

## Benchmarking Stem Cells and Transplantation in Psoriasis

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### Abstract

Psoriasis is a chronic systemic inflammatory disease with several abnormalities in hematopoiesis. During the last 30 years, stem cell science was intensively studied, also in the field of psoriasis, to discover therapeutic modalities by reversing the unbalance in lymphopoiesis. In fact, available results in literature have reported psoriasis remission after stem cell transplantation. The present review summarizes the current knowledge on psoriasis, stem cells and transplantation.

**Keywords:** Psoriasis; Transplantation; Stem Cells; Inflammation; Skin

### Psoriasis

Psoriasis is a chronic inflammatory disease characterized by scaling, infiltrating, erythematous and large edges desquamating lesions that are well defined [1-3]. Despite the reported prevalence of 3% in general population, pathogenesis of psoriasis still remains incompletely understood [4]. An increased body of evidence has linked psoriasis to several comorbidities affecting different tissues, other than skin, such as: lungs, cardiovascular and digestive systems [5-7]. Although psoriasis is easily diagnosed by clinical examination, the associated comorbidities still need less invasive, diagnostic instrumental approaches [8,9,10]. More understanding of psoriasis predisposing is achievable by investigating the inflammatory microenvironment, in which stem cells seem to play a key role. In fact, various reports and studies during the last 10 years pointed out that: a) several abnormalities in stem cells are present in psoriatic patients, b) the beneficial role of stem cells transplantation, suggesting the possibility of bone-marrow transplantation as future therapeutic modality to definitively cure the disease in refractory cases [11-14]. In this context, the present review aims to summarize the current knowledge and evidence regarding stem cells, their transplantation & applications in animal models and future perspectives on their therapeutic role in psoriasis.

### Stem Cells in Psoriasis

Sharpe & Ferguson (1988) were the first to suggest the role of stem cells in psoriasis [15], concluding that embryonic cells from the palate could differentiate through mesenchymal soluble factors and extracellular matrix molecules. The authors suggested that an unbalance of these signalling molecules might lead to cancer and autoimmune conditions such as psoriasis.

By analysing the genetic profile of stem cells from psoriatic patients, Campanati et al. [16] highlighted a similar imbalance between the Th1/Th17 and Th2 pathways commonly found in blood and skin samples [16]. Furthermore Charruyer et al. [17] described in both murine model and humans that the psoriatic stem cells increase the rate of asymmetric cell division in an IL-17A

dependent manner [17]. These findings might suggest that stem cells could play a key role in the initiation and maintenance of psoriasis.

### Embryonic stem cells (ESCs)

Embryonic stem cells (ESCs) are immortal cells that comprise the basal layer of the epidermis. Upon stimuli, ESCs into self-renewing cells and transient amplifying cells (TAs) which undergo differentiation after some other divisions, even if they have a limited proliferative capacity [14]. Characteristically, the epidermis overproliferates in psoriasis, leading to an increased turnover rate up to 5 times [4]. Inflammatory microenvironment and genetic susceptibility are manifested in altered ESCs and TAs phenotypes. In particular, Keratin 1/Keratin10<sup>-</sup> and  $\beta$ 1- Integrin<sup>+</sup> profiled cells, namely both ESCs and TAs, showed an increased rate of division [18], confirmed by an overexpression of fatty-acid binding protein 5 (FABP5) and Nestin, representing TAs and ESCs, respectively [19]. Consequently, psoriatic-epidermis hyperplasia is a result of an increase in ESC/TA compartment due to TH17 related cytokines, such as Interleukin (IL) -17 and IL-22 [19].

### Dermal-Mesenchymal Stem Cells (dMSCs)

Dermal-Mesenchymal Stem Cells (dMSCs) are multipotent stem cells with angiogenic ability, despite the fact that they might differentiate into chondrocytes, adipocytes and osteoblasts [20]. dMSCs are capable of full interaction with existent microenvironment and may develop into two main phenotypes: a pro-inflammatory (dMSC1) and anti-inflammatory (dMSC2) ones. The former phenotype is characterized

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by the activation of nuclear factor Kappa-light Chain Enhancer of Activated B cells (NF- $\kappa$ B)-p38, Mitogen Activated Protein Kinase (MAPK) and Jun N-Terminal Kinase (JNK) signaling pathways upon the stimulation of Toll like Receptor (TLR) 4 by lipopolysaccharide (LPS) or Th1 related cytokines.

As for the latter, it is characterized by the activation of Phosphatidylinositol-4-5biphosphate 3-kinase (PI3K- $\alpha$ ), Signal transducer and activator of transcription-1 (STAT-1) signaling pathways upon the stimulation of TLR-3 by double strand RNA [21].

Although the released spectrum of cytokines is different, IL-4 is regulated through the activation of (RANTES) which is expressed and secreted by normal T-cells. Activation can be also through C-C Motif Ligand (CCL)-10, IL1-Receptor Antagonist (RA), Macrophage Inflammatory Protein-1(MIP-1), C-X-C Motif Ligand (CXCL)-9, CXCL10 for MSC1, in comparison to IL-6, IL-8,IL-10, Indoleamine-pyrrole 2,3-dioxygenase (IDO) and Prostaglandin E-2 (PEG2) for MSC2 [21]. While MSC2 actively suppresses T cell proliferation and permits proliferation of regulatory T cells (TREGS), MSC1 seems to be involved in establishing and maintaining the pro-inflammatory microenvironment in psoriasis [22]. Furthermore, this type of stem cells plays an active role in establishing the inflammatory microenvironment through pro-inflammatory cytokines, by promoting angiogenesis by secreting Vascular Endothelial Growth Factor (VEGF) and Hypoxia Inducible Factor (HIF)-1 $\alpha$  [23]. The angiogenic-related profile has been thoroughly investigated, describing an increased Angiopoietin, Angiostatin, Neuropilin-2, Vasohibin-1 with a reported decrease in Insulin-like Growth Factor-binding Protein (IGFBP)-5 and Globin Transcription Factor 6 (GATA-6) [24,25]. In fact, dMSCs increase the transcription of miRNA-55 and inducible Nitric Oxide Sintetase (iNOS), upon pro-inflammatory stimulation. Conversely, subcutaneous injection with allogenic extracellular Superoxide Dismutase (SOD3)-transduced MSCs was able to prevent psoriasis like eruption in Imiquimod-treated mice [26].

### Bone marrow Hematopoietic Stem Cells (BmHSCs)

Bone marrow haemopoietic stem cells (BmHSCs) are multipotent stem cells that give origin to all peripheral immune cells. Recently, few studies have underlined abnormalities in BmHSCs with a hypothesis that psoriasis might be a result of an altered haematopoiesis [27]. In a fact, Zhang and colleagues described an alteration of the normal hematopoietic system characterized by an increased release of Stem cell factor (SCF) and Granulocyte- Colony Stimulating Factor (G-CSF), IL-6, with decreased levels of IL-3, IL-8, LIF, Epidermal Growth Factor (EGF), Hepatocyte Growth Factor (HGF), PDGF, VEGF, IL-1 $\alpha$ , IL-1 $\beta$ , TNF- $\alpha$  [27]. Nevertheless, no differences were reported in the Cytokine levels in supernatants of incubated bone marrow cluster differentiation (CD)-34<sup>+</sup> mononuclear cells, whether in psoriatic patients, aborted fetuses or normal subjects [28]. Both, genetic and biological profiles were further screened revealing an aberrant activity of bmHSCs with an increased apoptotic behavior [29]. In 2014, Zhang and colleagues reported an overexpression of a differentiation marker of bone marrow-derived T-cell progenitor in psoriatic BmHSCs and that this marker maintained higher levels also in peripheral blood cells (PBCs), which were correlated to the severity of the disease [30]. These findings strengthened the theory on the relation between psoriasis abnormalities and hematopoiesis.

### Xenotransplantation Model of Psoriasis

Despite the great importance of drug-induced and genetically

engineered mouse models in psoriasis, these models still do not replicate the immunological dynamics and microenvironment in humans, including stem cells [31]. Thus, more attention has grown towards xenotransplantation models due to their use of human tissues, which allows the study of the exact inflammatory microenvironment [32]. The two main xenotransplantation models are SCID and AGR129 mice [33].

SCID mice are mutant mice of the mouse strain CB-17, an Igh<sup>b</sup> congenital partner of the BALB/c (H-2<sup>d</sup>) mouse [33]. The mutation is autosomal recessive and localized in the centromere region of Ch16. The mutation involves SCID gene, a gene that encodes for DNA breaking repair enzyme and VDJ rearrangement [33]. This genetic defect results in the production of dysfunctional T and B- lymphocytes [32]. Such mice may be reconstructed with a xenograft of pre-psoriatic skin and a transfer of activated autologous T cells [33]. However, these mice present two main defects: a) mature natural-killer cells limit the grafting acceptance, b) the need to inject immunocytes or T cells into the graft to convert healthy skin into a diseased one, which is inadequate to observe early events in pathogenesis of psoriasis [32].

AGR129 mice are RAG-2(-)/(-), which lead to impairment in B and T lineages, and deficiency of IFN-  $\alpha$  and  $\gamma$  that negatively affect NK response [32]. No injections of cells in the graft are mandatory, making this model adequate to study the early events that characterize pathogenesis of psoriasis [33]. Summary of both mice models are represented in Table 1.

### Organs Transplantation and Stem Cells Transplantation

Although the real incidence of psoriasis, post-transplantation, is still matter of discussion, a recent retrospective study, named EUROCORD, reported that 726 cord blood transplanted patients developed at least one autoimmune disease (AD) and only 2 (0,003%) had psoriasis [34]. Within the first year, the rate became 5.5% and increasing up to 6.6% within the second year of follow-up [34]. Interestingly, ADs were more frequent among younger patients at least after 212 days of cord blood transplantation [34]. Despite the large number of patients in this study, another report described an incidence of post-organ-transplant psoriasis of 0.06% in patients that have experienced adverse events in follow-up visits after transplantation [35]. It was reported that 1% of the donors had psoriasis exacerbation [35]. However, all these studies did not take familiarity for psoriasis into consideration, when the post-transplantation psoriasis was assessed, taking into account that psoriasis has a high prevalence in normal population. Nonetheless, the previously mentioned studies might not represent the real risk of psoriasis in recipients. Psoriasis and its variant forms (erythrodermic, pustular, plaques) were reported to be elicited or exacerbated by transplantation, although sometimes resolved [36,37]. Few reports and case series described a stable remission with a follow up ranging from 6 to 120 months [14,38]. A comprehensive review was performed by Kaffenberger et al, describing that in HSCs allogenic transplant, 10 out of 13 subjects experienced a complete remission, in comparison to only 1 out of 6 with autologous transplants [13]. Despite this data, the hypothesized pathogenesis is yet to be elucidated.

### Therapies for Psoriasis in Solid Organ Transplant Recipients (SOTR)

Current literature on psoriasis in SOTRs is comprised mainly of case reports, with an absence of systematic clinical research, all of which limit the presence of high-level scientific evidence in this arena.

Xenotransplantation Model	Type of Mutations	Injection of Cells	Characteristics
<b>SCID Mice</b>	-Autosomal Recessive Mutation -Defect in SCID Gene - Defect in VDJ arrangement	Transfer of activated autologous T cells with the graft is needed	- Transferred cells increase the rate of graft rejection - Cell injection prevents the observation of early events in psoriasis pathogenesis
<b>AGR129 Mice</b>	- RAG-2(-)/(-) - Impaired B & T Lineages - Deficiency of IFN- $\alpha$ - Deficiency of IFN- $\gamma$	Injections of cells with the graft is not mandatory	- Lack of cell injection renders the model ideal to study early events in psoriasis pathogenesis

**Table 1:** Characteristics of Xenotransplantation models in Psoriasis

	Mild Psoriasis	Moderate to Severe Psoriasis
First Line	<ul style="list-style-type: none"> <li>• Calcipotriol + Betametasone topical preparation</li> <li>• Vitamin D analogs (calcipotriol or calcitriol)</li> </ul>	<ul style="list-style-type: none"> <li>• Acitretin + NB-UVB</li> <li>• NB-UVB + topical tazarotene gel or vitamin D analogs</li> <li>• Acitretin + topical calcipotriol</li> </ul>
Second Line	<ul style="list-style-type: none"> <li>• Calcineurin inhibitors (tacrolimus or pimecrolimus) in topical preparation</li> </ul>	<ul style="list-style-type: none"> <li>• Increase the antirejection drug dose: tacrolimus&gt;cyclosporine and tacrolimus + mofetil micofenolate&gt;azathioprine</li> </ul>
Third Line	<ul style="list-style-type: none"> <li>• Consider first line therapy of moderate to severe psoriasis</li> </ul>	<ul style="list-style-type: none"> <li>• TNF-blockers+ acitretin (if possible)</li> <li>• Ustekinumab</li> <li>• Apremilast</li> <li>• IL-17 blockers</li> <li>• MTX*</li> </ul>

Abbreviations: NB-UVB: narrow band ultraviolet B, TNF: Tumor necrosis factor, IL: interleukin, MTX: methotrexate. \*Avoid MTX in liver transplant and use with caution in kidney transplant.

**Table 2:** Guidelines in organ-transplanted patients with psoriasis.

Despite these obstacles, the National Psoriasis Foundation created an algorithm based on clinical experience and re-evaluation of literature (Table 2) [39].

For mild psoriasis, the first line therapy takes into consideration the topical approach with vitamin D analogues, with or without the combination of corticosteroids. However, the second-line treatment includes topical Calcineurin Inhibitors (CI), namely Tacrolimus and Pimecrolimus, and Tazarotene and Tar-based therapy [39].

Moderate to severe psoriasis remains a real matter of discussion due to the introduction of systemic therapy, which impacts the whole body that is already immune-compromised to withstand and transplanted organ [39].

First line therapy evaluates the synergic use of Acitretin plus narrow-band ultraviolet therapy, especially in Fitzpatrick skin phenotypes III and VI, or NB-UVB alone, if oral Retinoids are contraindicated. The NB-UVB in the last case might be more effective with the topical application of Tazarotene gel 0.1% or Vitamin D3 analogs [39]. Oral Acitretin together with topical Calcipotriol might represent an alternative approach, to avoid severe dysfunction of the liver and kidneys along with uncontrolled hyperlipidemia [39].

The second line therapy includes anti-rejection medications, namely Cyclosporine, Mycophenolate Mofetil (MMF), Tacrolimus, or mTOR inhibitors [39]. The choice of the drug is also strictly dependent on the type of transplanted organ and a set of particular considerations as the following: Cyclosporine has to be avoided in renal recipients, Tacrolimus is preferred over Pimecrolimus and Cyclosporine, Tacrolimus + MMF is preferred over Azathioprine, and mTOR inhibitors should be switched after 6 months of stable transplanted and functional organ [39].

The third line therapies displayed the highest evidence with Etanercept that improves OTRs psoriasis without increasing the risk of malignancy, infections and loss of graft function [39]. Methotrexate was only assessed in one case report, however, its use should be carefully evaluated due to the cumulative toxicity in liver transplants and systemic toxicity in kidney transplants [39]. Other TNF blockers,

Apremilast, Ustekinumab and IL-17 blockers are mentioned only in the third line of treatment because of available case reports, although their usefulness was suggested by analyzing trials from literature on psoriatic patients [39]. A retrospective study of 16 adults with kidney transplants that underwent anti-rejection therapy plus TNF-blockers described the efficacy of this combination in curing concurrent chronic inflammatory diseases, as psoriasis. However, A high risk of subsequent infections and careful use in patients older than 50 years of age were underlined [40].

The only contraindication as a therapeutic agent in OTRs patients was Psoralen with UVA (PUVA) because of its well-documented side effects such as: highly increased risk of melanoma and non-melanoma skin cancers [41].

## Conclusions

Stem cells abnormalities, their relation to peripheral blood cells and the increased number of psoriasis-related comorbidities highlight the multi-systemic inflammatory nature of this disease. Dysfunctions in bone marrow hematopoiesis might explain the abnormal activation of Th1-Th17 previously described in literature, offering at the same time a possible strategy to cure psoriasis in a safe and effective therapeutic model. However, a better understanding of the pathogenesis of psoriasis is mandatory to better design future trials regarding stem cells transplantation.

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## Conflicts of Interest

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