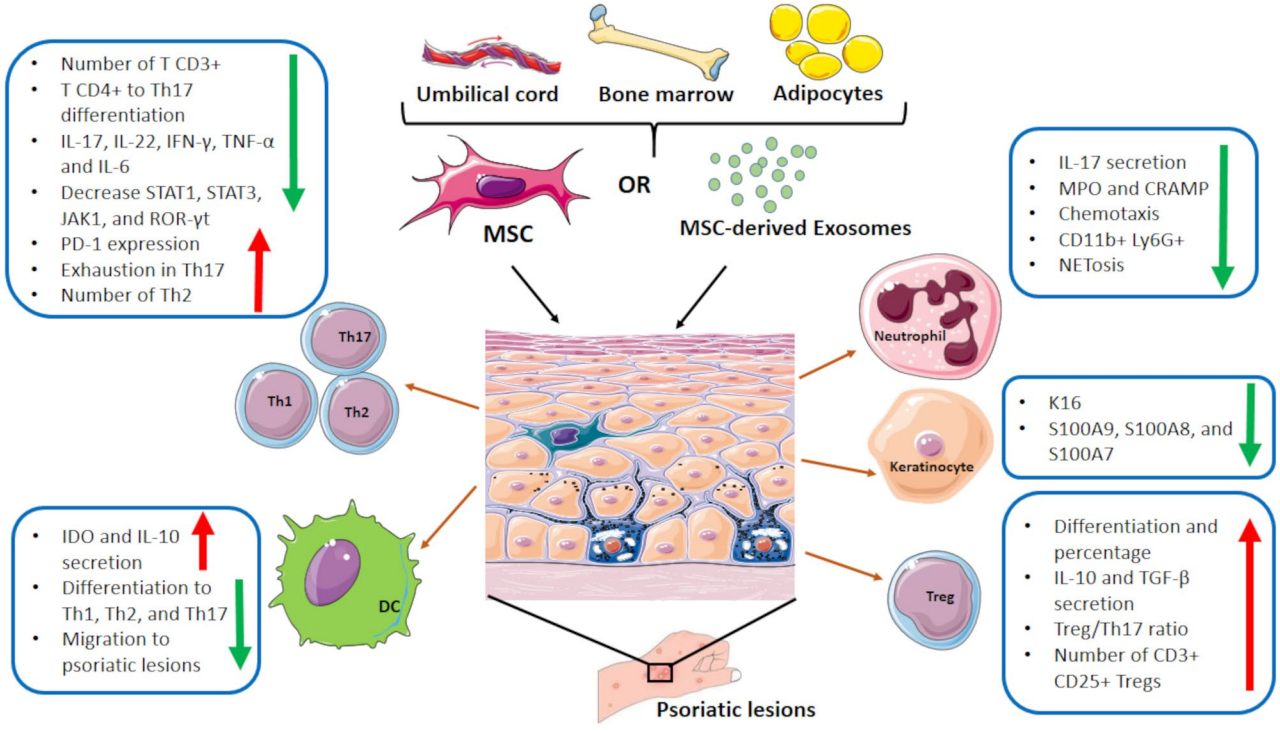


Fig. 2 interactions MSCs and immune cell in psoriatic lesions

migration) and inhibited STAT1 phosphorylation in keratinocytes [58]. According to the research, the use of MSCs ultimately causes damage to the skin tissue by preventing neutrophil chemotaxis to psoriatic lesions, IL-17 damage and formation of NETosis.

MSC and keratinocyte

As a part of the innate immune system, the skin epithelial barrier is instrumental in defending the body against a variety of detrimental factors [59]. As one of the most critical cells within this layer, keratinocytes play a pivotal role in regulating immune system responses by secreting immunoregulatory molecules [60, 61]. MSCs have been shown to affect the progression of psoriasis by acting on keratinocytes, with the potential to either improve or either exacerbate the disease depending on the surrounding microenvironment [62]. Chen et al. revealed that the level of keratin 16 (K16), which is considered as a marker of uncontrolled proliferation and differentiation of keratinocytes, significantly decreased in mice which treated with MSCs compared to the mice received IMQ, and the epidermis of the skin improved [56]. In addition, the molecules involved in keratinocyte differentiation, including S100A7, S100A8, and S100A9, showed a significant decrease in the treated mice in comparison with the sham group, suggesting a reduction in keratinocyte proliferation [56, 63]. The effect of MSCs on immune modulation was demonstrated in a study conducted by

Ren et al. The results showed that co-culture of MSCs with the THP-1 cell line led to a remarkable reduction in TNF-α concentration [64]. Furthermore, the researchers showed that TNF-α upregulate matrix metalloproteinase (MMP)-13 through the nuclear factor-kappa B (NF-κB) signaling pathway [64]. Considering these observations, the authors suggest that MSC therapy may be a promising approach for enhancing psoriatic lesions. Furthermore, the statistical analysis of the mathematical model of severe psoriasis in the study by Kushary et al. demonstrated that the combined treatment of a TNF-α inhibitor and MSCs effectively reduced the density of keratinocytes and other cells associated with psoriatic lesions [65]. The reduction in keratinocyte proliferation seen in the treated groups suggests that MSCs may provide a more comprehensive therapeutic approach for psoriatic lesions. Further studies are required to explore the mechanisms underlying this therapeutic effect and to optimize the treatment strategy for patients with severe psoriasis.

MSC and DC

DCs are recognized as a critical cell type, responsible for presenting antigens to T lymphocytes and initiating their activation [66]. In addition, another group of these cells, pDCs, play a pivotal role in antiviral defense by producing type 1 interferons [67]. However, in the immunopathogenesis of psoriasis, pDCs have the potential to initiate an immune system response and exacerbate psoriasis by producing IFN-α/β [68]. In addition, Lee et al., showed that human umbilical cord blood (hUCB)-derived MSCs increase the expression of IL-10 and IDO in DCs when co-cultured, thereby preventing the differentiation of CD4 + T lymphocytes [69]. Also, DCs in proximity to hUCB-MSCs block the differentiation of Th0 into Th1, Th2, and Th17 cells (under the conditions required for polarization of each cell type) [69]. The results of the flow cytometry analysis revealed that the migration and implantation of CD11c+, CD11b+, and CD4 + cells to the injection site of IL-23 (used to induce a mouse model of psoriasis) was effectively prevented [69]. These results indicate that the immunomodulatory properties of MSCs may effectively modulate dendritic cell responses in psoriasis.

MSC and Th1/Th17/Th2

In the immunopathogenesis of numerous autoimmune disorders, the balance between Th1/Th17 and Th2 lymphocytes can precipitate the onset and exacerbation of the disease or facilitate its recovery [70]. To this end, extensive research has been conducted with the aim of elucidating the underlying mechanisms involved in this balance, thereby facilitating the control of autoimmune disease recovery processes through a more comprehensive understanding of these mechanisms. In this context, MSCs with their regulatory properties have the potential to influence the balance of T lymphocytes [71]. In this regard, Lee et al. demonstrated that hUCB-MSCs inhibit T CD4 + to Th17 differentiation in vitro (co-culture) and increase regulatory T cells (Treg) differentiation, thereby preventing psoriasis [69]. Additionally, the pretreatment of an IL-23-induced psoriasis mouse model with MSCs led to a remarkable reduction in the level of pro-inflammatory cytokines, including IL-1, IL-6, IL-17, IL-22, IL-20, and TNF-α [69]. This observation suggests that MSCs have an inhibitory effect on the increase and exacerbation of inflammation. The inhibitory effect of tonsil-derived mesenchymal stem cells (T-MSC) on Th17 differentiation was demonstrated in a study by Kim et al. in a psoriasis mouse model [72]. In this study, the intrinsic expression of programmed cell death protein ligand 1 (PD-L1) on T-MSCs (as opposed to bone marrow (BM)- derived and adipose tissue (AT)-derived MSCs) in two membrane and secretory forms was observed to prevent Th17 differentiation, reduce the volume, mass, and number of splenocytes, decrease the Psoriasis Area and Severity Index (PASI) score, and reduce the expression of IL-17, IL-22, IL-23, TNF-α, IFN-γ, K6, K16, and CCL20 genes, resulting in amelioration of psoriasis symptoms [72]. Additionally, T-MSCs enhanced the efficacy of PD-L1 by expressing IFN-γ, thereby increasing the expression of PD-1 in T lymphocytes [72]. In the study by Zhang et al., small EVs derived from IFN-γ-activated hUCB-MSCs were observed to induce Th17 exhaustion, increase Th2 differentiation, and reduce the expression of inflammatory mediators including IL-17 A, IFN-γ, IL-6, and TNF-α in the splenic tissue and lesions [73]. As a result, the redness, scaling, thickness, and PASI score of the skin of the psoriasis mouse model were found to be reduced [73]. Furthermore, the encapsulation of EVs isolated from IFN-γ-activated hUCB-MSCs with ASO-210 has been shown to inhibit the activity of the miR-210 molecule, which plays a role in the differentiation of Th1 and Th17 cells and the exacerbation of psoriasis symptoms [73, 74]. This process ultimately leads to regulation of the immune system and the improvement of psoriasis. In the study conducted by Gomes and colleagues, in the mouse model of psoriasis, intravenous administration of BM-MSCs and AD-MSCs for seven days resulted in a reduction in clinical symptoms, as evidenced by a decrease in PASI score, scaling, redness, psoriatic area thickness, and epidermal thickness. The number of CD3 + cells was reduced, as well as the expression of S100A9/7 (keratinocyte differentiation index) and CCL17. Conversely, an elevation in the relative expression of TGF-β and IL-17 A was seen in the PBS-received mice [75]. In this regard, another study by Kim et al. showed that the administration of 5.2×10^6

human embryonic-derived MSCs (hE-MSC) for six consecutive days led to a reduction in the secretion of Th1 factors (such as TNF-α, IFN-γ, IFN-α, and IL-27) and Th17 (IL-17 A and IL-23), which led to a decrease in the clinical symptoms observed in the mouse model of psoriasis in comparison with control group [76]. In a separate study, Cho et al., revealed that T-MSCs produced osteoprotegerin (OPG), an inhibitory protein of osteoclast differentiation, and inhibited the crosstalk of the receptor activator of nuclear factor κ B (RANK)/RANKL interaction between Th17 and osteoclast [77]. The reduction of osteoclastogenesis by osteoclasts, which are important molecules in the differentiation and maturation of osteoclasts, ultimately leads to a reduction in the severity of inflammation and psoriatic arthritis [77, 78]. In another study by Chen et al., a remarkable reduce in the levels of pro-inflammatory factors, including IL-17, IL-23, IL-6, and IL-1β, as well as Th1 and Th17 lymphocytes, was observed on the eighth day of MSC administration in a psoriasis mouse model. Conversely, the expression of IL-10 and the number of Th2 lymphocytes showed an increase in the treated group [56]. These results suggest that MSCs have a significant impact on the immune response and inflammatory processes involved in psoriatic arthritis.

It has been demonstrated that Superoxide dismutase 3 (SOD3) has been shown to be responsible for the development of inflammatory symptoms in skin lesions [79]. In addition, Sah et al., demonstrated that the treatment of an IMQ-induced psoriasis mouse model with MSCs and SOD3-induced MSCs resulted in a significant reduction in clinical symptoms, psoriatic epidermal thickness, and the mass and number of spleen and lymph nodes cells when compared to the IMQ group [80]. Additionally, the number and proliferation of T lymphocytes, neutrophils, and dendritic cells were observed to be significantly reduced compared to the IMQ group. Conversely, an increase in immune system inhibitory molecules such as IL-10, TGF-β, and forkhead box P3 (Foxp3) transcription factor and a decrease in pro-inflammatory molecules including IL-17, IL-22, IL-6, and IL-23, and transcription factors such as STAT1, STAT3, JAK1, and RoR-γt were observed as a result of an increase in the number of Treg and a decrease in the frequency of Th17 and Th1 cells. This led to the conclusion that treatment with MSCs and SOD3-induced MSCs is an effective approach for treatment of psoriasis [80]. Furthermore, the present study demonstrated that treatment with MSCs and SOD3-induced MSCs suppressed the activation of NF-κB and mitogen-activated protein kinase (MAPK) as two signaling pathways involved in inflammation by preventing TLR-7 signaling and P38 phosphorylation, respectively, compared to the IMQ group. Conversely, the increase in cyclic adenosine monophosphate (cAMP) in the MSCs and the SOD3-induced MSC-treated group induces protein kinase A/cAMP response element binding protein (PKA/CREB), thereby producing an anti-inflammatory phenotype in the mouse model of psoriasis. The present study demonstrated that treatment with SOD3-MSC resulted superior outcomes compared to MSC in the majority of parameters assessed [80].

In conclusion, the shift towards anti-inflammatory cytokines and T lymphocytes in response to MSC treatment underscores their potential therapeutic benefits in the treatment of autoimmune diseases.

MSC and treg

Treg lymphocytes are recognized as a crucial element in maintaining environmental tolerance and suppressing autoreactive lymphocytes [81]. Defects in this cell, such as mutations in its transcription factor Foxp3, can result in immune dysregulation, polyendocrinopathy, enteropathy, and the X-linked syndrome (IPEX), which is characterized by uncontrolled immune system responses [82]. Treg have been shown to play an essential role in the immunopathogenesis of numerous autoimmune disorders [82, 83]. Deficiencies in the differentiation, proliferation, or reduced production of Treg regulatory mediators have been shown to be associated with the onset and severity of psoriasis [84, 85]. In this context, novel therapeutic strategies aimed at enhancing Treg function in autoimmune disorders have been explored [86]. In another study in a murine model of psoriasis, gingiva-derived mesenchymal stromal/stem cells (G-MSC) were found to have the ability to modulate the immune system [87]. Thus, the administration of these cells for a period of eight days was observed to result in a reduction in the redness, scaling, and thickness of the psoriatic area, as well as a reduction in the PASI score [87]. Furthermore, the study showed that the administration of G-MSCs resulted in a remarkable increase in the percentage of CD3 + CD25 + T lymphocytes and a remarkable reduction in the percentage of CD3 + IL-17 + T lymphocytes in the spleen [87]. This suggests an elevation in Treg and a decrease in Th17 cells [87]. Furthermore, the study demonstrated a decrease in the concentration of cytokines such as IL-6, IL-17 A, IL-17 F, IL-21, and TNF-α, accompanied by a significant elevation in the serum concentration of IL-10 in the MSC-treated group [87]. Cheng et al. showed that the intravenous administration of hUCB-MSCs significantly increased the population of CD3 + CD4 + CD25 + CD127-/low Tregs and CD3 + CD8 + CCR7 + CD45RA- memory T cells after 6 months in psoriatic patients, highlighting the role of MSCs in modulating immune responses [88]. This treatment demonstrated a reduction in clinical symptoms, including PASI score, Body Surface Area (BSA), which indicates the percentage of the total skin affected by

psoriasis, and Physician Global Assessment (PGA), which is related to the assessment of psoriasis severity specifically related with fingernails [88]. Additionally, there was a reduction in neutrophil count, IgG titer, blood urea nitrogen (BUN) levels, and pro-inflammatory mediators including TNF-α, IL-1, IL-6, and IL-17 when compared to pretreatment levels. Their research further demonstrated that the use of MSCs did not result in significant adverse effects in patients, highlighting the safety associated with MSC administration [88]. In a separate study, Meng and colleagues examined the co-culture of dental pulp-derived stem cells (DPSC) overexpressing hepatocyte growth factor (HGF) and HGF-transgenic DPSCs (HGF-DPSC) with peripheral blood mononuclear cells (PBMC) [89]. The results showed a reduction in Th1 and Th17 cells and an increase in Treg cells. Furthermore, the researchers demonstrated that DPSCs and HGF-DPSCs were able of alleviate psoriasis symptoms, including reduced redness, scaling, and thickness of psoriatic lesions [89]. In addition, they observed a reduction in the expression of cytokeratin 6 (CK6) and CK17, as well as a decrease in the production of pro-inflammatory factors such as IFN-γ, TNF-α, and IL-17 A. Conversely, they reported an increase in serum IL-10 expression in the psoriasis mouse model. The study showed a decrease in the relative expression of T-bet, RoR-γt, IL-17 A, IL-17 F, and IL-23, along with an increase in Foxp3 expression, suggesting that MSCs have immunomodulatory effects via increased Treg and regulatory molecule expression [89].

In another study, Jiao et al. demonstrated that the co-culture of dermal MSCs and CD3 + T lymphocytes increased the expression of the TGF-β receptor and its associated signaling pathway, specifically the TGF-β/SMAD pathway. This resulted in the regulation of the immune system in psoriasis, as evidenced by the increased ratio of Tregs to Th17 cells [90]. However, the presence of a TGF-β receptor inhibitor showed that these effects were diminished, indicating the influence of the surrounding microenvironment on the immunomodulatory function of MSCs [90]. In addition, Lee et al. demonstrated that hUCB-MSCs enhanced Treg differentiation [69]. The ability of MSCs to increase the percentage of Tregs and decrease pro-inflammatory T lymphocytes could have significant implications for the treatment of autoimmune diseases and inflammatory disorders. Collectively, the results of these studies support the therapeutic application of MSCs in modulating immune responses and promoting immune tolerance.

Conclusions

The effects of MSCs on immune system cells have led to the development of novel therapeutic approach for a variety of disorders. These cells have emerged as a promising target for disease treatment, as evidenced by the results of numerous studies in cell lines, experimental animal models, and patients. Despite the lack of clarity regarding the regulatory or activating capabilities of MSCs on the immune system, numerous studies have demonstrated that they possess immunomodulatory properties. This underscores the critical need for extensive research in this area. As mentioned above, current research indicates that MSCs have the ability to enhance the treatment of psoriatic lesions by suppressing the release of pro-inflammatory mediators, inhibiting the proliferation and differentiation of innate and adaptive immune cells, and increasing the expression of immunoregulatory molecules. Given the complex nature of psoriasis, it is not surprising that the clinical manifestations of the disease vary widely in severity and type. On the other hand, the limitations of current research on MSCs, such as high cost, lack of production standards, inadequate dosage information, and unclear administration methods and storage techniques, underscore the need for additional studies on these cells. Although MSCs have shown considerable potential in the treatment of autoimmune disorders, novel approaches including exosomes and microvesicles (MVs) derived from these cells represent promising avenues for further investigation. These approaches offer several advantages over traditional cell-based therapies, including ease of production and application, low immunogenicity, drug delivery properties, and reduced risk of altering tissue structure. In addition, the use of exosomes and MVs may allow for more targeted and efficient delivery of therapeutic molecules to specific tissues or organs, potentially increasing the overall efficacy of treatment. In addition, these approaches have shown promising results in preclinical studies for a variety of autoimmune diseases, suggesting that they may offer a viable alternative or complementary treatment option to traditional MSC-based therapies. As research in this area continues to evolve, it is becoming increasingly clear that MSC-derived exosomes and MVs hold great promise for the future of autoimmune disease treatment. In addition, the use of exosomes and MVs may also allow for more targeted and efficient delivery of therapeutic molecules to specific tissues or organs, potentially increasing the overall efficacy of treatment. In addition, these approaches have shown promising results in preclinical studies for a variety of autoimmune diseases, suggesting that they may provide a viable alternative or complementary treatment option to traditional MSC-based therapies. As research in this area continues to evolve, it is becoming increasingly clear that exosomes and MSC-derived MVs hold great promise for the future of autoimmune disease treatment. These small vesicles have the potential to revolutionize the way autoimmune diseases are treated by providing a more precise and effective method

of delivering therapeutic agents. Their ability to target specific tissues and organs while minimizing off-target effects could significantly improve patient outcomes and quality of life. As further progress is made in understanding the mechanisms behind exosome and MV therapy, it is likely that these innovative approaches will become a cornerstone in the treatment of autoimmune diseases. In addition, the use of exosomes and MVs in the treatment of autoimmune diseases may also reduce the need for systemic immunosuppressive drugs, which can have numerous side effects. By harnessing the natural communication system of cells, these vesicles offer a more tailored and personalized approach to therapy. A deeper understanding of the mechanisms underlying the immunopathogenesis of psoriasis and the regulatory functions of MSCs and their MVs and exosomes on immune cells and metabolic pathways involved in psoriasis will facilitate the removal of obstacles in this process, increase the efficacy of this treatment, and ultimately lead to the alleviation of symptoms experienced by psoriatic patients.

Abbreviations

AD-MSC	Adipose tissue-derived mesenchymal stem/stromal cell
AMP	Antimicrobial peptide
ANCA	Antineutrophil cytoplasmic antibody
Ang	Angiopoietin
APS	Antiphospholipid syndrome
bFGF	Basic fibroblast growth factor
BM-MSC	Bone marrow-derived mesenchymal stem/stromal cell
BSA	Body Surface Area
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CDH13	Cadherin 13
CK	Cytokeratin
CRAMP	Cathelin-related antimicrobial peptide
CTL	Cytotoxic T lymphocyte
CVD	Cardiovascular disease
DC	Dendritic cell
DPSC	Dental pulp-derived stem cells
EV	Extracellular vesicle
FDA	Food and Drug Administration
Foxp3	Forkhead box P3
G-MSC	Gingiva-derived mesenchymal stromal/stem cell
GLUT	Glucose transporter
hE-MSC	Human embryonic mesenchymal stromal/stem cell
HGF	Hepatocyte growth factor
HIF-1α	Hypoxia-inducible factor 1-alpha
HGF	Hepatocyte growth factor
HGF-DPSC	HGF-transgenic DPSC
HK2	Hexokinase 2
hUCB-MSC	Human umbilical cord blood-derived mesenchymal stem/stromal cell
IDO	Indoleamine 1, 3-dioxygenase
IFN-α/β	Interferon-alpha/beta
IFN-γ	Interferon-gamma
IL	Interleukin
IMQ	Imiquimod
iNOS	Inducible nitric oxide synthase
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome
JAK	Janus kinase
K16	Keratin 16
MAPK	Mitogen activated protein kinase
miR-155	microRNA-155
MSC	Mesenchymal stem/stromal cell
MMP	Matrix metalloproteinase
moDc	Monocyte-derived dendritic cell
MPO	Myeloperoxidase
MQ	Macrophage
MV	Microvesicle
NF-κB	Nuclear factor-kappa B; MSCs from normal healthy individuals
NCD	Non-communicable disease
NET	Neutrophil extracellular trap
NK	Natural killer cell
NO	Nitric oxide
OPG	Osteoprotegerin
P-MSC	MSCs isolated from psoriatic lesions
PASI	Psoriasis Area and Severity Index
PBMC	Peripheral blood mononuclear cell
PBS	Phosphate buffered saline
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death protein ligand 1
pDC	Plasmacytoid dendritic cell
PGA	Physician Global Assessment
PGE2	Prostaglandin E2
PKA/CREB	Protein kinase A/cAMP response element binding protein
PRR	Pattern recognition receptor
RA	Rheumatoid arthritis
RANK	Receptor activator of nuclear factor κ B
SFRP2	Secreted frizzled related protein 2
SLE	Systemic lupus erythematosus
SOD	Superoxide dismutase
t-bet	T-box transcription factor
T-MSC	Tonsil-derived mesenchymal stem cell
TGF-β	Transforming growth factor-beta 1
Th	Helper T cell
TNF-α	Tumor necrosis factor-alpha
Treg	Regulatory T cell
TSG-6	Tumor necrosis factor-inducible gene-6
UV	Ultraviolet
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
Wnt	Wingless-related integration site

Supplementary Information

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Supplementary Material 1

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The authors declare that they have not use AI-generated work in this manuscript.

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