Dermatology Practical & Conceptual

Stem Cell Therapy: A New Approach and Effective Treatment for Psoriasis

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Key words: Psoriasis, Stem cell therapy, Interleukin, Regenerative medicine, Immune modulation

Citation: Saadh MJ, Ahmed HH, Kareem RA, et al. Stem Cell Therapy: a New Approach and Effective Treatment for Psoriasis. *Dermatol Pract Concept.* 2025;15(3):5333. DOI: https://doi.org/10.5826/dpc.1503a5333

Accepted: February 23, 2025; **Published:** July 2025

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Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication. Authors are grateful to the Researchers Supporting Project (ANUI2024M111), Alnoor University, Mosul, Iraq.

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ABSTRACT

Introduction: The underlying mechanisms behind the development of psoriasis have become better understood in recent years. Key factors involved include the heightened reactivity of certain T cell subsets (Th1 and Th17 cells) as well as dysregulation of regulatory T cell (T-reg) function. Additionally, the complex interplay between immune cells, skin cells (keratinocytes), and the blood vessel endothelium has been shown to play an important role in the pathogenesis of psoriasis.

Objectives: A more thorough investigation of these mechanisms could present an opportunity to devise novel therapeutic approaches.

Methods: In this study, we reviewed the evidence regarding the role played by stem cells in the pathogenesis of psoriasis as well as initial attempts at leveraging stem cells as a treatment modality.

Results: Investigations uncovered the impact that epidermal stem cells and their interactions with T cells have in psoriasis. Importantly, malfunctions across diverse stem cell types may constitute a central mechanism underlying the dysregulated inflammatory processes that characterize this condition.

Conclusions: Nonetheless, a more thorough investigation of these mechanisms could present an opportunity to devise novel therapeutic approaches.

Introduction

More than 125 million people worldwide suffer from the chronic condition of psoriasis, and data suggest that this number has been increasing over time [1,2]. Psoriasis is a systemic inflammatory process that increases the risk of metabolic disorders, including insulin resistance, unhealthy cholesterol levels, high blood pressure, and cardiovascular disease, by about two times the normal population rate. Consequently, this heightens the risk of premature mortality [3]. Furthermore, this condition diminishes the quality of life for affected individuals and results in retreat from communal life and the emergence of mood disorder. Research has shown that patients suffering from psoriasis exhibit a markedly elevated probability of harboring suicidal thoughts, making suicide attempts, and, tragically, completing suicide [4]. This dermatological condition represents a grave economic and societal burden, taxing not merely the individuals suffering from it but also the medical infrastructure responsible for their treatment [5].

Although recent years have seen considerable progress in discovering the mechanisms of psoriasis pathogenesis, its full elucidation is still a long way away. Hyperreactivity of Th1, Th17, dysregulation of regulatory T cells (Tregs), and the complex relationships between immune system cells and keratinocytes and vascular endothelium obviously play a significant role [6]. The interleukin (IL)-23/Th17/IL-17 axis and Th1/IFN-γ axis play a critical role in psoriasis inflammation (Figure 1) [7]. The effect of epidermal stem cells and stem cells on T cells is currently receiving attention. Therefore, the dysfunction of certain types of stem cells could be the root cause of dysregulation of the inflammatory response in psoriasis.

Epidermal Stem Cells

Epidermal stem cells (EpSCs), which can replicate indefinitely, are unusual cells located in the basal layer of the epidermis. When prompted by a signal indicating growth, EpSCs undergo an asymmetrical division, resulting in two distinct cell types. One group consists of self-renewing cells that retain the stemness property, while the other group comprises transient amplifying cells (TA cells), which have limited proliferative capacity. The TA cells divide multiple times before ultimately undergoing terminal differentiation. This process gives rise to a substantial number of keratinocytes [8]. It is noteworthy that keratinocytes were the initial focus of psoriasis research due to their origin from EpSCs. Psoriasis is mainly characterized by the excessive growth of keratinocytes. The epidermal turnover time, which refers to the duration needed to replace all the keratinocytes in the epidermis, serves as a significant measure for assessing keratinocyte proliferation activity [9]. Current evidence suggests emphasizes that determining the time it takes for the epidermis to regenerate itself involves considering the turnover times of various layers present in the epidermis. These layers consist of the stratum basale, the differentiated compartment, and the stratum corneum. Several factors play a role in influencing the renewal process, including cell density, cell proliferation activity, desquamation, apoptosis, and other cellular processes [10]. Recent studies confirm an increased number of EpSCs or TA cells become active in the cell cycle during psoriasis. In psoriasis, it is observed that β1-integrin+ cells that possess keratin 1/keratin 10 but lack EpSCs/TA cells demonstrate an augmented involvement in the cell cycle [11]. This augmented presence of β1-integrin+ cells is thought to indicate the heightened proliferation of TA cells [12]. An immune staining test revealed that the top layer of the psoriatic lesion had high levels of two proteins: FABP5, which is a marker for TA cells, and nestin, which may be a marker for ESCs [13]. The studies concluded that the excessive proliferation of keratinocytes led to an increase in the growth of EpSCs/TA cells. The environment in which stem cells reside partially controls their growth and specialization.

Concurrent with the advancement in theoretical frameworks elucidating the relationship between stem cells and their supportive microenvironmental niche, researchers have dedicated increased attention to investigating the specific environmental factors that promote the enhanced proliferation of embryonic stem cells and transit-amplifying cell populations. The immunomodulatory signaling factors produced by the T helper (Th) 17 lymphocyte subset, such as the cytokines interleukin-17A and interleukin-22, which were most implicated in the pathogenesis of the inflammatory skin disease

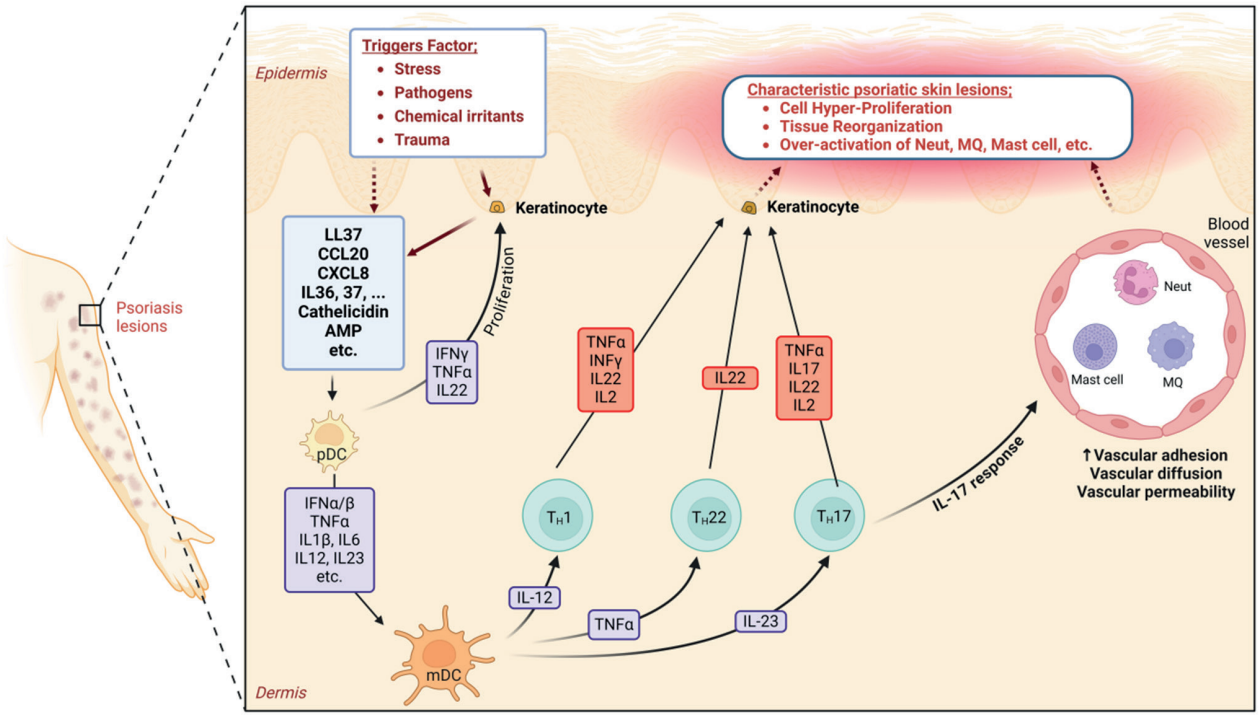

Figure 1. Mechanism of immunopathogenesis of psoriasis. The role of dendritic cells (DC) and keratinocytes in the activation of different types of T lymphocytes has been shown. Also, the role of different lymphocytes in injury and inflammation caused by vascular permeability has been shown. [Created with BioRender.com]

psoriasis, possess the capacity to stimulate the EpSC populations to transition from a quiescent state into a hyperproliferative state, yet simultaneously impede the differentiation of the epidermal keratinocytes [11,14]. The overexpansion of embryonic stem cells and transit-amplifying cells in psoriasis is widely accepted to be a secondary phenomenon, driven by the niche factors originating from the infiltrated immune cells, along with the inflammatory cytokines and growth factors secreted by those immune cells.

Mesenchymal Stem Cells (MSC)

Mesenchymal stem cells represent a heterogeneous group of self-renewing, multipotent cells that are distinct from hematopoietic stem cells [15,16]. These MSCs possess the capacity to regulate immune responses, stimulate the formation of new blood vessels, mitigate inflammation, and prevent apoptotic cell death [17]. MSCs possess several advantageous properties that make them an ideal cell therapy for various conditions, especially immune-mediated inflammatory diseases (IMIDs).

MSCs are easily isolated from human tissues and exhibit low immunogenicity due to lacking major histocompatibility complex (MHC)-II and costimulatory molecules (CD80/CD86), minimizing allogeneic rejection [18,19]. They also do not have many MHC class I molecules. This enables the use of MSC-based therapies without the need for cytotoxic conditioning regimens, which can potentially harm patients [20]. MSCs can be found in many body tissues, but bone marrow MSCs (BM-MSCs), umbilical cord-derived MSCs (UC-MSCs), placental materials, Wharton's jelly, blood, dental pulp, and adipose deposits are the main places from which they are taken [21]. The source of MSCs can impact their biological properties, such as their differentiation potential, paracrine capabilities, and immunomodulatory attributes. Sox2 and Oct4 are stemness markers that are expressed in BM-MSCs and ADSCs when they are cultured in vitro. This helps them keep their ability to differentiate over time (20). ADSCs, on the other hand, have a stronger inhibitory effect on B cells, T cells, and natural killer (NK) cells in vitro compared to BM-MSCs and UC-MSCs [22]. However, the three types can all contribute to the polarization of Tregs and Th1 cells. The increased expression of transcription factors FOXP3 and T-bet within activated T cells serves as evidence of this. These three types also cause activated NK cells to make less of the effector molecules TNF-α and perforin [22]. Mesenchymal stem cells, through their immunoregulatory functions, modulate both innate and adaptive immune responses.

These functions are exerted via direct interactions with various immune cell types, including T cells, B cells, natural killer cells, macrophages, monocytes, dendritic cells, and

neutrophils as well as through paracrine signaling mechanisms [23-27]. The extracellular vesicles released by mesenchymal stem cells contain a secretome comprising numerous cytokines, growth factors, and chemokines. This repertoire includes, but is not limited to, transforming growth factor-beta 1 (TGF)-b1, TNF- α, prostaglandin E2, interferon- γ (IFN-γ), fibroblast growth factor, hepatocyte growth factor, indoleamine-pyrrole 2,3-dioxygenase, and nitric oxide [28,29].

Scalability is one of the key obstacles in the translational application of mesenchymal stem cells. In this context, liposuction procedures readily harvest ADSCs in large volumes, making them the preferred option [30,31]. Additionally, ADSCs demonstrate enhanced proliferative abilities, higher cell yields, slower rates of cellular senescence, and better maintenance of a normal diploid chromosomal complement relative to BM-MSCs [32-35]. Early phase clinical trials have shown that MSCs are safe and effective for treating a variety of IMIDs. These include rheumatoid arthritis, systemic lupus erythematosus (SLE), lupus nephritis, Sjögren's syndrome (SS), graft-versus-host disease (GVHD), multiple sclerosis, type 1 diabetes mellitus, autoimmune hepatitis, and inflammatory bowel disease (IBD) [36-43].

A study of 477 Crohn's disease patients with fistulas found that those with severe disease healed their fistulas much faster and had lower recurrence rates when they were treated with allogeneic ADSCs instead of dose-adjusted BM-MSCs. The optimal therapeutic cell dose was found to be 2-4 x 10^7 cells mL^{-1}, indicating the considerable promise of mesenchymal stem cells for the treatment of IBD [44]. A recent phase II randomized controlled trial assessing the efficacy of autologous mesenchymal stem cell administration in 48 individuals with multiple sclerosis (MS) revealed that 58.6% of the treatment group exhibited disease remission, a significantly higher proportion than the 9.7% observed in the sham-treatment cohort, with no safety concern identified throughout the study [43]. The majority of mesenchymal stem cell-based clinical trials targeting immune-mediated inflammatory diseases remain in early phase I or II, demonstrating some promising results without any observed toxicity thus far.

Nevertheless, larger controlled trials are still required to definitively confirm the efficacy and long-term safety of these stem cell-based interventions [35,36,38,39,42,43]. Researchers have identified the potential for carcinogenesis as a theoretical pitfall or concern associated with the use of MSC therapies [18,45,46]. The accumulating knowledge and clinical experience with mesenchymal stem cell therapies have not yet led to the establishment of a standardized dosing regimen, as the cell dose and administration frequency continue to vary across different trials. Therefore, we have yet to definitively determine the optimal dosing parameters for these therapeutic approaches.

Regulatory T cells

Regulatory T cells (Tregs) plays a suppressive role, modulating the responses of other immune cells to the body's own environment and antigens. This regulatory function of Tregs works to prevent the onset of autoimmune disorders and chronic inflammatory states. Tregs utilize multiple methods to execute their regulatory and suppressive roles, including releasing inhibitory cytokines like IL-10, interfering with the metabolism of other immune cells, altering the maturation and functioning of dendritic cells, binding lymphocyte-activation gene 3 to MHC class II, and carrying out cytolysis via granzyme A/B and perforin [47]. Numerous therapies for psoriasis seem to increase the quantity of Tregs and enhance their regulatory function in individuals with psoriasis. Anti-TNF therapies, particularly the drug etanercept, have the effect of boosting Treg levels and reducing the expression of the inflammatory cytokines IL-6 and IL-22 [48]. Elevated numbers of these suppressor T cells seem to correlate with enhanced clinical results for individuals. Moreover, the anti-TNF drug infliximab appears to promote a more varied T cell receptor array [49]. One investigation discovered that suppressing TNF led to elevated secretion of inflammatory cytokines and heightened effector Th17 cell function. Conversely, the quantity of suppressor Tregs and their Foxp3 marker were diminished. This ultimately culminated in exacerbation of the pathological state [50].

A number of biologic drugs have received approval for the treatment of psoriasis, such as anti-IL-23 therapies including the p40-targeted medication ustekinumab and the p19-targeted drug guselkumab, as well as the anti-IL-17A agent secukinumab [51-55]. Beyond the previously cited biologics, there are other anti-IL-23 medications such as risankizumab, guselkumab, briakinumab, and tildrakizumab, in addition to anti-IL-17 agents like ixekizumab and brodalumab, that have been approved and are commercially available [52,53,56]. Studies have indicated that both anti-IL-17A and anti-IL-23 treatments can enhance the numbers of Foxp3-expressing regulatory T cells. The restoration of a healthy Th17/Treg balance through anti-IL-17 treatment may therefore serve to reduce inflammation and ameliorate the disease in psoriasis patients. A recently conducted preliminary clinical study evaluated the use of low-dosage interleukin-2 therapy in patients diagnosed with a range of autoimmune diseases. For the psoriasis patients examined, the findings indicated elevated levels of regulatory T cells as well as enhancements in body surface area and PASI (Psoriasis Area and Severity Index) outcome measures

[57]. Consequently, a therapeutic intervention involving the administration of diminished quantities of interleukin-2 in conjunction with a treatment modality that rehabilitates the functional capacities of suppressor T cells, such as phototherapy or the pharmacological agent sotrastaurin, appears to be an encouraging prospective strategy for managing the psoriatic condition. The stability and proper functioning of Tregs rely on epigenetic mechanisms that control their gene expression and cellular identity. Individuals with psoriasis exhibit expression of the histone deacetylase 1 (HDAC1) enzyme in their affected tissues. Research has shown that trichostatin A, an inhibitor of HDAC proteins, can shift the characteristics of Tregs towards an IL-17-producing cell profile [58]. This observation implies that drugs which block HDAC enzymes could potentially be helpful in treating psoriasis. Therapies using Tregs may have the potential to disrupt the development of psoriasis by rebalancing the ratio of Th17 to Treg cells and reducing certain inflammatory T cell subsets, despite the high costs and risks associated with such cell-based treatments [59].

Hematopoietic Stem Cells

Bone marrow-derived hematopoietic stem cells (HSCs) serve as the principal source for generating all peripheral immune cell populations. The clinical evidence that allogeneic HSC transplants can either cure or worsen psoriasis has given rise to the theory that the immunological dysregulation underlying psoriasis may stem from defects in the bone marrow HSC compartment [60,61]. Zhang et al. conducted a comparative analysis to determine whether the T cells of psoriasis patients exhibit an inherent dysfunction. They compared in vitro-induced T cells and CD4+CD25+ Tregs derived from the bone marrow CD34+ cells of psoriasis patients against the analogous cell types isolated from the peripheral blood of psoriasis patients. T cells generated in vitro from the CD34+ cells of individuals with psoriasis exhibited elevated proliferative activity and an enhanced ability to produce Th1 cytokines upon exposure to Streptococcus A. Additionally, these T cells showed the capacity to upregulate the expression of the c-myc and Ki67 genes when cultured together with keratinocytes [62]. Numerous studies have found that in psoriasis, the CD4+CD25+ Tregs present in the peripheral blood, and skin lesions display a reduced inhibitory effect on effector T cells [63-65]. This diminished Treg function results in accelerated proliferation of the pathogenic/effector T cell populations in psoriasis. The regulatory T cells harvested from the bone marrow of psoriasis patients displayed functional characteristics analogous to those isolated from the circulating blood of individuals with the same condition. Notably, these disease-associated Tregs exhibited reduced secretion of the anti-inflammatory cytokines IL-2 and IL-10 when stimulated with the streptococcal superantigen. Furthermore, the capacity of these Tregs to suppress the proliferation of activated effector T cells was diminished relative to Tregs obtained from healthy subjects [66]. The reported results imply that the aberrant behavior of immune cells in psoriasis may trace back to the HSCs located in the bone marrow. In other words, the immunological abnormalities characteristic of psoriasis appear to have their origins within the bone marrow compartment.

Advantages of Stem Cell Therapy for Psoriasis

The analysis by the researchers [67] has documented the "cure" of an extreme, treatment-resistant skin condition in a 35-year-old individual who underwent an allogeneic blood stem cell transplant from his unaffected sibling for the management of acute myelomonocytic blood cancer. The patient continued to be free of psoriasis symptoms for five years after receiving the stem cell transplant. The specific reasons why allogeneic HSCT is effective for treating psoriasis are not fully understood. However, it is believed that the immunosuppressive drugs and immune system depletion required for the HSCT procedure eliminate the self-reactive T cells that drive the psoriasis. The transplanted immune cells from a donor without psoriasis then rebuild the patient's immune system in a way that is less reactive and prone to causing the disease. The idea that allogeneic HSCT can treat psoriasis by resetting the immune system is supported by published reports documenting long-term, full resolution of psoriasis (lasting up to 20 years) in patients who underwent allogeneic HSCT, as opposed to autologous HSCT [68-70]. Interestingly, the occurrence of graft-versus-host disease (GVHD) appeared to be associated with long-term, full remission of psoriasis in several reported cases [60,68-90]. This suggests that the 'graft-versus-autoimmunity' effect of allogeneic HSCT, where the donor immune cells actively suppress or eliminate the recipient's autoimmune system, may be an important mechanism behind the lasting resolution of psoriasis [70,76]. Many of the patients in these reports received immunosuppressive conditioning regimens as well as concurrent therapies like methotrexate and cyclosporin. These additional treatments are important confounding factors that complicate the assessment of HSCT's therapeutic benefit for psoriasis (Figure 2). The improvements seen in these patients cannot be attributed solely to the HSCT procedure itself due to these confounding factors. In one reported case, the patient developed psoriasis within 10 days after receiving the HSCT. The psoriasis persisted and remained unresponsive to treatment, even after the patient underwent a second

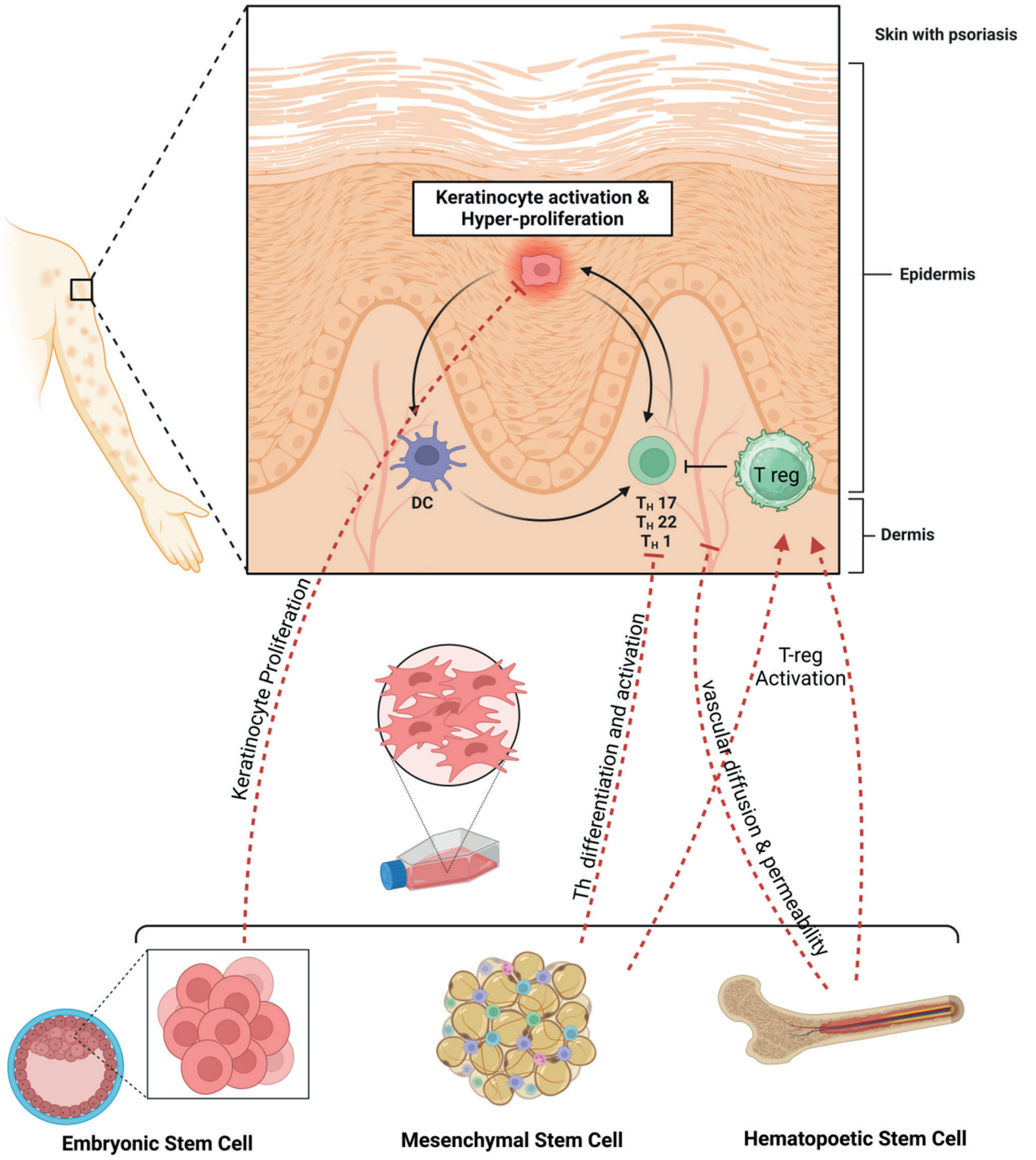

Figure 2. The role of stem cells in inhibiting the immunopathogenesis mechanisms of psoriasis. [Created with BioRender.com]

HSCT using stem cells from the same donor. Additionally, the patient also went on to develop psoriatic arthritis alongside the intractable psoriasis. This case illustrates that the cellular components driving psoriasis appear to be transmissible through adoptive cell transfer. In contrast, autologous HSCT does not appear to be an effective curative approach for psoriasis. Relapses of the condition are frequent following autologous HSCT and may occur more than a decade after the transplantation procedure. Based on the available evidence, out of the 11 psoriasis patients who underwent autologous HSCT, five of them experienced a relapse of their condition within two years after the transplantation procedure. Additionally, one patient relapsed after a longer period of 13 years post-transplantation [85]. The study conducted by Chen et al. leveraged the imiquimod-induced mouse model of psoriasis to explore the mechanistic underpinnings of UC-MSCs and their therapeutic efficacy for this condition. The researchers noted a significant reduction in the severity of psoriatic symptoms following the infusion of human umbilical cord-derived MSCs [91]. A key characteristic of the

response was the diminished generation of type I interferons by plasmacytoid dendritic cells. Wang et al. employed five infusions of allogeneic gingival MSCs to treat a 19-year-old patient with severe plaque psoriasis that had proven recalcitrant to systemic therapeutic regimens. The selection of gingival MSCs was motivated by their immunomodulatory and anti-inflammatory properties. Following the sixth infusion, the patient's psoriasis completely resolved, and the patient remained free of psoriasis for the subsequent three years [90].

Conclusion

The current evidence indicates that psoriasis is a multi-system disorder characterized by the abnormalities of various stem cell and progenitor cell populations. These disruptions in stem/progenitor cell biology appear to be either the primary driver or an associated feature of the aberrant immune responses observed in psoriasis patients. The data collected to date points to psoriasis being a multifaceted condition rather than one solely limited to skin pathology or immune system dysregulation. The HSCs of individuals with psoriasis appear to give rise to a T cell subpopulation that has an increased tendency to secrete Th1-type cytokines. Additionally, there seems to be a functionally impaired Treg subgroup associated with the psoriatic HSC compartment. These alterations in T cell differentiation and Treg function originating from the dysregulated psoriatic HSCs likely contribute to the abnormal immune profiles observed in psoriasis. Psoriatic T cells are primed to mount a Th1 immune response when triggered. This Th1 response induces the expansion of TA cells from ESCs, leading to excessive keratinocyte proliferation. The Th1 response also promotes MSCs to transform into an inflammatory MSC1 phenotype. These MSC1 cells secrete inflammatory factors that contribute to increased angiogenesis and lymphocyte infiltration in the dermal layer, further perpetuating the local Th1 response. In this way, the Th1 response driven by psoriatic T cells drives both the hyperproliferation of keratinocyte and inflammation in the dermis, amplifying the pathological processes of psoriasis.

Abbreviations

regulatory T-cell (T-reg), interleukin (IL), dendritic cells (DC), transient amplifying cells (TA cells), epidermal stem cells (EpSCs), T helper (Th), immune-mediated inflammatory diseases (IMIDs), umbilical cord-derived MSCs (UC-MSCs), bone marrow (BM), natural killer (NK), transforming growth factor-beta 1 (TGF-b1), interferon- γ (IFN-γ), fibroblast growth factor, mesenchymal stem cells (MSCs), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), graft-versus-host disease (GVHD), inflammatory bowel disease (IBD), multiple sclerosis (MS), histone deacetylase 1 (HDAC1), extracellular matrix (ECM), cluster of differentiation (CD), human leukocyte antigen (HLA).

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