Review Article

Severe combined immunodeficiency mouse-psoriatic human skin xenograft model: A modern tool connecting bench to bedside

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ABSTRACT

Psoriasis is a multifactorial chronic inflammatory disease. Research into the pathogenesis of this disease is hindered by the lack of a proper animal model. Over the past two decades, many scientists were involved in the development of animal models that nearly mirror the immunopathogenesis of psoriasis. One such model, which has opened doors to the study of molecular complexities of psoriasis as well as its treatment, is the severe combined immunodeficiency (SCID) mouse-human skin chimera model. This model not only mirrors the clinical and histopathological features of psoriasis but also help in the study of cell proliferation, angiogenesis, function of T cells, neurogenic inflammation and cytokines involved in inflammatory reactions. In this article, we have reviewed the prospects and the limitations of the SCID mouse model of psoriasis.

Key words: Acanthosis, hypogranulosis, lymphomononuclear cells, parakeratosis, psoriasis, severe combined immunodeficiency mice

INTRODUCTION

Psoriasis, described in Corpus Hippocraticum,[1] is a chronic inflammatory disease of skin and joints involving a complex interaction of genetic, environmental, and immunologic factors.[2-4] It affects 2-3% of Caucasians[5,6] mainly in early adulthood.[7] It is characterized by epidermal hyperplasia (acanthosis) with elongated rete ridges, hypogranulosis, parakeratosis, and $CD4^+$ T lymphocytes predominating in the dermis and $CD8^+$ T lymphocytes infiltrating the epidermis.[8-10] Due to the heterogeneity of the disease, in spite of intense research, the precise pathogenesis of psoriasis is still uncertain.

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Most of the features of psoriasis occur exclusively in humans and are generally absent in animals except in rhesus and cynomolgus monkey.[11,12]

Thus, research into the pathogenesis of this mysterious disease was greatly handicapped by the need for an appropriate animal model. However, advancement of science and technology has led to the development of numerous murine, non-murine, and *in vitro* human epidermal models mirroring various aspects of psoriasis. Every model is based on different pathogenetic mechanisms and each one displays similarities as well as differences from psoriasis.[13]

In this article, we will review the efficacy of different animal models in exploring the pathogenesis of psoriasis as well as for development of potential therapeutic agents. We will also highlight in detail the effectiveness of the severe combined immunodeficiency (SCID) mouse psoriasis xenograft model.

ANIMAL MODELS OF PSORIASIS

Apart from the obvious size difference between

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human and mouse skin surface area, the fundamental morphological differences between mouse models as opposed to psoriatic skin include absence of parakeratotic scaling and epidermal hypogranulosis and marked follicular hyperplasia rather than true elongation of epidermal rete ridges.[14] Moreover, mouse has an additional subcutaneous muscle layer (panniculus carnosus) that is almost absent in humans which may release myokines that contribute to inflammatory reactions. Commonly, the mouse models of psoriasis can be divided into spontaneous mutant models, genetically engineered murine models, and immune cell transfer and xenotransplantation models [Table 1]. To be an ideal model of psoriasis, the model has to reproduce some histopathologic features with an almost similar pathogenic mechanism to psoriasis and respond similarly to antipsoriatic treatments.[15]

Spontaneous mouse models

Spontaneous mouse mutations that gave rise to psoriasiform phenotypes, the flaky skin (*fsn*), chronic proliferative dermatitis (*cpd*), and homozygous asebia (*ab*/*ab*) mutant have been used to study pathogenesis of psoriasis.[16,17] All these mutants show histopathological features of psoriasis such as acanthosis, infiltration of mast cells and macrophages, and angiogenesis in the dermis.[18] However, the deficiency of T cells in these infiltrates[19] and inefficacy of antipsoriatic drugs suggest that these pathological features are not similar to psoriasis.

Genetically engineered mouse models of psoriasis

In the majority of these models, either increased expression or knockout of particular genes is directed to the basal layer of the epidermis, or to the suprabasal layer or to those that target leukocytes or keratinocytes, or those that target vascular endothelium and different cytokines, such as interleukin (IL)-1, IL-6, IL-8, the cytokine 'regulated on activation, normal T-cell expressed and secreted' (RANTES), transforming growth factor (TGF)-α, tumor necrosis factor (TNF)-α, vascular endothelial growth factor (VEGF), and interferon (IFN)-γ, which have been proposed to play an active part in the pathogenesis of psoriasis.

CD18 hypomorphic mouse developed a psoriasiform phenotype with predominant lymphocytic infiltration,[20-22] was nonresponsive to dexamethasone,[23] and was devoid of hyperproliferative keratin expression. Likewise, p40 keratin (K) 14 transgenic mouse,[24,25] developed skin inflammation similar to eczema and atopic dermatitis, lacking significant cutaneous $CD8^+$ T cell infiltration. αE integrin (CD103) knockout mouse developed cutaneous inflammation with significant ulceration but with very few cutaneous $CD8^+$ T cells compared to psoriasis.[26] In VEGF K14 transgenic mouse, the mice developed a cutaneous inflammatory disease with hyperplasia and inflammation of dermal vasculature, and epidermal acanthosis similar to psoriasis but the lesions were largely vascular and there was dermal infiltration of mast cells.[27,28] Tie2 transgenic mouse had the same features as VEGF K14 mouse but the lesions were shown to be responsive to cyclosporin A.[29] Similarly, all transgenics targeting epithelial growth factors such as TGF-α, keratinocyte growth factor (KGF), and TGF-β, mimicked the epidermal acanthosis of psoriasis[29-31] but lesions from K5-TGFβ1 model also appeared to show increased expression of psoriasis-associated genes specifically expressed by T-cells, dendritic cells, and macrophages.[32] In transgenic mouse models overexpressing IL-1α and K14, there was infiltration of macrophages and monocytes within the dermis with acanthosis and parakeratosis.[33] In IFN-γ/involucrin transgenic mice, there was keratinocyte hyperproliferation, major histocompatibility complex (MHC) class II, intercellular adhesion molecule (ICAM)-1 induction and enlargement of dermal capillaries but without epidermal T cell infiltrates.[34] PL/J mouse overexpressing leukocyte β2 integrins, manifested epidermal hyperplasia, hyperkeratosis, parakeratosis, and lymphocyte exocytosis. IL-20 also initiated a psoriasiform lesion in the absence of cutaneous inflammation in K14 promoter epidermal targeted transgenic mice.[35]

K5-Stat3 transgenic mice developed epidermal acanthosis in areas of friction, and also had a dermal $CD4^+$ and epidermal $CD8^+$ lymphocytic infiltrate.[36,37] The human leukocyte antigen (HLA)-B27/human β2 microglobulin transgenic rat showed epidermal acanthosis with epidermal infiltration of both $CD4^+$ and $CD8^+$ T cells but the incidence of skin lesions was less reliable than the incidence of immune-mediated arthritis and inflammatory bowel disease. Moreover, evidence of response to antipsoriatic treatment was lacking.[38,39]

Limitations of transgenic model

The main disadvantages of these models are that they are generally produced by manipulation of a single gene, and psoriasis, being a polygenic disease, cannot be accurately reproduced in them. Various features of psoriasis are evident in the

Table 1: Animal models of psoriasis: Giving an insight into the pathogenesis of the disease

Type	Method	Macro and microscopic features	Pathology	Inferences
A. Spontaneous mutation	Asebia	Moderate acanthosis, ↑ vascularity, ↑ mast cell infiltrate, no intraepidermal microabscesses	Unclear	No T cell and neutrophil infiltrate
	Chronic proliferative dermatitis	Marked acanthosis, epidermal hyperproliferation, ↑ vascularity, focal parakeratoses, neutrophil infiltrate, intraepidermal microabscesses	Unclear	Skin lesions not induced by hematopoietic cells in synergistic recipients
	Flaky skin	Severe acanthosis, focal parakeratoses, epidermal hyperproliferation, ↑ vascularity, intraepidermal microabscesses	Unclear	Neutrophil and T cell infiltrate, skin lesions develop in *fsn*, *scid* homozygous mice
B. Genetically engineered a) Transgenic	K14/IL-6	Epidermis unaltered, no inflammatory infiltrate	↑ cytokines	No psoriasiform phenotype
	K14/KGF	Marginal alteration of KC proliferation and differentiation	↑ cytokines	No psoriasiform phenotype
	K14/TGFα	Acanthosis and ↑ proliferation in basal layer, inflammatory infiltrate in severely affected mice	↑ cytokines	Low frequency of psoriasiform phenotype
	K14/IL-1α	Acanthosis and parakeratosis with mixed inflammatory infiltrate in severely affected mice only	↑ cytokines	Low frequency of psoriasiform phenotype
	Involucrin/IFNγ	KC proliferation and differentiation is altered, ↑ vascularity, dermal infiltration of T cells, neutrophils	↑ cytokines	KC biology is altered like psoriasis
	K10/BMP-6	Marked acanthosis and parakeratosis with moderate and patchy transgene expression	Altered responses of KCs	Psoriasiform changes with weak patchy expression
	K14/VEGF	↑ vascularity, dilated and contorted microvessels, ↑ number of dermal mast cells	VEGF regulated angiogenesis	Acanthosis, altered KC differentiation not seen
	β_1 integrin	Acanthosis, focal parakeratosis, ↑ vascularity, inflammatory infiltrate	↑↑expression of adhesion molecules	Epidermal hyperplasia in absence of inflammatory infiltrate
	PL/J/CD18 hypomorphic mice	Acanthosis, focal parakeratosis, ↑ vascularity, inflammatory infiltrate, intraepidermal microabscesses, lymphocytic exocytosis	↓ expression of adhesion molecules	Phenotype depends on genetic background
b) Knockout	Human skin transplant	Maintenance of psoriatic phenotype for >2 months	Proliferation by infiltrating mouse T cells	Absence of parakeratosis and granular layer
i. nu/nu	$CD4^+/CD45RB^{hi}$ T cell transfer	Acanthosis, ↑ vascularity, mixed cellular infiltrate	Dysregulated T cells, ↑ proinflammatory cytokines, GM-CSF	Pathogenesis of psoriasiform phenotype is T cell dependant
ii. scid/scid	Human skin transplant	Maintenance of psoriatic phenotype and experimental induction	T cells, GF responsible for psoriasiform phenotype	Unique tool for pathogenesis studies and drug development

KC: Keratinocyte, GF: Growth factors, IFN: Interferon, TNF: Tumour necrosis factor, IL: Interleukin, GM-CSF: Granulocyte macrophage colony stimulating factor, TGF: Transforming growth factor, VEGF: Vascular endothelial growth factor, K: Keratin, SCID: Severe combined immunodeficiency

above-mentioned transgenic models but none of them demonstrates the true clinical and histological picture of psoriasis.

Immune transfer and xenotransplantation model

The $CD45RB^{Hi}$ $CD25^-$ T cell immune transfer model and the human psoriatic skin xenotransplantation model use SCID mice as the transplant recipients.[40,41] In the $CD45RB^{Hi}$ T cell immune transfer model, SCID mice are injected with MHC major matched but MHC minor mismatched $CD4^+$ $CD45RB^{Hi}$ $CD25^-$ naive T cells. A chronic persistent cutaneous inflammation mirroring many features of psoriasis were seen when these $CD25^-$ naive T cells were stimulated with lipopolysaccharide (LPS) or IL-12.[40,42,43] As in psoriasis, the fundamental pathogenesis of the cutaneous inflammation was Th1-driven, and in contrast to psoriasis, IFNγ did not play a role and no $CD8^+$ lymphocytes were present in the inflammatory infiltrate. Another important finding was the positive response shown by the cutaneous lesions to cyclosporin A, corticosteroids, and anti-IL-12.[40,42,43]

The ultimate and possibly the most reliable animal model of psoriasis involved transplantation of human psoriatic skin onto immunodeficient mice. These models permit exploration of disease pathology in a microenvironment simulating its natural background and without graft rejection. However, these models rely on a stable supply of human psoriatic skin and need a well-controlled pathogen-free environment to survive.[41,44-48] Among these, nude mice and SCID mice have been used for over two decades.[49-51] Recently, another model using AGR129 mice has been described.

Epidermal Jun protein deletion model

Deletions of JunB and c-Jun in epidermal cells of mice led to many changes strikingly similar to the histological and molecular features of psoriatic skin as well as arthritis. The disease was noticeable in hairless areas of the skin (ears, paws, and tail), but was also present in hairy back skin, and the symmetrical distribution was suggestive of psoriasis in humans. Arthritic lesions strongly mirrored the inflammatory aspect of psoriatic arthritis along with massive bone destruction. Moreover, the diseased epidermis reflected the changes in the cytokine and chemokine network described for psoriasis.[52]

Nude mice

Initially, athymic nude mice lacking the T cell arm of the immune system were used by investigators. The transplanted psoriatic phenotype persisted for more than 2 months in these mice but in contrast to psoriasis, their histopathology showed absence of parakeratosis and the presence of a granular layer. Moreover, circulating immunoglobulins impaired immunohistochemical assessment.[51]

SCID mice

SCID mice are devoid of humoral and cellular immunity due to a mutation in the DNA dependent protein kinase gene that is required for functional T-cell receptor and immunoglobulin gene rearrangements crucial for T and B cell development. Many investigators have reported that the clinical as well as the histopathological features of psoriasis are maintained on transplanted SCID mice for prolonged periods.[51] The homozygous *scid* mutation that takes place in the BALB/c mouse affects Variable, Diverse and Joining (V(D)J) gene rearrangement[53] and double-strand break repair.[54,55] This rearrangement prevents development of mature B and T cells[56] and makes xenogenic transplantation into SCID mice possible without major graft rejection.[57,58]

MISCELLANEOUS MOUSE MODELS OF PSORIASIS

Imiquimod -induced psoriasis-like mouse model

This model reiterated several signature features of human psoriasis including clinically, hyperkeratosis, erythema, and scaling, and immunologically neutrophil microabscesses and infiltration of γδ T cells and Th17 cells to the skin.[59] This model induced a fast, reproducible, and efficient psoriasis-like pathology, which was based on the IL-23/IL-17 axis.[60] Moreover, Imiquimod (IMQ)-induced skin inflammation was profoundly suppressed in mice with a complete deletion of the IL-17RA receptor as compared with wild type control mice.

SEVERE COMBINED IMMUNODEFICIENCY MOUSE-HUMAN SKIN XENOGRAFT MODEL: A VALUABLE TOOL TO EXPLORE THE IMMUNOPATHOGENESIS OF PSORIASIS AND A GUIDE FOR NEW DRUG DEVELOPMENT

Exploring pathogenesis of psoriasis

The SCID mouse model for psoriasis was first described in 1994.[61] Over the years, it has proved to be a scientific 'gold mine' in the study of pathogenesis of psoriasis.

We have observed that apart from slight morphological variations of the transplanted plaques from mature human plaques, most of the clinical as well as histopathological features of psoriasis are reflected in the grafts.[62] These features persist for 12-16 weeks [Figure 1]. The transplanted plaques are hyperpigmented, rough and dry with few scales and lacking Auspitz's sign. Histological features are similar to psoriasis except that sometimes the granular layer is present. Immunological features reflect chronic plaque psoriasis with presence of $CD4^+$ and $CD8^+$ T cell infiltrates and expression of adhesion molecules like ICAM-1 and vascular cell adhesion molecule (VCAM)-1.[50] Gilhar *et al*.[63] reported waning of epidermal thickness with loss of HLA-DR expression and decrease in ICAM-1 expression in the transplants after 10 weeks of transplantation. Moreover, after 22 weeks of grafting, apart from persistence of acanthosis and hyperkeratosis there was resolution of Munro's microabscesses, loss of parakeratosis, and decrease in lymphocytic infiltrates in the transplanted grafts.[64] However, in transplanted grafts, all the pathological features of psoriasis could be maintained longer by intradermal or intravenous administration of T cells derived from psoriatic plaques, but not from peripheral blood mononuclear cells (PBMCs).[64]

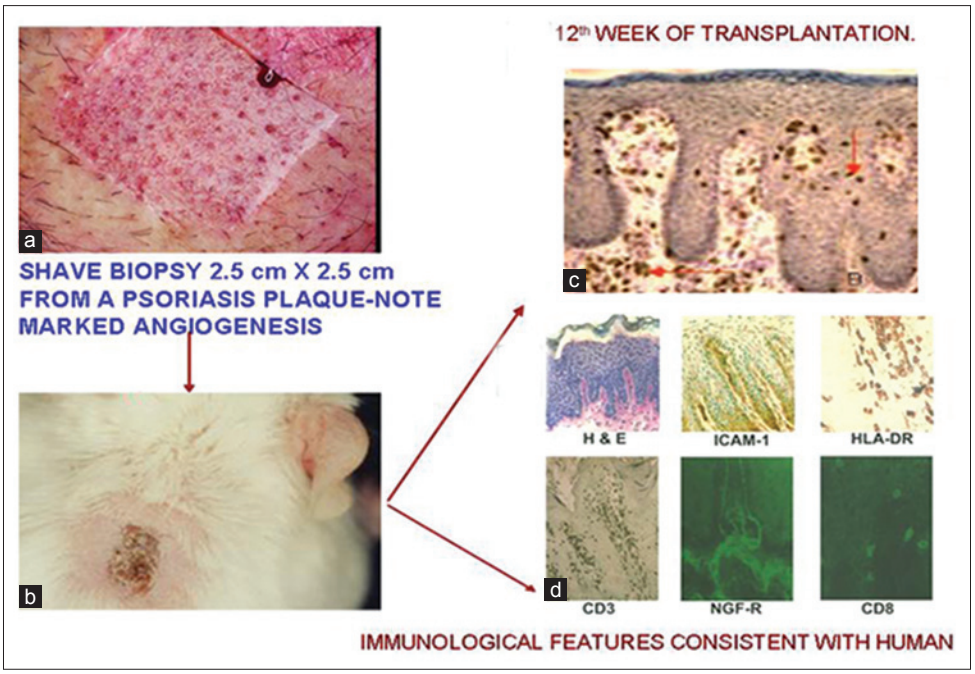

Figure 1: (a) Human skin shave biopsy from a psoriatic plaque. (b) Transplanted plaque with scales and erythema (c) and (d) Typical histopathological features of psoriasis: Long rete pegs, suprapapillary thinning and dermal/epidermal infiltrates of CD3 lymphocytes. (c) Arrows indicate CD3$^+$ lymphocytes. (d) Increased expression of ICAM-1, HLA-DR$^+$ CD3$^+$ T cells, nerve growth factor receptor and CD8$^+$ T cells. Magnification ×20

Interestingly, injection of autologous immunocytes activated with *Staphylococcus enterotoxins* (SEB and SEC2) and IL-2 into non-lesional skin grafts from psoriatic patients induced immunological as well as histopathological features of psoriasis.[47,48] In another study, administration of PBMC, stimulated by superantigen (staphylococcal superantigen exfoliative toxin) into non-lesional psoriatic skin resulted in histopathological features of psoriasis as well as infiltrates of CD3 positive cells expressing cutaneous lymphocyte associated antigen.[65] According to Nickoloff *et al.*,[46] clinicopathological features of psoriasis can be induced in transplanted normal skin by superantigen activated allogenic immunocytes from psoriatic patients. The role of T cells in the immunopathogenesis of psoriasis was strongly supported by the fact that transplanted non-lesional psoriatic skin on SCID mice could be converted to an active plaque by intradermal injection of antigen activated T cells and the plaques could be cleared after therapy directed against CD4[66] (monoclonal CD4 antibody) and IL2-R (diphtheria fusion protein).[67] But the factors responsible for T cell activation are still unknown. It was shown that non-lesional skin can be converted to active psoriatic plaque not only by superantigen activated autologous lymphomononuclear cells[66] but also T cells activated with substance *P* (SP) and nerve growth factor (NGF).[68]

Apart from neuropeptide-induced T cell activation, stress-induced onset and exacerbation of psoriasis,[69] upregulation of neuropeptides with proliferation of terminal cutaneous nerves in psoriatic plaques,[70-72] positive response to capsaicin, somatostatin and peptide T,[73-76] and disappearance of active plaques at sites of local anesthesia[77] supported the role of neurogenic inflammation in psoriasis.

Some investigators noted that keratinocytes in lesional and nonlesional psoriatic tissue not only express high levels of NGF[78,79] but also nerve growth factor receptor (NGF-R) is upregulated in the terminal cutaneous nerves of the lesions.[80] Raychaudhuri *et al.*[62] further demonstrated that increased levels of NGF in transplanted psoriatic plaques led to marked proliferation of murine cutaneous nerve fibers with upregulation of neuropeptides in transplanted plaques as compared with transplanted normal human skin on SCID mouse. Thus the SCID model has proved to be a very effective model to explore the role of neurogenic inflammation in psoriasis and has opened a door to the development of drugs targeting the NGF/NGF-R system.[73,74,81-83]

In psoriasis there is increased expression of endothelial cell adhesion molecules (E-selectin, ICAM, VCAM),[84-87] angiogenesis with upregulation

of endothelial cell-stimulating angiogenesis factor (ESAF) and VEGF[88,89] activated T-cells (CD4, CD8, NK cells) infiltrates[90-93] neutrophils (Munro's and Kogoji microabscess), mast cells,[93,94] upregulation of chemokines such as IL-8, RANTES, fractalkine,[17,95-97] and neuropeptides.[71,72,98,99] Likewise, the transplanted psoriatic plaques in SCID mice, demonstrate upregulation of molecules like p38 MAPK, STAT3, ICAM, CXCR3, fractalkine, IL-8, CD3, CD4, CD8, CD40, CD80, CD86, HLA-DR, OX-40R, K16, Ki67, SP, NGF, and NGF-R. Upregulation of CD80/CD86 supports the role of CD28/B7 co-stimulatory cascades in psoriatic inflammation.[100]

The effector memory T cells play an important role in various autoimmune diseases. The membrane potential of effector memory T cells is maintained by Kv1.3 voltage-gated potassium channels.[101-103] It has been shown earlier that there was an increased number of Kv1.3 infiltrating T cells in dermis and in the synovial tissue of arthritic joints of psoriatic patients. Gilhar *et al*.[104] showed that dermal T cell infiltrates of psoriatic plaque of SCID mouse model, expressed Kv1.3 channels, but to a lesser extent than in psoriatic patients. This indicates that stronger and continuous antigenic stimulation may be responsible for the presence of Kv1.3 positive effector memory T cells within psoriatic lesions.

Drug development using the SCID mouse human skin xenograft model

The SCID psoriasis model bridges the gap between late preclinical research and clinical development of novel therapeutic agents. Many investigators regard this model as the perfect model because of the ease of application of drugs directly at the site of lesion, and determination of responsiveness by noting clinical improvement. The drugs with proven efficacy in this model are cyclosporine A, glucocorticosteroids, Vitamin D derivatives (calcipotriol), efalizumab, etanercept, CD80/CD86 antisense oligonucleotide, anti-CTLA4 IgG, a humanized Fc silent anti-CD28 antibody, FR255734, and K252a, a high affinity NGF R blocker. Several of these drugs are already in use for the treatment of psoriasis. Evaluation of efficacy of some novel compounds targeting different pathological aspects of psoriasis are given below.

Drugs targeting proliferation and differentiation

The effectiveness of calcipotriol as an antipsoriatic agent has mainly been attributed to its effects on epidermal proliferation and differentiation[105-107] although the effects on skin infiltrating T cells are also relevant to its mode of action.[108,109] There was a reduction of $CD3^+$ $CD4^+$ $CD8^+$ memory T cells in psoriatic skin[110] as well as significant reduction in biomarkers of epidermal proliferation, differentiation, and lymphocyte infiltration.[110-112] Likewise, in a study with K252a, a high affinity NGF-R blocker, we have shown that within 2 weeks of administration in SCID mouse psoriatic xenograft model, it reduced clinical, immunological as well as pathological characteristics of psoriasis.[113]

Drugs targeting angiogenesis

Both pro-angiogenic factors like VEGF and anti-angiogenic factors like pigment epithelium-derived factor (PEDF) are upregulated in psoriasis. Abe *et al*.[114] demonstrated high levels of PEDF in psoriatic epidermis as well as dermis but it may not be sufficient to counteract effects of VEGF on angiogenesis. In SCID mice, local application of PEDF resulted in reduction of acanthosis attributed to reduced angiogenesis and basal cell proliferation.

Drugs targeting T cell activation and cytokine upregulation

Using this model we have demonstrated that targeting the CD28/B7 cascade in psoriasis with a humanized anti-CD28 monoclonal antibody for a month led to significant thinning of epidermis, reduced HLA-DR-positive lymphocytic infiltrates and also decreased length of rete pegs.[115] In another study, using CTLA4IgG, we have shown that there was significant improvement of transplanted psoriatic plaques, reduction in length of rete pegs and reduction in number of lympho-mononuclear cells and HLA-DR.[100]

Targeting the voltage sensitive Kv1.3 channels in effector memory T cells in psoriasis will be an effective novel therapeutic option in the near future. It has been shown that ShK, a potent and selective blocker of Kv1.3, is a potential therapeutic option for autoimmune diseases.[101,102,115-117] Gilhar *et al*. found that there was suppression of development of psoriatic features in the SCID mice model by ShK. It also reduced T cell infiltrates and cytokine (IFN-γ and TNF-α) production. However, there was incomplete recovery of the psoriasiform grafts with ShK treatment. This may be due to production of TNF-α by keratinocytes,[118] Langerhans cells,[119] and mast cells,[120] which most likely are not affected by ShK. The effects of the clinically efficacious anti-TNF-α biologic, etanercept have also been demonstrated in

the psoriasis xenograft SCID mouse model. Etanercept induced significant reduction in epidermal thickness as well as a decrease in the number of proliferative cells.[121] Thus, drugs effective in SCID mice have the potential to be highly effective antipsoriatic agents in humans later on.

LIMITATIONS OF THIS MODEL

SCID mouse psoriasis xenograft model is relatively expensive. Due to immunodeficiency, mice are prone to infections so they require a pathogen-free environment for maintenance. Moreover, a localized cutaneous infection may occur after transplantation of skin. Up to 20% of CB17 SCID mice become 'leaky', that is, the genetic defect is reversed leading to immunocompetence.[57] These mice then fail to accept the human skin graft. Selective inbreeding is recommended as the leakiness among SCID colonies decreases exponentially in the F2 and F3 generation compared with F1.[122] The SCID beige[123] and C3H SCID,[124] two new strains of SCID mice, have a more severe immune defect than CB17 SCID mice and do not show 'leakiness'.

AGR129 MICE

This is the most recent xenotransplantation model used for studying pathogenesis of psoriasis.[45] These AGR 129 mice are triple knockout mice deficient in type I and type II IFN receptors and also lack the recombinase activating gene-2 gene. They do not have T and B cells and have immature NK cells with severely impaired cytotoxic activity both *in vitro* and *in vivo*. They develop psoriatic lesions spontaneously when psoriatic skin is grafted onto them.[44]

FUTURE PERSPECTIVES

The tremendous advancement of science and technology including genetic engineering and xenotransplantation has given significant insights into the pathology and treatment of several immune-mediated diseases such as psoriasis, rheumatoid arthritis, and atopic dermatitis. The SCID mouse–human skin chimeras are a valuable animal model not only to study the pathogenesis but also to discover new drugs for the treatment of this enigmatic disease. Incorporation of human skin on SCID mice has demonstrated a significant role of the immune system in inflammatory processes of psoriasis. This model also made it possible to investigate the molecular and cellular events associated with key biological processes such as cell proliferation, angiogenesis, homing in of T cells in target tissues, neurogenic inflammation and cytokine/chemokine cascades involved in an inflammatory reaction. Moreover, humanization of SCID mouse has made it possible to develop potential novel therapeutic agents against chronic inflammatory diseases such as psoriasis.

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