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REVIEW

Role of mesenchymal stem cells in the pathogenesis of psoriasis: current perspectives

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Abstract: Mesenchymal stem cells (MSCs) are multipotent nonhematopoietic stromal cells studied for their properties and importance in management of several skin diseases. This review collects and analyzes the emerging published data, which describe the function of MSCs in the pathogenesis of psoriasis.

Keywords: mesenchymal stem cells, pathogenesis of psoriasis, review

Introduction

Mesenchymal stem cells (MSCs) are multipotent nonhematopoietic stromal cells. They have been identified from several sites of adult, perinatal, and fetal tissues.[1] These tissues are the bone marrow, adipose tissue, periosteum, Wharton's jelly, umbilical cord blood, placenta, amniotic fluid, and the skin.[2–11]

MSCs have been studied for their properties and importance in the management of several skin diseases such as wound healing,[12,13] burn injuries,[14] epidermolysis bullosa,[15] systemic lupus erythematosus (SLE),[16] dermatomyositis (DM),[17] systemic sclerosis,[18] photoaging,[19] acne,[20] atopic dermatitis (AD),[21,22] and psoriasis.[23,24]

Psoriasis is a multifactorial immune-mediated inflammatory disease, which involves skin, joints, or both. It is associated with several comorbidities, including metabolic and other chronic inflammatory diseases.[24–28]

The activation of T-cell leads to the increased release of associated cytokines, expression of inducible nitric oxide synthase (iNOS) and vascular endothelial growth factor (VEGF), and increased total antioxidant capacity (total oxyradical scavenging capacity). All these pathways have been studied largely in the skin cells of psoriatic patients. However, to date, in literature, there are few studies evaluating the same markers in MSCs and undifferentiated cells collected from the skin.[29]

The goal of this review is to collect and analyze the published data concerning the role of MSCs in psoriasis pathogenesis.

Methods

A PubMed search from 1988 to November 2016 was performed to identify any reports on stem cells and psoriasis. We detected the articles of interest using the keywords "mesenchymal stem cells", "stem cells, skin", "stem cells, psoriasis", or "stem cells, psoriatic skin". Only studies in English were reviewed. All studies that met the criteria were included and are summarized in this review.

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Pathogenesis of psoriasis

Psoriasis is among the most frequent T-cell-mediated disorders.[30] Different subsets of T-cells play different functions in the pathogenesis of psoriasis. A crucial role is the proliferation and activation of the T-helper (Th) cells Th17, Th22, and Th1, which leads to the release of associated cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-22, and interferon-γ (IFN-γ), in the skin.[31,32]

Th1 cells have been proposed to be more important in the initial phase of the disease, upstream of the IL-17-driven proinflammatory loop. Th1 cells, along with other cells, produce IFN-γ, which is increased in the involved skin of psoriatic patients.[33] IFN-γ induces the production of CCL20 ligand of CCR6 and the secretion of IL-23 by myeloid dendritic cells. This, in turn, promotes the recruitment and expansion of IL-17-producing cells.[34]

Recently, research interest has been focused on IL-17-producing cell types, such as the Th17 cells, γδ T-cells, and CD8 T-cells.[35,36] Accordingly, activated Th17 cells can enhance the inflammatory response. Th17 cell expression appears to be higher in the involved skin than in healthy skin.[37] These cells play a crucial role in the production of IL-9, IL-22, IL-17A, and IL-17F, which favors the inflammatory response of keratinocytes (KCs).[38] Th-17 cytokines, especially IL-17A, have been demonstrated to have an important role in the maintenance of inflammation in psoriatic plaques.[39] The IL-17-induced pathway includes cytokines, antimicrobial peptides, and chemokines (CCL20, CXCL1, CXCL3, and CXCL8) that amplify the immune response in psoriatic plaques.[40,41]

The production of IL-22 by Th22 cells occurs in the absence of IL-17.[42] IL-22, together with the other cytokines mentioned earlier, contributes to the formation of the network, which is the basis of the different pathogenic features of psoriasis.[43] The activation of KCs and the formation of epidermal acanthosis – typical of psoriasis – are connected to IL-22.[31,44]

Th9 cells may also be connected to the start and the maintenance of cutaneous inflammation in psoriasis.[45] Th9 cells act in a paracrine way by inducing IFN-γ, IL-17, and IL-13 production by CLA+ Th1, Th2, and Th17 cells and in an autocrine way by inducing further IL-9 production.[45]

Th21 cells also could have a role in the pathogenesis of psoriasis by expanding other pathogenic Th cell subsets and by exerting a mitogenic effect on KCs.[46]

Psoriasis is, to date, defined as a state of systemic inflammation, which involves other organs, besides the skin, through the systemic circulation: this concept is known as the "psoriatic march".[47] The most important soluble mediators responsible for the psoriatic march are serum VEGF, TNF-α, MCP-1, IL-12, S100A8/A9, and circulating IL-17A.[48] The angiogenesis consists in the growth of new blood vessels, which is essential for psoriasis.[49] The increase of VEGF-A in skin and plasma has been correlated with psoriasis. Its downregulation is associated with clinical improvement after some specific treatments.[50]

MSCs and psoriasis

MSCs are pluripotent cells localized primarily in the bone marrow and secondarily in other tissues. These cells have the ability of self-renewal and proliferation, and they are able to proceed in the differentiation toward more specific cell lines. The MSCs, therefore, are not specialized cells and are characterized by the ability to undergo replication by a process of mitosis defined as "asymmetric" or "differentiation", which gives rise to two daughter cells. Only one of them proceeds toward the differentiation, while the other maintains the phenotypic characteristics of the stem cell.

Such replicative property is critical to maintaining tissue homeostasis, ensuring the physiological turnover of cells in almost every region. MSCs are fibroblast-like cells and, in the healthy adult, serve as a backup facility for replacement of mature cells after their early death caused by pathological insults.

MSCs are derived strictly from the mesenchymal tissue, the primitive embryonic tissue from which the final connective tissues, such as cartilage, bone, adipose tissue, dermis, and blood, originate. The most recent literature is particularly rich in studies that show the process of differentiation in osteoblasts, chondroblasts, and lipoblasts and in the fibroblasts of the dermis.[86] These cells can be isolated (surgically accessible sites) and propagated well in vitro, although heterogeneously. They also have remarkable plasticity and are capable of generating cell types distant from the lineage of neurons, cardiomyocytes, hepatocytes, etc. MSCs are mostly isolated from the bone marrow; for this reason, sometimes, they are called bone marrow stromal cells.

Beyond this "functional" definition, MSCs can be distinguished based on distinct surface markers (clusters of differentiation or CDs). MSCs are classified based on their origin into the following types:

- Embryonic stem cells (ESCs) (arising from embryonic blastoderm);
- stem cells derived from the umbilical cord;
- adult or somatic stem cells.

According to their differentiation capacity, they are classified into the following:

- Totipotent MSCs: these are able to differentiate into all types of cells and then able to create all the embryo tissues, including embryonic appendages such as the placenta and the cord. Typically, embryonic cells retain this ability for up to 4–5 days after the formation of the zygote.
- Pluripotent MSCs: they have the ability to generate the cells of the three germ layers.
- Multipotent MSCs: they generate the cells that are derived from the same germ layer.
- Specific tissue MSCs: these cells retain the ability to generate their own tissue cells in which they reside.

ESCs and adult tissue-specific cells are different in many ways, and each type has some advantages and some disadvantages. ESCs, eg, can be divided over the Hayflick limit and remain stable in the phenotype. The Hayflick limit is the maximum number of cell divisions (~50) that somatic cells can have, because of the telomeric shortening during their life.[51,52] From these pluripotent cells can arise any cell of the body, including gametes; they also aggregate spontaneously to form embryoid bodies, spheroidal aggregates that start the differentiation. ESCs represent an irreplaceable tool for the investigation of developmental biology in mammals. They have also been adopted as an in vitro model for the screening of drugs, in relation to toxicity studies. However, the use of these cells also entails serious disadvantages. Primarily, their isolation means the death of the embryo that is developing and, therefore, such approach raises ethical obstacles. Second, the systemic administration of primitive embryonic cells can lead to the formation of tumors (teratomas). Finally, the recipient patient, due to histocompatibility problems, would reject a similar cell therapy. For all these reasons, many researchers focus their studies on adult stem cells (tissue-specific cells). The latter, derived from the tissues of the same patient who receives it, would be histocompatible and accepted by the host immune system. Not all tissues are, however, easily accessible; only a few of them can be a reservoir for the isolation of adult stem cells. Given this limitation, adult stem cells, as multipotent types, represent an ideal source for tissue repair. These cells can be isolated from well-defined surgical sites, and currently, they are easily grown in vitro, even in a heterogeneous way. Cells of different lineages can generate bone, cartilage, fat, and tendon. They also have remarkable plasticity and are capable of generating cell types distant from the lineage of derivation, such as neurons, cardiomyocytes, hepatocytes, etc.

MSCs are used to accelerate the healing process of wounds and damaged tissues. They interact with the epithelial cells, a crucial event for the repair of tissues and for the morphogenesis of organs. They may also modulate the responses of the immune system through their immunosuppressive and anti-inflammatory properties. The individual categories of MSCs are examined in the following sections, in order to highlight their main features.

ESCs as a subtype

ESCs are qualified as totipotent cells. They are extracted from the embryo blastoderm and maintained in culture on a "layer feed" of embryonic fibroblasts or in a medium containing leukemia inhibitory factor (LIF). In these conditions and in the absence of specific inducements, the ESCs maintain their proliferative capacity and their undifferentiated state indefinitely.[53] The omnipotence of the ESCs has been amply demonstrated in the literature since the 1990s; they can generate neurons, smooth muscle cells, skeletal cells, and cardiac myocytes.[54–58]

However, although these cells exhibit enormous regenerative potential, their use is limited because of ethical implications.

Stem cells from the umbilical cord

Recent studies on stem cells from the umbilical cord have shown that their use can bring about positive results in leukemia therapy and in the treatment of diseases linked to cellular degeneration such as Alzheimer's and Parkinson's diseases.[59–61]

The transplantation of cord blood cells has many benefits over bone marrow cell transplant. These include the largest number of donors and the absence, in the umbilical cord blood, of cytomegalovirus (CMV), a virus currently very widespread and accounting for 10% of deaths due to bone marrow transplant from adult donors. However, some disadvantages must be put in perspective, among which the most important is the reduced number of stem cells extracted from the umbilical cord. There are ongoing studies to improve the ability to extract the greatest number of viable stem cells from the umbilical cord in an attempt to have the largest populations to implement cell therapy, in addition to having "reserve pools".

Adult or somatic stem cells

The cellular exchange phenomena determined by physiological events, during growth or more generally aging, or during pathological states, continually occur in all adult tissues.

Somatic stem cells have this ability and they are deputed to the maintenance of tissue homeostasis.[62] The presence of such cells has been demonstrated in many regions of the organism: bone marrow, blood, epidermis, and striated muscle, as well as the heart, liver, and brain.[61,63–66] Adult stem cells therefore have the task of ensuring cell turnover within the specific tissue. The most representative example is the basal layer of cells: in this region, stem cells undergo several cycles of asymmetric divisions while simultaneously resulting in memory "cells" that remain in their undifferentiated state and process cells that begin to differentiate into KCs. For the first time, adult stem cells have been observed in the bone marrow.[108] Subsequently, according to the behavior in culture and the presence of specific surface markers, two distinct populations have been identified: hematopoietic stem cells (HSCs) and MSCs.[67] HSCs are round cells, which grow in suspension. They have high differentiation capacity and they give rise to cells of the hematopoietic system and further cells such as smooth muscle cells and skeletal cells when placed in an appropriate microenvironment.[68] This property is due to the presence of precursor cells that can be identified by their high proliferative activity and the expression of specific markers on the surface.[69] Recently, it has been highlighted that HSCs originate from the population of progenitor cells of the endothelium, which reside in the marrow, peripheral and other tissues, and that, as a result of ischemia of the skeletal or cardiac tissue, they can be mobilized and recruited to form new vessels in damaged tissues.[70] Initially, multipotent MSCs were identified as cells with only the function of support for HSCs and therefore were used as the base on which to cultivate in vitro HSCs. Only in 1978 did Friedenstein[71] characterize their osteogenic potential. He used a procedure that took advantage of the ability of MSCs to adhere to the culture surface and noticed that the MSCs had high proliferative capacity, were clonogenic, were able to form colonies of varying sizes and densities, and had fibroblastoid morphology.[71] In humans, MSCs reside in the bone marrow of the iliac crest. They are isolated by suction.[72]

During their growth, the MSCs do not undergo spontaneous differentiation, but their capacity to differentiate into different cell types is harnessed after their stimulation with cytokines and growth factors.[73] Several studies underline that MSCs can differentiate into osteoblasts, chondrocytes, and adipocytes.[74]

The presence of a "reserve" of stem cells in the bone marrow has led the scientific community to formulate a number of hypotheses on the role of general homeostasis of the organism. The most striking is certainly the following: subsequent to tissue damage, stem cells are enrolled from the bone marrow to the damaged site after the release of chemotactic factors into the bloodstream.

Quaini et al[75] first supported this hypothesis experimentally. The migration of precursors to the heart in patients who had undergone a heart transplant has been highlighted by the technique called sex mismatch.

In vitro experiments have established that some of the factors released from both the skeletal and the cardiac damaged muscles, such as stem cell factor (SCF), VEGF, granulocyte/macrophage colony stimulating factor (GM-CSF), stromal-derived growth factor 1 (SDF-1), and granulocyte colony stimulating factor (G-CSF), have chemotactic and mitogenic effects.[76]

Signaling between MSCs and resident adult cells

The processes that regulate the activation of the proliferation of the stem cell compartment also involve the differentiated adult cells of the tissues: in fact, these cells can induce – with appropriate signaling – the activation and subsequent reproduction of MSCs distributed over the tissue in question or of the mesenchymal cells of the bone marrow or of other body parts.

Moreover, just as in the turnover of skin tissue during tissue development, or even in skin repair following traumatic insults, the signaling proceeds not only to affect the stem cell compartment, which responds with an increase in metabolic activity and proliferation, but it also helps to stimulate the metabolism of the components of the mature tissue cells, which react by providing the spaces and the fundamental structures for housing the new population of cells derived from MSCs. In the case of epithelial tissue, eg, first there is a longitudinal increase of turnover and the thinning of the extracellular matrix (ECM) because of the tension to which the tissue is subjected. The elongated cells proliferate, under stimulation by soluble growth factors, with an increase in cell mass. Numerous extracellular environmental factors are integrated and "interpreted by the cell" to produce a precise phenotypic differentiation.

Evidence in favor of skin MSCs and their homing

There have been numerous controversies concerning the localization of the stem cell population in the skin, because it is a crucial clue to the understanding of skin cancers.

Huge amounts of conflicting data have been obtained from analysis of the human and murine skin; however,

recent studies that have used instrumentation that is more sophisticated have solved the dilemma of the similarities and differences between the two experimental models.[109] These data represent crucial assets because much of the information regarding the dermal carcinogenicity derived from studies of mouse models and clinical analysis come from human tumor cells. To date, it seems clear that the hair follicle cells retain all the biological properties of the stem cell population, comprising the multipotential for reproduction of the entire population of the epidermis and adnexal structures.[77]

Interfollicular skin has a basal population of adhesive clonogenic cells, which have the ability to regenerate the epidermis and produce autonomous proliferative units (epidermal proliferative units [EPUs]) that originate from the same ancestor line.[78–80]

It can be assumed that stem cell compartments can present in different varieties and can give rise to equally various differentiated cell populations as well as skin cancer phenotypes.

The first phenotypic marker for the stem cell of the skin has been identified as a result of the identification of a population of cells with slow replication cycle, which were holding a specific DNA marker for a period that was "excessive", compared to the basal layer cells.[110]

Through the clonogenic capacity or location at the follicle bulge, recent studies have identified a number of surface or intracellular antigens such as stem cell markers.[110] Among these, the increase of β4 or β1 integrins and the downregulation of the receptor of transferrin or connexin-43 are considered as quantitative markers, while the exclusive expression of keratins 15, 17, and 19 is accepted as a qualitative marker for the isolation of stem cells.[78,79,81–83] What was missing in this analysis was, however, the molecular evidence that these markers were exclusive to the stem cells. Because many of these markers have also been observed in skin tumors, the understanding of the cutaneous cell cycle, as well as the ability of self-renewal and multipotency, will yield – in the near future – many substantial implications for a clear comprehension of the pathogenesis of these lesions.

In addition, genetic studies of epidermal cells prepared using transgenic or knockout techniques have revealed numerous routes of intracellular signaling associated with this cell population, as well as with neoplastic cells.

Cutaneous stem cells

Withers first had the intuition that the basal layer, the proliferative compartment of the epidermis, was heterogeneous and enclosed a stem cell subpopulation.[111] This figure was soon associated with other data from studies on the kinetics and cellular organization of tissues to form a concept of EPU. This led to the perception that the basal layer consists of a series of small clusters of cell lines, organized on a spatial and functional basis, which is focused on the turnover of the superficial layer of the epidermis, the stratum corneum. This concept shows that the stratum corneum is a direct consequence of the proliferation of a number of individual EPUs. In detail, each unit shows a line of stem cells capable of self-renewal – centrally disposed – therein, as well as a line of "short stem cell-derived" destined for differentiation, located on the outside. The differentiated cells derived from the extremity of these EPUs have the property of migration from the basal layer toward the other epidermal layers in an orderly arrangement, determining the thin and flattened cells of the stratum corneum. The cells assume a stacked columnar arrangement, with a reduction of the concentration of cells, as one gets closer to the surface.

The applicability of this EPU model in humans, however, remains still discussed: in many human body sites, in fact, a similar arrangement of cells can be observed, although not in all sites and not constantly. It is hypothesized that the EPU stem cells have an asymmetric replication mode in steady state conditions, as only a stem cell is localized within an EPU. The epidermal microcolony assay, a diagnostic test created by Al-Barwari and Potten,[84] suggested that after a trauma such as irradiation, the stem cells of the EPU can modify their replicative structure, varying it from asymmetrical to symmetrical for a transitional period, enough to repopulate the epidermis.[84] The studies by Al-Barwari and Potten[85] indicated that a fundamental help to the reepithelialization could be from the higher compartment of the hair follicle. Investigations on the histological organization of the epidermis after a trauma have also clarified that to restore a spatial distribution of the cells, the epidermal layer reorganizes with a hyperplasia in which stem cells are sorted as spatially replenishing EPUs.

The skin contains another important population of stem cells, which is associated with the growth of hair follicles. The hair is developed as a result of a prolonged period of fast cell divisions (anagen) of the germinal region of the hair follicle. For this high rate of cell division in the germinal matrix of the follicle, a certain population of resident stem cells is needed. However, little is known concerning these cells. A complex aspect is that in humans, the follicle may hold a mature hair and the proliferative activity may stop.

In the telogen period, the follicle becomes quiescent because the telogen follicle, compared to the growing follicle, contains a lower amount of quiescent stem cells retriggerable for a new growth cycle. In any case, there are controversies with regard to this idea. It seems that the skin has a third compartment of stem cells, which would be under the sebaceous glands, in the outer sheath of the hair follicle. This cell population has been localized precisely in this bulge by a swelling of the outer sheaths. A series of experiments have shown that these cells of the bulge (bulge stem cells) could, under specific stimulation, rebuild the hair follicle and reepithelialize the epidermis.[112] There are disputes concerning whether these normally quiescent stem cells of the bulge can reestablish an anagen follicle. The best hypothesis is that these cells are not indispensable for the anagen recovery, and for their recruitment, there must be some alteration of the normal pathway. This disproves the concept that stem cells are anchored to a region and is also against the concept that the corneal epithelium is a tight barrier and impassable from the underlying cells. It seems that stem cells of the hair follicle and the EPU stem cells have a similar skin ontogenesis, or both originate from bulge stem cells. The bulge stem cells then become quiescent, forming a stem reserve activatable in case of skin damage to provide for the reepithelialization.

The International Society for Cellular Therapy[86] supports two theories establishing new specific nomenclature and minimal criteria for defining the MSC phenotype. These criteria are as follows: 1) adherence to tissue culture plastic; 2) greater than 95% of the population should be positive for the cell surface markers CD73, CD90, and CD105, and greater than 98% of the population should be negative for CD11b, CD14, CD19, CD34, CD45, CD79a, and human leukocyte antigen (HLA)-antigen D-related (DR) surface molecules; and 3) the ability to differentiate into osteoblasts, adipocytes, and chondroblasts under standard in vitro differentiating conditions should be retained.[86]

Discussion

The attention of researchers on MSCs is continuously growing because of their unique immunoregulatory effects and their multipotency.

Studies have been more focused on these topics: signaling of mucosal MSCs in psoriatic patients; psoriasis and aberrant hematopoiesis, with reference to BMSC profile; MSCs, inflammation, angiogenesis, and psoriasis; genetic investigations of dermal MSCs (DMSCs) of psoriatic skin; effect of TNF-α inhibitors on psoriatic MSCs; MSCs as a treatment for psoriasis.

Signaling of mucosal MSCs in psoriatic patients

First, in 1988, Sharpe and Ferguson[87] considered the role of MSCs in several diseases, including psoriasis, studying the embryonic palate cells of mice. They reported that mesenchymal signaling is characterized by a bifurcating action of numerous soluble growth factors, eg, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF)-α, and TGF-β, on the mesenchyme. These factors induce the synthesis of specific ECM molecules by the palate mesenchymal cells and the expression of their receptors on epithelial cells. In this way, epithelial basal stem cells are stimulated to synthesize specific proteins, which then may lead to the differentiation of daughter cells. Abnormalities in this epithelial–mesenchymal link produce a variety of diseases, such as psoriasis and premalignant and malignant lesions.[87]

Psoriasis and aberrant hematopoiesis with reference toBMSC profile

Psoriasis is a chronic inflammatory skin disease often associated with a variety of immune abnormalities. Zhang et al,[88] in 2010, proposed that psoriasis is associated with aberrant hematopoiesis, which is caused by the differential hematopoietic microenvironment. They compared the levels of cytokines secreted by BMSCs in psoriatic patients and healthy volunteers. Flow cytometry was performed for the evaluation of the amount of positive cells and direct enzyme-linked immunosorbent assay (ELISA) was used to detect the concentrations of cytokines secreted from BMSCs in psoriatic patients and healthy volunteers. Compared with those from normal controls, BMSCs from psoriatic patients expressed increased secretions of IL-6, SCF, and G-CSF, as well as decreased secretions of IL-3, IL-8, LIF, hepatocyte growth factor (HGF), PDGF, IL-1α, IL-1β, TNF-α, epidermal growth factor (EGF), VEGF; moreover, the levels of IL-7, IL-11, GM-CSF, CD29, CD34, CD45, and HLA-DR surface markers were the same. These results demonstrated the alteration of the hematopoietic microenvironment in psoriatic patients and Zhang et al[88] hypothesized that an aberrant hematopoietic microenvironment may represent one of the pathogenic mechanisms of the disease.

Liu et al,[89] in 2015, isolated and cultivated bone marrow CD34(+) mononuclear cells of psoriatic patients and aborted fetuses to investigate the differences between them. There was no statistically significant difference between the bone marrow MSC (BMMSC) culture supernatant of patients with

psoriasis and aborted fetuses on the one hand and the bone marrow CD34 (+) cell proliferation in normal subjects.[89]

Hou et al,[90] in 2014, studied the gene expression pattern and biological characteristics of BMMSCs in psoriatic patients, comparing them with healthy controls. Both the psoriatic and normal BMMSCs were negative for HLA-DR, CD34, and CD45 and positive for CD29, CD73, and CD90; these were able to differentiate into osteoblasts and adipocytes after induction. Psoriatic BMMSCs showed differentiation potential, phenotype, and ability to support CD34+ cell proliferation similar to normal BMMSCs, but they showed a characteristic gene expression profile, an increased apoptosis rate, and aberrant proliferative activity. The authors[90] supposed that an abnormal immune response in psoriasis could cause these aberrations, resulting in BMMSC dysfunction and that the functionally altered BMMSCs would not be able to suppress overactive immune cells, thereby corresponding with the psoriasis pathogenesis.

The altered activity of T-cells in psoriatic patients is attributed by several authors to BMHSCs. Zhang et al[91] performed a differential gene expression analysis by suppression subtractive hybridization of the BMHSCs from a patient with psoriasis and a healthy control. They identified 17 differentially expressed sequence tags (ESTs). CD45, overexpressed in the psoriatic BMHSCs, was than analyzed using relative quantitative polymerase chain reaction (PCR). Moreover, the levels of CD45 were markedly increased in the peripheral blood cells (PBCs) of the psoriatic patients and closely associated with the severity of disease. They speculated that hematopoiesis may transfer the defects of hematopoietic progenitor cells, eg, CD45 overexpression, to PBCs and that this could promote the psoriasis-inducing properties of activated T-cells.[91]

MSCs, inflammation, angiogenesis, and psoriasis

In 2011, Orciani et al[92] studied the MSC profile in psoriasis. MSCs from seven psoriatic patients, seven patients with acute AD, and seven healthy subjects were isolated and characterized by fluorescence-activated cell sorting analysis. Nitric oxide (NO) and VEGF levels were measured in conditioned medium and the expression of VEGF and iNOS was analyzed by immunohistochemistry. In addition, the total oxyradical scavenging capacity was evaluated with reference to peroxynitrite. VEGF level was the highest in the medium conditioned by psoriatic perilesional MSCs, whereas NO concentration was maximum in the medium conditioned by MSCs isolated from lesional psoriatic skin. The capacity to neutralize the oxidizing effects of peroxynitrite was lower for MSCs isolated from lesional psoriatic skin compared with that of other MSCs, except for the MSCs of lesional atopic skin. The authors of that study[92] concluded that the microenvironment in psoriasis differs from those of the healthy skin and in the AD skin and that it could stimulate resident MSCs to produce proinflammatory and angiogenic mediators, with the resultant reduction in the antioxidant capacity of these cells, concurring with the development of skin lesions in psoriasis.

The same group,[92] in 2012, studied the sequel of TNF-α inhibition on cutaneous MSCs in psoriasis. They evaluated VEGF expression and production, NO production, iNOS expression, and the antioxidant response of MSCs both before and after 12 weeks of treatment with adalimumab or etanercept. These evaluations were performed by morphological, immunohistochemical, and biochemical analyses of MSCs isolated from nonlesional, perilesional, and lesional skin of patients with psoriasis, both before and after the treatments.

The treatments reduced the production and expression of VEGF, the production of NO, and the expression of iNOS in the MSCs of psoriatic patients. TNF-α inhibitors also downregulated the oxidative injury in MSCs. They concluded that TNF-α inhibitors modify the physiopathological pathway of psoriasis, and that their effects already start at the level of MSCs, which probably represent the cells primarily enrolled in the "psoriatic march".[93]

In 2013, Liu et al[94] studied the alteration in cytokine secretion in the MSCs from psoriatic skin lesions. MSCs from psoriatic skin lesions and healthy human skin were obtained and identified through a cell differentiation assay and flow cytometry; they measured with the cytokine concentrations in the culture supernatants using ELISA. Moreover, cytokine concentrations in the culture supernatants of MSCs derived from psoriatic skin lesions, as well as those from healthy human skin, were compared.

Secretion of IL-11, SCF, and EGF was increased in the MSCs of psoriatic skin lesions compared with those from healthy control skin tissue; instead, levels of IL-3, IL-6, IL-8, basic FGF (bFGF), and HGF were decreased; secretion of TNF-α, IL-1, IL-7, IL-10, VEGF, M-CSF, G-CSF, GM-CSF, and LIF had no significant difference. Differentiation capacity and surface markers of cells from the two specimens were similar. This study showed the abnormalities of MSCs obtained from psoriatic skin lesions; this would represent one of the pathogenetic mechanisms of psoriasis.[94]

To support the hypothesis that MSCs in psoriatic skin lesions have biological characteristics, which might reproduce

the pathogenesis of psoriasis, Liu et al,[95] in 2014, investigated the consequences of MSC behavior on T-cell proliferation in psoriatic skin. They evaluated the MSCs extracted from psoriatic skin lesions and healthy human skin by flow cytometry and cell differentiation assays. To assess changes in T-cell proliferation, MSCs were cocultured with normal peripheral blood T-cells. Concentrations of IL-6, IL-11, TGF-b1, and HGFin the MSC culture supernatants were quantified by ELISA tests.

MSCs from both sources showed similar differentiation capacities and surface markers. The result underlines the weak inhibition of T-cell proliferation by MSCs in psoriatic skin lesions and the increased secretion of IL-11. Moreover, secretion of IL-6 and HGF was reduced and TGF-β1 secretion was unchanged. MSCs of normal skin have immunosuppressive properties, and with this study, the authors[95] demonstrated that the changes in MSCs derived from psoriatic skin lesions could lead to a weak inhibitory effect on T-cell proliferation, which is one of the pathogenetic mechanisms of psoriasis.

The same authors[95] investigated how MSCs from skin lesions of psoriatic patients influence the cell proliferation and apoptosis of cultured human KC cells (HaCaT). The psoriasis group and healthy control group showed similar cell morphologies and multipotency features of skin MSCs, with limited expression of CD34, CD45, and HLA-DR and high levels of CD29, CD44, CD73, CD90, and CD105. The authors[95] concluded that high KC proliferation and abnormal apoptosis in psoriasis skin lesions are promoted by MSCs in skin lesions of psoriatic patients, with consequent abnormal thickening of the epidermis.[96]

In the same year, Niu et al[97] studied the molecular regulation of angiogenesis by DMSCs investigating the mRNA and protein expression of AMOT, EDIL3, and ECM1 in DMSCs isolated from psoriatic skin, with the aim of a better identification of the molecular pathway of angiogenesis in psoriatic skin.

EDIL3 is an ECM protein that contributes to regulation of inflammation and angiogenesis; ECM1 acts as a paracrine factor conditioning the regulation of skin KC differentiation and is able to stimulate vascular endothelial cell proliferation and blood vessel formation. AMOT is a receptor for the angiogenesis inhibitor angiostatin, and it is as an attractive molecule to specifically target EC migration and angiogenesis.

The authors of that study[97] cultured DMSCs, identified by morphology, immunophenotype, and multipotential differentiation, derived from 12 patients with psoriasis and 14 healthy controls. They also evaluated the mRNA and protein expressions of ECM1, EDIL3, and AMOT in the DMSCs using real-time reverse transcription–PCR and Western blotting. The mRNA expression analysis showed that ECM1, EDIL3, and AMOT were expressed at 2.11-fold, 2.54-fold, and 1.90-fold higher levels, respectively, in psoriatic DMSCs compared with the DMSCs from healthy controls. Protein analysis showed significantly higher concentrations of ECM1, EDIL3, and AMOT in the psoriasis group than in the HC group.[97]

The immunomodulatory effect of MSCs has been investigated by Sah et al[98] in 2016 to introduce a novel therapeutic approach to psoriasis with subcutaneous injection of extracellular superoxide dismutase (SOD3)-transduced allogeneic MSCs in a mouse model of imiquimod (IMQ)-transduced psoriasis-like inflammation. This treatment significantly prevented psoriasis development, probably through a suppression of proliferation and infiltration of various effector cells into the skin, with a concomitant modulated cytokine and chemokine expression and inhibition of signaling pathways such as nuclear factor-kappa B, p38 mitogen-activated kinase, and toll-like receptor-7; activation of Janus kinase signal transducer and adenosine receptor; as well as activation of transcription.[98]

Genetic investigations of DMSCs from psoriatic skin

In 2013, Hou et al[99] studied DMSCs from patients with psoriasis, investigating their gene methylation profile. DMSCs from psoriatic patients and normal controls were isolated and expanded using the attachment assay, and genomewide DNA methylation profile and gene ontology analyses were performed through microarray. They identified the cultured cells as MSCs using surface marker and differentiation assays. The genomewide promoter methylation profile of the normal derma-derived MSCs was significantly different from that of the MSCs from psoriatic derma. There was a different methylation pattern of the surface receptor signaling pathway, genes involved in cell communication, cellular response to stimulus, and cell migration. There was differential expression of several aberrantly methylated genes related with angiogenesis, epidermal proliferation, and inflammation in psoriatic patients. These results indicated that the MSCs from the derma of psoriatic patients are probably in the pathogenesis and development stages of psoriasis because they have a distinguishable promoter methylation profile compared with those from normal derma and because several epidermal proliferation-, angiogenesis-, and inflammation-related genes are significantly differently methylated and expressed.[99]

In 2014, DMSCs from psoriatic patients and normal controls were isolated and expanded by Hou et al[100] using the attachment assay. They also performed gene ontology and mRNA expression profile analyses using microarray. The expression of VEGF-A was higher, whereas GATA6, IGFBP5, CXCL14, and IL-1B were lower, in psoriatic DMSCs than in normal MSCs. These results underline that the inflammatory cytokines involved in the psoriatic microenvironment might influence the DMSC expression of angiogenesis-related genes, primarily with an upregulation of the proangiogenesis gene VEGF-A and with a downregulation of the antiangiogenesis genes GATA6 and IGFBP5.[100]

In 2014, Campanati et al[29] evaluated MSCs from the skin of psoriasis patients, comparing them with MSCs isolated from the skin of healthy subjects, for the relative expression of 43 genes encoding Th1, Th2, and TH17 cytokines. The MSCs isolated from the skin of psoriasis patients showed an increased relative expression of genes encoding Th1 and Th17 cytokines than healthy subjects. The cytokines studied were TNF-α, IL-6, IL-8, IL-17C, IL-17F, IL-17RA, IL-21, IL-23A, IFN-γ, CCR5, CCL2, CCL20, CXCL9, CXCL10, CXCL2, CXCL5, and TLR2. The relative expression of the genes encoding Th2 cytokines IL-2, IL-4, IL-13B, IL-22, IL-27, TGF-β1, CCL1, CXCL12, and CCL22 was similar between the MSCs isolated from psoriatic patients and healthy subjects. They concluded that the well-known abnormal balance between the Th2 and Th1–Th17 pathways, demonstrated in differentiated skin cells, characterize the MSCs isolated from psoriasis skin. With this evidence, they corroborated the assumption that MSCs are involved in an early stage of psoriatic pathogenesis.[29]

Chang et al,[101] in 2015, studied the gene and protein expressions of dual-specificity protein phosphatase 1 (DUSP1), angiogenesis-related hematopoietically expressed homeobox (HHEX), and inflammation-related lipopolysaccharide-induced TNF-α transcription factor (LITAF) in MSCs isolated from the skin lesions of psoriatic patients. The gene expression of DUSP1, HHEX, and LITAF in DMSCs was quantified at the mRNA level using reverse transcription–PCR, and the expression of the corresponding protein was evaluated by Western blotting analysis. DMSCs in psoriasis patients had significantly lower gene and protein expression levels of DUSP1, HHEX, and LITAF compared to those in controls. These results suggested that DMSCs in psoriatic skin lesions might be involved in the regulation and progression of localized inflammatory deregulations, with a reduction of proteins related to inflammation and angiogenesis, such as DUSP1, HHEX, and LITAF.[101]

In 2016, Li et al[102] quantified the mRNA expression in healthy and psoriatic human DMSCs. They identified 23 differentially expressed genes through the use of microarray and RNA sequencing (RNA-Seq) analyses. Both platforms expressed similar upregulation or downregulation for 14/23 genes and 100% coincidence rate was observed by real-time PCR. For all of the differentially expressed genes that were studied with real-time PCR, the coincidence rate for RNA-Seq and real-time PCR was remarkably higher than that for microarray analysis and real-time PCR. Furthermore, >2300 novel transcription tags were revealed through RNA-Seq. They concluded that DMSCs of psoriatic patients had gene expression profiles remarkably different from those of normal DMSCs and that in the microarray analysis, differentially expressed genes in DMSCs are more precisely identified through RNA-Seq.[102]

In 2016, Li et al investigated the mRNA and protein expression of MCAM, VASH2, STAB1, FGD5, PECAM1, and PTGS1 during angiogenesis and investigated the probable mechanisms in psoriasis. They expanded and identified MSCs obtained from the dermis of 14 healthy controls and 12 patients with plaque psoriasis. They observed an important decrease of PTGS1, PECAM1, MCAM, and FGD5 expression at both protein and mRNA levels in the MSCs from psoriatic skin lesions compared with nonlesional MSCs from healthy controls. These result proved that proangiogenic genes and MSCs might play a crucial role in pathological dermal angiogenesis mechanisms of psoriatic disease.[103]

Effect of TNF-α inhibitors on psoriatic MSCs

We have assumed that psoriasis is a disease in which there is an imbalance between Th1–Th17 and Th2 inflammatory axes and the involvement of MSCs is from the early stage of disease. Moreover, MSCs are characterized by a major relative expression of several genes encoding Th1 and Th17 cytokines. Our research group wanted to assess the effect of TNF-α inhibitors on the cytokine milieu expressed by the MSCs of psoriatic patients. We isolated and characterized resident MSCs from the skin of psoriatic patients and healthy subjects and we studied them by ELISA and PCR for the expression of 22 cytokines involved in Th2, Th1, and Th17 pathways, both before and after 12 weeks of treatment with TNF-α inhibitors.[113–118]

This treatment reduced the expression of several Th1–Th17 cytokines whose levels were elevated at baseline (IL-6, IL-8, IL-12, IL-23A, IL-17C, IL-17F, IL-21, TNF-α, CCL2, CCL20, CXCL2, CXCL5, G-CSF, and IFN-γ). It also

increased the expression of several Th2 cytokines, which are underexpressed at baseline (IL-2, IL-4, and IL-5), decreasing the expression of those overexpressed at baseline (TGF-β and IL-13).

With these results, we speculate that TNF-α inhibitors would contribute to downregulate the pathological imbalance between the Th1–Th17 and Th2 axes in the MSCs of psoriatic patients.[104]

We also evaluated the influence of etanercept on VEGF production by MSCs from psoriatic patients by the isolation of MSCs from lesional and perilesional skin. We quantified the VEGF production at baseline and after 12 weeks of treatment with etanercept. There was a significant reduction in VEGF production compared with baseline in both lesional MSCs and perilesional MSCs after the treatment. These results can lead to the conclusion that etanercept is able to reduce the production of VEGF in MSCs, which could influence angiogenesis and help to prevent the onset of the "psoriatic march".[105]

MSCs as a treatment for psoriasis

MSCs have been also proposed as a treatment of psoriasis.

Chen et al,[106] in 2016, reported two cases of patients affected by psoriasis vulgaris treated with umbilical cord-derived MSCs (UC-MSCs). Both of them had no recurrence for 4 years. They assumed that MSCs might be involved in the following four aspects: migration to skin lesions, immunomodulation, limitation of autoimmunity, and local paracrine effects. However, they caution that more cases are needed to determine the efficacy of MSCs and their infusion dose, method, and delivery time.[106]

Moreover, De Jesus et al,[107] in 2016, proposed transplantation of autologous MSCs as a safe and tolerable treatment of psoriasis. Autologous MSCs were cultured from lipoaspirates and infused intravenously at a dose of 0.5–3.1 million cells/kg in one patient with psoriatic arthritis (PA) and another with psoriasis vulgaris (PV). The PA patient, who did not improve with standard treatments, showed a decrease in the Psoriasis Area and Severity Index (PASI). The PV patient, who previously responded only to methotrexate, had a decrease in PASI from 24.0 to 8.3 after three infusions. The PV patient had a significant decrease in reactive oxygen species (ROS) activity, while a minimal reduction in serum TNF-α, was noted.[107]

Conclusion

This review emphasizes the role of MSCs in the pathogenesis of psoriasis and their possible use in new therapeutic approaches. To date, we do not know exactly how MSCs are involved in all the molecular and pathophysiological mechanisms leading to psoriasis. From this review, it emerges that MSCs are involved in the immunoregulation and angiogenesis of psoriasis and that they are probably related to some modification occurring in psoriasis (capillary proliferation, angiectasias, or inflammatory infiltration).[93,94,97]

It also emerges that psoriatic patients have DMSCs with gene expression profiles significantly different from those of normal DMSCs and that umbilical stem cells could be used for psoriasis treatment.[104] Patients with psoriasis have an aberrant T-cell activity, which several authors attribute to BMHSCs: the alteration starting from BMHSCs may then contribute to the pathogenesis of psoriasis through an ineffective suppression of overactive immune cells.[90,99]

Eventually, TNF-α inhibitors could condition the physiopathological pathway of psoriasis, and their therapeutic action could have an effect on MSCs, which probably represent the cells primarily involved in the "psoriatic march".[104,105]

In conclusion, it might be hypothesized that MSCs could have potential applications due to their implication in regenerative medicine for the control of psoriasis; thus, a larger number of studies is necessary to evaluate the role of MSCs in clinical practice for treatment of psoriasis, focusing on long-term safety, efficacy, method, infusion dose, and delivery time.[106]

Disclosure

The authors report no conflicts of interest in this work.

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