

# Severe combined immunodeficiency mouse–human skin chimeras: a unique animal model for the study of psoriasis and cutaneous inflammation

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## Summary

Elucidation of the molecular and cellular mechanisms responsible for the pathogenesis of psoriasis had been significantly handicapped due to lack of an ideal animal model. To overcome this hurdle several investigators have developed a number of animal models for psoriasis. Recent establishment of the SCID-human skin chimeras with transplanted psoriasis plaques has opened new vistas to study the molecular complexities involved in psoriasis. This model also offers a unique opportunity to investigate various key biological events such as cell proliferation, angiogenesis, homing in of T cells in target tissues, neurogenic inflammation and cytokine/chemokine cascades involved in an inflammatory reaction. The SCID mouse model will be of immense help to target the cellular and molecular events associated with these pathogenic processes and develop novel drugs for psoriasis and other inflammatory diseases. In this article we have reviewed the prospects and the limitations of the SCID mouse model of psoriasis.

*Key words:* inflammation, mouse-human skin chimera, psoriasis, SCID mouse

Psoriasis is a multifactorial chronic inflammatory disease. A significant world population suffers from this disease: billions of dollars are spent on treatment. Despite intense research work on psoriasis the aetiology is unknown and its treatment remains palliative. Lack of an animal model has been a major hurdle for the investigation of the cause and cure of psoriasis. To overcome this hurdle several investigators have developed a number of animal models for psoriasis in the last 10 years. In this article we will review certain aspects of these animal models and share some of our observations on the severe combined immunodeficiency (SCID) mouse model for psoriasis. We will also discuss the usefulness of the psoriasis SCID mouse model for research on the pathophysiology of cutaneous inflammation, and the development of new generations of anti-inflammatory drugs.

## Animal models of psoriasis

The major pathological features of psoriasis are characterized by hyperproliferation and abnormal

differentiation of keratinocytes, infiltration of inflammatory cells, angiogenesis and dilation of dermal blood vessels. Since there are no naturally occurring diseases in animals that exhibit all the phenotypic and immunological features of psoriasis, several approaches have been utilized, which include studies on mutant strains of mice, development of transgenic mice and xenotransplantation models.

### *Studies on mutant strains*

Before the development of transgenic mice, three spontaneous mouse mutations reflecting psoriasiform phenotypes, the flaky skin (*fsn*), chronic proliferative dermatitis (*cpd*) and homozygous asebia (*ab/ab*) mutant mice were used to study the pathophysiology of psoriasis. All these mutants display pathological features of psoriasis such as acanthosis, infiltration of mast cells and macrophages and increased vasculature of the dermis.<sup>1</sup> However, the absence of T cells in these infiltrates<sup>2,3</sup> and ineffectiveness of cyclosporin treatment suggest that these pathological features are not comparable with psoriasis.<sup>3</sup>

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*Transgenic animal model*

Various 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)- $\alpha$ , tumour necrosis factor (TNF)- $\alpha$ , vascular endothelial growth factor (VEGF) and interferon (INF)- $\gamma$ , have been proposed to play an active part in the pathogenesis of psoriasis. Transgenic mice that overexpress various cytokines in the epidermis lead to alterations of keratinocyte function and generate psoriasiform phenotypes. Therefore, transgenic animals with targeted expression of cytokine within the skin have been used to study the roles of these cytokines in the pathogenesis of psoriasis. In transgenic mice that overexpress IL-1 $\alpha$  and keratin (K)14, there is infiltration of macrophages and monocytes within the dermis. In some cases inflammatory lesions are observed, with acanthosis and parakeratosis. This model supports the role of IL-1 $\alpha$  as an inducer of inflammation.<sup>4</sup> IFN- $\gamma$ /involucrin transgenic mice show hyperproliferation of keratinocytes. There is induction of major histocompatibility complex (MHC) class II, intercellular adhesion molecule (ICAM)-1, and the dermal capillaries are enlarged. Although there is infiltration of T cells in the dermis, there is no epidermal T-cell infiltrate.<sup>5</sup> In psoriatic skin, VEGF has been implicated in angiogenesis. In VEGF/K14 transgenics there is an increased number of dermal mast cells and enhanced leucocyte adhesion and extravasation. Thus VEGF may contribute to migration of inflammatory cells in psoriatic lesions.<sup>6</sup> Overexpression of leucocyte  $\beta$ 2 integrins such as LFA-1 and MAC-1 in the PL/J mouse strain is associated with chronic skin inflammation, epidermal hyperplasia, hyperkeratosis, parakeratosis and lymphocyte exocytosis.<sup>7</sup> Thus this strain manifests several histological features typical of psoriasis. Transgenic rats expressing human HLA-B27 and  $\beta$ <sub>2</sub> microglobulin have also been reported to have several clinical and histological characteristics of psoriasis such as scales, erythema, dystrophic nails, acanthosis and lymphomononuclear cell infiltration.<sup>8</sup>

*Xenotransplantation model*

Animal models based on transgenic technology have been used extensively to study the pathogenesis of various diseases, including psoriasis. As these models are created by manipulating a single gene, usually they do not represent the phenotype of these complex inflammatory diseases. Psoriasis especially, being a polygenic disease, cannot be truly reproduced in a

model system by the manipulation of a single gene. The above-mentioned transgenic models manifest various features of psoriasis, but none of them demonstrates the complete clinical and histological morphology characteristics of psoriasis. In that respect xenogenic transplantation models allow investigation of a disease process in a microenvironment resembling its natural milieu.

Genetically immunodeficient mice have been used in a xenograft model as they fail to reject skin grafts. Among the xenogenic transplantation models, nude mice and SCID mice have been used to elucidate the pathogenesis of psoriasis.<sup>9,10</sup> The thymus is not functional in the nude mouse. Thus the nude mouse lacks the T-cell arm of the immune system. Transplanted psoriatic plaques in nude mice develop certain histological changes that are not typical of psoriasis, such as absence of parakeratosis and the presence of a granular layer. In addition, circulating immunoglobulins impair immunohistochemical evaluation.<sup>11</sup> SCID mice lack both humoral and cellular immunity. Several investigators have reported that transplanted psoriasis plaques on SCID mice retain the typical clinical and histological features of psoriasis for a prolonged period.<sup>10</sup>

*Severe combined immunodeficient mice: the scid mutation*

The *scid* mutation occurring in the BALB/c mouse affects V(D)J rearrangement<sup>12</sup> and double strand break repair.<sup>13,14</sup> V(D)J rearrangement in SCID mice is characterized by defective coding joint formation, which prevents the development of mature B and T cells.<sup>15</sup> The absence of a functioning immune system allows xenogenic transplantation into SCID mice without major graft rejection.<sup>16,17</sup>

To appreciate the complexities of the *scid* mutation as it relates to the SCID mouse as an animal model for studying human disease, it is essential to understand the mechanistic basis of lymphoid V(D)J recombination. Functional immunoglobulin and T-cell receptor (TCR) genes are assembled from separate gene elements via somatic gene rearrangement—V(D)J recombination, during lymphoid differentiation. The gene elements (V, variable; D, diversity; and J, joining) targeted for rearrangement are flanked by conserved signal sequences, which mediate the rearrangement event and regulate the recombination machinery comprising several gene products.<sup>18</sup> In the SCID mouse a number of these gene products are defective, and thus there is a gross defect in V(D)J recombination, leading to

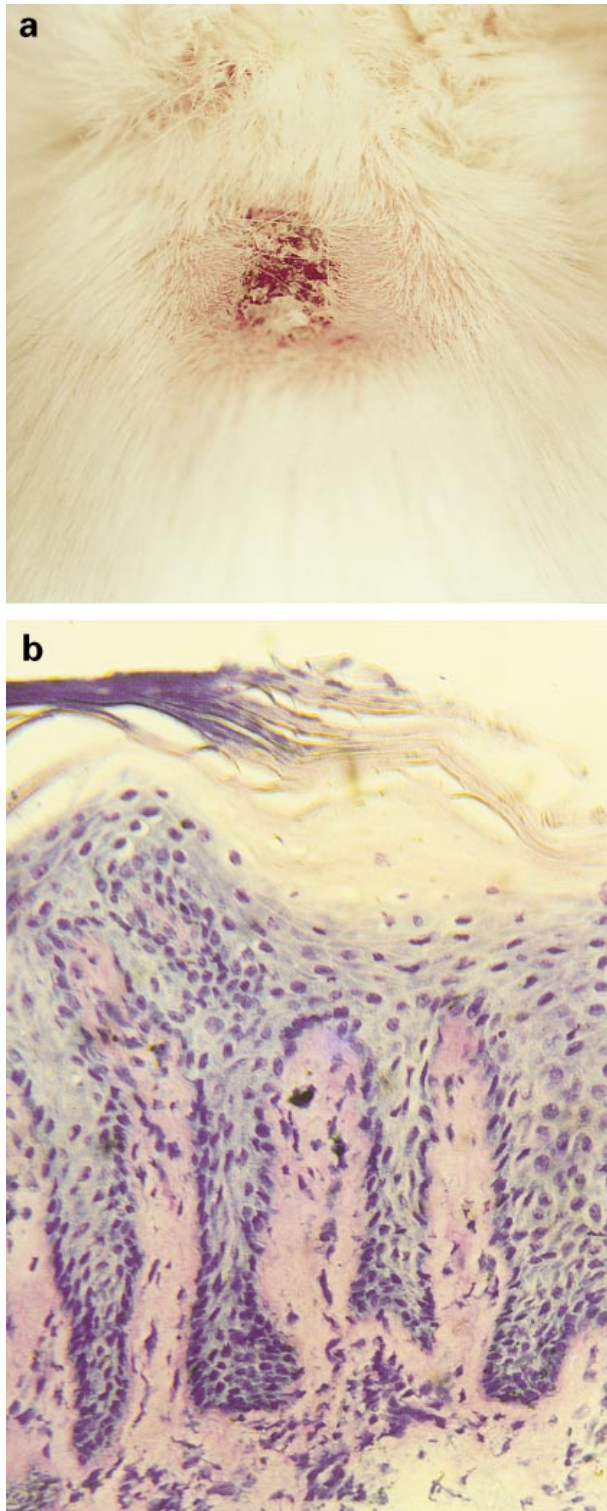
impaired antibody production and TCR expression. Hence, there is a lack of both humoral and cellular immune response giving rise to combined immunodeficiency. SCID mice have a low number of circulating

leucocytes due to a paucity of lymphocytes. Differential counts show an increased proportion of granulocytes. Serum IgG concentrations are usually less than  $0.02 \text{ mg mL}^{-1}$ .

### The psoriasis severe combined immunodeficiency mouse model: a unique tool for investigating the molecular and cellular events in inflammatory processes and development of novel anti-inflammatory drugs

#### *A model for studying the pathogenesis of psoriasis*

As SCID mice lack both B and T cells they are better recipients of grafts than nude mice. SCID mice have been successfully used to study the pathophysiology of psoriasis. Significant insights into the pathogenesis of psoriasis have been obtained from the studies by Nickoloff *et al.*<sup>10</sup> in the SCID mouse xenograft model. Histological features in transplanted skin have been reported to be maintained for several months. In transplanted grafts of psoriatic tissue we have noticed that the clinical, histological and immunological features of psoriasis could be maintained for a duration of 12–16 weeks. Figure 1(a,b) demonstrate certain clinical and histological features typical of psoriasis from a transplanted plaque of 12 weeks duration. The transplanted plaques have subtle morphological variations from the mature plaques of human beings. Lesions are hyperpigmented, scales are fewer and so far we have failed to elicit Auspitz's sign. Lesions are very rough and dry; this could be secondary to the denervation of the sweat glands. Histologically, except for occasional presence of a granular layer, transplanted lesions manifest the characteristics of psoriasis, such as hyperkeratosis, parakeratosis, intraepidermal microabscesses, suprapapillary thinning, angiogenesis and marked dermal infiltrates mainly composed of lymphomononuclear cells and dermal dendritic cells. In chronic psoriasis plaques the granular layer may often be not totally absent. Infiltrates of CD4 and CD8 positive T cells, and expression of adhesion molecules such as ICAM-1 and vascular cell adhesion molecule (VCAM)-1, were reported to be identical to those in chronic plaques of psoriatic patients.<sup>10</sup> Gilhar *et al.*<sup>19</sup>



**Figure 1.** Clinical and histopathological features of a transplanted psoriatic plaque. (a) A transplanted plaque after 12 weeks of grafting showing scales, erythema and thickening. (b) Histological section from this transplanted plaque demonstrating typical features of psoriasis: parakeratosis, acanthosis, elongated rete ridges, suprapapillary thinning, lymphomononuclear infiltrates in the papillary dermis.

observed that after 10 weeks of transplantation there was regression of epidermal thickness of the transplants with loss of HLA-DR expression and slight decrease in ICAM-1 expression. Sugai *et al.*<sup>20</sup> reported that 22 weeks after grafting of psoriatic skin there was loss of parakeratosis, resolution of Munro's microabscesses and decrease in infiltration of lymphocytes, although acanthosis and hyperkeratosis remained. Interestingly, intradermal or intravenous injection of T cells derived from psoriatic plaques, but not peripheral blood mononuclear cells (PBMC) from psoriatic patients, were able to maintain all the pathological features of psoriasis in the grafts for longer durations.<sup>20</sup> In untreated grafts, 10 weeks after engraftment both epidermal thickness and the number of T cells had decreased, whereas the number of T cells and epidermal thickness in psoriatic grafts treated with autologous T-cell infiltrates remained statistically equivalent to the pregrafted plaques.<sup>20</sup> When autologous immunocytes (PBMC) activated with *Staphylococcus* enterotoxins (SEB and SEC2) and IL-2 were injected into grafts of non-lesional skin from psoriatic patients, there was induction of typical features of psoriasis such as parakeratosis, loss of granular layer, acanthosis, elongation of rete ridges, infiltration of CD4 and CD8 positive lymphocytes in the epidermis and dermis, and dilation of dermal blood vessels.<sup>21</sup> There was epidermal expression of HLA-DR, ICAM-1,  $\beta$ 1 integrins and involucrin resembling the pathophysiology of psoriasis. Subsequently, it was shown by Nickoloff and Worne Smith<sup>22</sup> that the autologous activated CD4 positive T cells collected from PBMC of psoriatic patients were responsible for inducing the psoriatic phenotype in the non-lesional skin grafts, whereas administration of CD8 positive T cells did not induce any clinicopathological features of psoriasis. However, following intradermal administration of activated CD4 positive T cells, stimulation of the resident CD8 positive T cells in the non-lesional psoriatic skin grafts, with the expression of activation markers such as CD69 and CD25 were noted. The immunocytes also expressed natural killer (NK) cell receptors such as CD94 and CD158b. Boehncke *et al.*<sup>23</sup> demonstrated that administration of superantigen (staphylococcal superantigen exfoliative toxin) stimulated PBMC in non-lesional psoriatic skin resulting in exocytic infiltrates of CD3 positive cells expressing the cutaneous lymphocyte-associated antigen, along with other histological features of psoriasis.

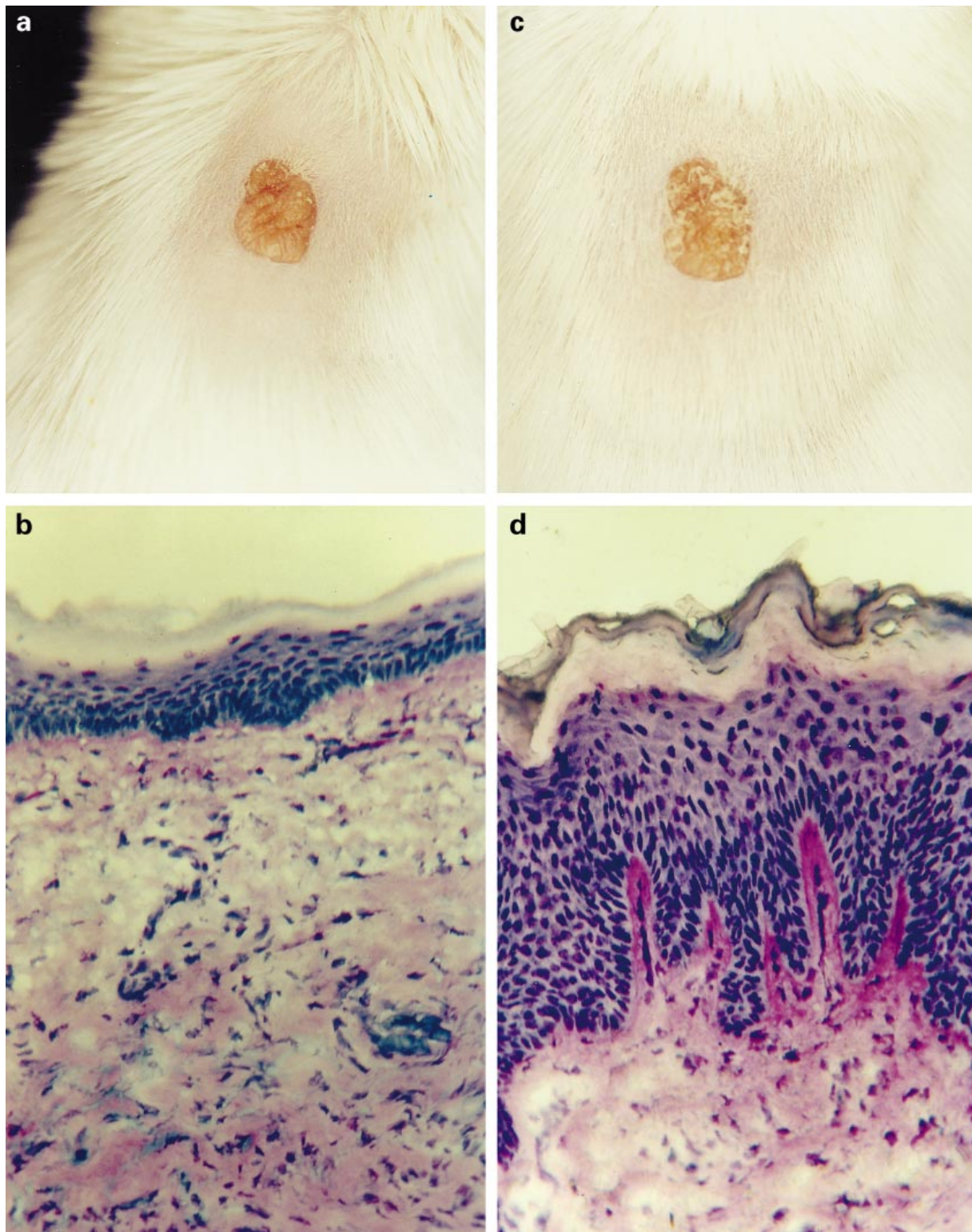
It has been also reported that superantigen activated allogenic immunocytes (PBMC) from psoriatic patients

were able to induce clinicopathological changes characteristic of psoriasis in transplanted normal skin on the SCID mouse. The skin grafts showed infiltration of CD4 and CD8 positive T cells in the epidermis and dermis. The T cells also expressed NK cell receptors CD94, CD158b and CD161. The keratinocytes expressed MHC class I, such as CD1d protein, which is a specific ligand for T cells expressing CD161. In view of these findings, the authors have proposed that NK T cells can directly interact with the keratinocytes and thus the T cells in psoriatic plaques may be activated without an exogenous antigen.<sup>22</sup>

In the last two decades, extensive work has been done to explore the immunological mechanisms involved in psoriasis. An active role of T cells is strongly substantiated by the following observations: (i) immunotherapy targeted specifically against CD4 (monoclonal CD4 antibody)<sup>24</sup> and IL-2-R (diphtheria fusion protein)<sup>25</sup> clears active plaques of psoriasis, and (ii) in SCID mice, transplanted non-lesional psoriatic skin converts to a psoriatic plaque after intradermal administration of T cells activated with an antigen cocktail. However, it is equally true that agents, such as calcipotriol and etretinate, which affect the differentiation process of keratinocytes, are very effective in psoriasis. Neither calcipotriol nor etretinate are effective in other T-cell-mediated cutaneous diseases, such as atopic dermatitis or contact dermatitis.

Though psoriasis has been claimed to be an autoimmune disease, the antigen, or specific endogenous factors responsible for the activation of T cells in psoriasis is still unknown. Regarding the induction of psoriasis in transplanted non-lesional skin on the SCID mouse by injecting autologous lymphomononuclear cells, it is worth noting that activation of T cells does not necessarily have to be by a superantigen or by an antigen cocktail. Nickoloff and his group reported that they could induce psoriasis by injecting lymphomononuclear cells activated with substance P (SP) (personal communication). We have noted a novel observation that autologous immunocytes activated with nerve growth factor (NGF) can convert non-lesional skin to a psoriatic plaque in 3 weeks. Figure 2(a) shows transplanted non-lesional skin of 4 weeks duration. The same skin shows typical clinical features of psoriasis subsequent to intradermal administration of autologous immunocytes stimulated with NGF (Fig. 2b). Histological sections from the plaque shown in Figure 2(c) also had all the morphological features of psoriasis (Fig. 2d). As an artificial antigen cocktail is not present in psoriatic skin, this suggests that local





**Figure 2.** (a,b) Non-lesional psoriatic skin with its histological section, 4 weeks after transplantation on the severe combined immunodeficient mouse. (c) The same transplanted plaque at 8 weeks following three intralesional injections of autologous peripheral blood mononuclear cells ( $2 \times 10^6$ ) activated with nerve growth factor ( $100 \text{ ng mL}^{-1}$ ) demonstrating classical morphology of a psoriatic plaque. (d) Histological section of the plaque shown in (c) reveals characteristic features of psoriasis.

dermal and epidermal factors such as NGF, SP and RANTES involved in the neuroimmunological cascades may play a part in activation (initiation or maintenance) of the lesional T lymphocytes.<sup>26</sup>

A critical analysis is required of the observations made by Nickoloff and his colleagues that activated lymphocytes from patients with psoriasis can induce clinical and histological changes consistent with psoriasis not only in non-lesional psoriatic skin transplants, but also in transplanted normal human skin and mouse skin. We are aware that various cutaneous diseases, including lichen simplex chronicus, subacute lupus erythematosus and mycosis fungoides, can clinically mimic psoriasis. Similarly, the histological features are not specific to psoriasis. For example, intraepidermal microabscesses along with psoriasiform changes can be observed in lesions of tinea corporis.

A diagnosis of psoriasis requires composite clinical and histological features, which include chronicity, involvement of the typical sites, symmetry, an isomorphic response, a variable clinical course and typical histopathological changes. Many of these clinical features that are diagnostic of psoriasis cannot be reproduced in the SCID mouse model. Regarding the claim that histopathological changes typical for psoriasis can be induced in normal and mouse skin certain confusion and contradictions need to be clarified. In contrast to Nickoloff and Worne Smith's<sup>22</sup> observation, Boehncke *et al.*<sup>23</sup> could not demonstrate induction of psoriasis in normal skin by intradermal administration of activated lymphocytes from psoriatic patients. Hyperproliferative changes in mouse skin induced by psoriatic lymphocytes lacks parakeratosis and demonstrates a prominent granular layer. Schön *et al.*<sup>27</sup> reported that SCID mice injected with MHC-matched but minor histocompatibility-mismatched CD4+/CD45 RB<sup>hi</sup> T lymphocytes developed a psoriasiform phenotype after 4–8 weeks. When lipopolysaccharide and IL-12 were coadministered with CD4+/CD45 RB<sup>hi</sup> T lymphocytes the severity of psoriasis was enhanced.<sup>28</sup> Thus psoriasiform dermatitis needs to be excluded when considering claims that psoriasis can be induced in normal and mouse skin.<sup>29</sup>

#### *Development of immunomodulatory and anti-inflammatory drugs*

In recent years, progress in molecular medicine has generated potential for the development of new generations of anti-inflammatory drugs. Effective therapeutic measures for rheumatoid arthritis targeting the

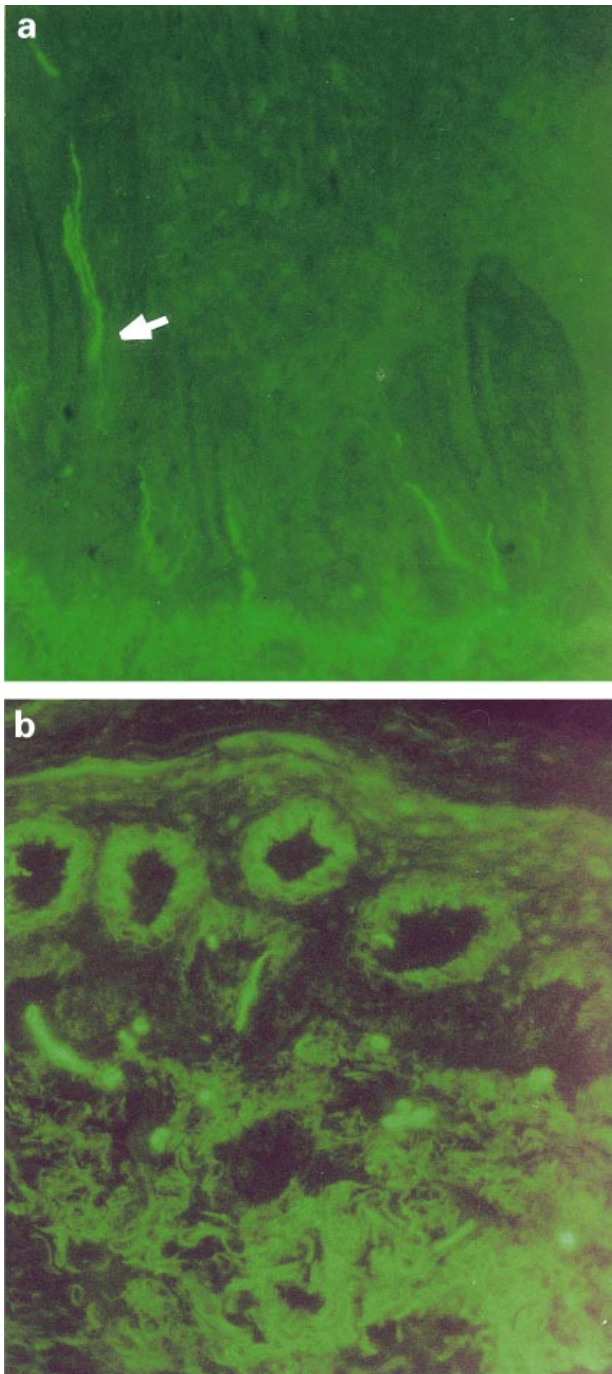
TNF/TNF-R system and the IL-1 receptor have been developed.<sup>30–32</sup> Immune-based therapy targeted against CD4, CD3 and the IL-2 receptor have been found to be clinically and histopathologically effective in psoriasis.<sup>24,25,33</sup> As such medicines can be delivered at the site of the lesion, and a therapeutic response can be determined without many investigations, many investigators consider psoriasis an ideal disease model for evaluating the efficacy of new-generation anti-inflammatory drugs. The inflammatory reaction in psoriasis is uniquely characterized by increased expression of adhesion molecules on the endothelial cells (E-selectin, ICAM, VCAM),<sup>34–38</sup> proliferation of vessels (angiogenesis) with upregulation of endothelial cell-stimulating angiogenesis factor (ESAF) and VEGF,<sup>39,40</sup> infiltrates containing activated T cells (CD4, CD8, NK cells),<sup>29,41,42</sup> neutrophils (Munro's and Kogoji microabscess), mast cells,<sup>43,44</sup> marked upregulation of chemokines such as IL-8, RANTES, fractalkine<sup>45–48</sup> and neuropeptides.<sup>49–52</sup> Thus the SCID mouse model will be of immense help to target any of these molecules and develop novel drugs for psoriasis and other inflammatory diseases.

#### *Study of neurogenic inflammation*

A role of neurogenic inflammation in psoriasis is substantiated by several key observations such as: (i) the symmetrical distribution of psoriatic lesions; (ii) exacerbation or onset induced by emotional stress;<sup>53</sup> (iii) proliferation of terminal cutaneous nerves with upregulation of neuropeptides [SP, vasoactive intestinal peptide, calcitonin-gene-related peptide (CGRP)] in the psoriatic plaques;<sup>49–52</sup> (iv) therapeutic response to neuropeptide modulating agents, such as capsaicin, somatostatin and peptide T;<sup>54–57</sup> and (v) the clearance of active plaques of psoriasis at the sites of local anaesthesia following traumatic denervation of cutaneous nerves.<sup>58</sup> These unique observations, that psoriasis resolves at sites of anaesthesia, that neuropeptides are upregulated and there is a marked proliferation of terminal cutaneous nerves in psoriatic plaques, encouraged us to search for a mechanism of neural influence. As NGF plays a part in regulating innervation<sup>59</sup> and upregulating neuropeptides<sup>60,61</sup> we decided to investigate the expression of NGF in lesional and non-lesional psoriatic skin, normal skin and skin in other inflammatory skin diseases.

In immunohistochemical studies we found that keratinocytes in lesional and non-lesional psoriatic tissue express high levels of NGF<sup>62</sup> and that there is a marked upregulation of nerve growth factor receptor





**Figure 3.** Regeneration of nerve growth factor receptor (NGF-R) positive mouse nerve fibre into the transplanted skin. (a) A marked proliferation of mouse nerve fibres into transplanted psoriatic plaque. Arrow indicates a long nerve fibre. (b) As compared with the transplanted psoriatic plaque very few nerve fibres are seen in transplanted normal skin. For the identification of the NGF-R-positive nerve fibres, immunofluorescence staining was carried out with a monoclonal NGF-R antibody at a dilution of 1 : 20.<sup>63</sup>

(NGF-R) in the terminal cutaneous nerves of psoriatic lesions.<sup>63</sup> Fantini *et al.*<sup>64</sup> observed similarly that levels of NGF are higher in tissue extracts from psoriatic lesions.

Keratinocytes of psoriatic plaques express increased levels of NGF; therefore, it is likely that murine nerves will promptly proliferate into the transplanted plaques on a SCID mouse. Indeed we have noted marked proliferation of nerve fibres in transplanted psoriatic plaques compared with the few nerves in transplanted normal human skin (Fig. 3a,b). By double label immunofluorescence staining we have further demonstrated that in these terminal cutaneous nerves there is a marked upregulation of neuropeptides, such as SP and CGRP. This further substantiates the role of the NGF/NGF-R system in the inflammatory process of psoriasis.

A contributing role of neurogenic inflammation has provided a new dimension in understanding the pathogenesis of various cutaneous and systemic inflammatory diseases such as atopic dermatitis, urticaria, rheumatoid arthritis, ulcerative colitis and asthma.<sup>65–68</sup> A new discipline has emerged in clinical pharmacology focusing on the development of drugs targeting the neuropeptides, neuropeptide receptors and the NGF/NGF-R system.<sup>54,55,69–71</sup> It is anticipated that the psoriasis SCID mouse model will be utilized to elucidate the molecular and cellular events involved in the inflammatory processes induced by sensory nerves, along with their neuropeptides. At the Psoriasis Research Institute, we are evaluating antagonists and agonists to selected neuropeptides, with the expectation of identifying pharmacological agents to counter neurogenic inflammation.

It is essential to understand the limitations of this model. SCID mice are expensive and require a pathogen-free environment for maintenance. Being immunodeficient they are prone to infections. In addition, transplantation of skin may cause a localized cutaneous infection. Three of 80 transplants we have done so far had cellulitis secondary to Gram-positive infections. All three mice received skin from the same donor. In up to 20% of CB.17 SCID mice there is reversion of the genetic defect, leading to immunocompetence.<sup>15</sup> Such 'leaky' mice fail to accept the human skin graft. As the leakiness among SCID colonies decreases exponentially in the  $F_2$  and  $F_3$  generation compared with  $F_1$ , selective inbreeding is suggested.<sup>72</sup> Two new strains of SCID mice, the SCIDbeige<sup>73</sup> and C3H SCID,<sup>74</sup> have a more severe immune defect than CB.17 SCID mice and do not revert.

The SCID-human skin chimeras have provided a valuable animal model to study the pathogenesis of psoriasis. By reconstituting the human immune system in SCID mice, significant insights in respect to the role of the immune system in the inflammatory processes of psoriasis have been gained. This model also offers a unique opportunity 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.

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