Animal Models of Psoriasis – What Can We Learn from Them?

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Research into the pathogenesis of psoriasis has been hampered by the lack of an animal disease resembling this common human skin disorder. Over the past few years, however, various rodent models that mirror aspects of the psoriatic phenotype and pathogenesis have become available. Here, the most prominent models are compared with human psoriasis and potential uses for psoriasis research are reviewed. Asebia (ab), flaky skin (fsn), and chronic proliferative dermatitis (cpd) are spontaneous mouse mutations with psoriasiform skin alterations of unclear pathogenesis. Transgenic mice with cutaneous overexpression of cytokines, such as interferon-γ, interleukin-1α, keratinocyte growth factor, transforming growth factor-α, interferon-6, vascular endothelial growth factor, or bone morphogenetic protein-6, are valuable tools for studying in vivo effects of individual cytokines in the pathogenesis of psoriasiform features. Psoriasiform lesions also were seen in β2-integrin hypomorphic mice backcrossed to the PL/J strain and in β1-integrin transgenic mice. A T cell-based immunopathogenesis of psoriasiform features was shown in a form of graft-versus-host disease in scid/scid mice reconstituted with CD4+/CD45RBhi T lymphocytes as well as in HLAB27/hB2m transgenic rats, demonstrating that dysregulated T cells can induce psoriasiform skin alterations without a primary epithelial abnormality. Finally, xenotransplantation models using human skin grafted on to immunodeficient mice are attractive, as different cell types and some environmental factors leading to psoriasiform features may be studied in human tissue. Overall, although there is no animal model imitating psoriasis completely, many aspects of this common human skin disorder are mirrored in the currently available models and psoriatic plaques can be created in xenotransplantation models. Key words: adaptive transfer/cytokines/pathogenesis/transgenic/xenotransplantation. J Invest Dermatol 112:405–410, 1999

Psoriasis, affecting about 2% of the population, is one of the most common, yet enigmatic human skin disorders. It is characterized by complex alterations of various cell types (summarized in Fig 1). These include epidermal keratinocyte hyperproliferation and altered differentiation, as well as angiogenesis and dilation of dermal blood vessels. In addition, a mixed leukocytic infiltrate is seen. It is composed of activated T lymphocytes, neutrophils within the dermis and epidermal microabscesses, lining macrophages, and an increased number of dermal mast cells (Christophers and Sterry, 1993). Cytokines including tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) (Kupper, 1990), interferon-γ (IFN-γ) (Livden et al, 1989; Barker et al, 1991b), IL-6 (Grossman et al, 1989; Neuner et al, 1991), IL-8 (Barker et al, 1991a), vascular endothelial growth factor (VEGF) (Detmar et al, 1994), and transforming growth factor-α (TGF-α) (Gottlieb et al, 1988; Elder et al, 1989; Prinz et al, 1994) are thought to mediate the psoriatic tissue alterations.

It has been difficult to delineate definitively whether psoriasis results from a primary abnormality in the epidermis or is immunologically based. Overwhelming circumstantial evidence is accumulating, however, to indicate that it has an immunologic basis (Christophers, 1996). As there is no naturally occurring animal disease mirroring both phenotype and immunopathogenesis of psoriasis, research into the pathogenesis of this common disorder has been severely hampered. Several spontaneous mutations, transgenic animals, xenotransplantation models, or T cell transfer models, however, have been utilized to study aspects of psoriasis. Some of these models corroborated existing hypotheses, others allowed important and sometimes unexpected new insights into steps of the pathogenic cascade. Here, the major animal models and their potential value for psoriasis research are reviewed. Their major characteristics are summarized in Table I.

**PSORIASIFORM PHENOTYPES IN SPONTANEOUS MOUSE MUTATIONS**

Until the availability of transgenic animals and the advent of the flaky skin (fsn) and chronic proliferative dermatitis (cpd) mutations, mice homozygous for the asebia (ab/ab) mutation (Gates and Karasek, 1965) were used to study therapies directed at hyperkeratotic disorders (Sundberg et al, 1994). This mutation features moderate epidermal acanthosis, increased dermal vascularity (Sundberg et al, 1990), and a dermal infiltrate composed of macrophages and mast cells (Brown and Hardy, 1988). For the absence of T cell and neutrophil infiltrates (Gates and Karasek, 1965; Brown and Hardy, 1988), however, these skin alterations do not mirror psoriatic lesions. In addition, the etiology of this disorder is poorly understood, and alterations of the cutaneous lipid
metabolism (Wilkinson and Karasek, 1966) suggest a pathogenesis distinct from psoriasis.

A more psoriasiform phenotype occurred in mice homozygous for the chronic proliferative dermatitis (cpd) or the flaky skin (fsn) mutations. These animals were characterized by skin alterations including epidermal hyperproliferation, a mixed inflammatory infiltrate with neutrophils accumulating in epidermal microabscesses, and enlarged and dilated dermal blood vessels (HogenEsch et al, 1994; Sundberg et al, 1994). Backcrosses to different mouse strains suggested several modifier genes affecting the expression of the fsn phenotype (Sundberg et al, 1994). As cyclosporine A, in contrast to glucocorticosteroids, was not effective when used for topical or systemic treatment of fsn lesions (Sundberg et al, 1994), it appears that there is no immunologic basis for these lesions. In addition, a T cell based immunopathogenesis of the fsn phenotype is unlikely, as skin lesions develop in mice doubly homozygous for fsn and scid (severe combined immunodeficiency), which lack mature T and B lymphocytes (Sundberg et al, 1994). Likewise, homopoietic cells from cpd/cpd mice failed to induce skin lesions in syngeneic recipients, and cyclosporine A did not alleviate cpd lesions (HogenEsch et al, 1994).

Overall, both the cpd and the fsn mutations appear to be useful models for comparing local pathogenic events, such as regulation of neutrophil infiltration and microabscess formation, epidermal hyperproliferation, or dermal angiogenesis. In this respect, these models offer a tool for assessing in vivo interactions between resident and immigrating cells in the skin. Their value for psoriasis research is limited by the lack of a T cell based immunopathogenesis. In addition, as immunosuppressive therapeutic regimens used to treat psoriasis fail to improve skin lesions in these mutations, it appears uncertain whether they can be used to test potential therapeutic compounds.

MORE TO PSORIASIS THAN SINGLE CYTOKINES

Based upon expression in inflammatory skin disorders and functional properties in vivo, a number of cytokines have been proposed to play crucial parts in the pathogenesis of psoriasis: IL-6 and TGF-α enhance keratinocyte proliferation (Elder et al, 1989; Grossman et al, 1989); IL-1, TGF-α, TNF-α, and VEGF induce angiogenesis and attract inflammatory cells in vivo (Schreiber et al, 1986; Frater-Schroder et al, 1987; Leibovich et al, 1987; Detmar et al, 1994); IL-1, IFN-γ, and TNF-α induce expression of ICAM-1 and major histocompatibility complex (MHC) class II (Dustin et al, 1986; Nickoloff, 1988; Barker et al, 1988; Detmar et al, 1992; Strange et al, 1994); IL-1, granulocyte-macrophage colony-stimulating factor, and TNF-α induce activation, maturation, and migration of dendritic cells, and IL-1 activates mast cells (Subramanian and Bray, 1987). Therefore, transgenic mice with targeted cytokine expression within the skin provided promising tools for studying possible roles of these cytokines in the pathogenic cascade of psoriasis.

Surprisingly, K14 promoter-driven epidermal overexpression of the IL-6 (Turksen et al, 1992), keratinocyte growth factor (Guo et al, 1993), or TGF-α (Vassar and Fuchs, 1991), resulted in no (in IL-6 transgenics) or marginal (in TGF-α and keratinocyte growth factor transgenics) alterations of keratinocyte proliferation and differentiation. In addition, with the exception of some severely affected TGF-α transgenics, inflammatory infiltrates or vascular changes were not reported. Thus, although it is possible that higher expression levels might have evoked more psoriasis-like features in IL-6 transgenic, keratinocyte growth factor transgenic, or TGF-α transgenic mice, a more complex pattern, possibly including synergistic actions of these and other cytokines, may be necessary to achieve a psoriatic phenotype.

Dermal infiltrates of macrophages/monocytes within the dermis of clinically uninvolved skin were seen in transgenic mice with epidermal overexpression of K14/IL-1α, suggesting a role of IL-1α for macrophage attraction (Groves et al, 1995). In severely affected animals, inflammatory lesions occurred that were characterized by a mixed inflammatory infiltrate, and by acanthosis and parakeratosis in some cases. The effect on keratinocyte differentiation, however, appeared to be subtle in IL-1α transgenic mice, suggesting that other mediators present in psoriatic skin are lacking in these skin lesions. Slightly decreased numbers of γδ T cells and Langerhans cells within the epidermis of IL-1α transgenic mice with relatively low expression of the transgene, suggest a regulatory role of IL-1α for migration and localization of Langerhans cells and some T cell populations. Clearly, IL-1α transgenic mice
Table I. Animal models of psoriasis. Synopsis of cutaneous alterations and putative pathogenesis

<table>
<thead>
<tr>
<th>Model</th>
<th>Acanthosis and hyperproliferation</th>
<th>Altered keratinocyte differentiation</th>
<th>Induction of MHC Class II and ICAM-1</th>
<th>Increased vascularity</th>
<th>Increased mast cells</th>
<th>T cell infiltrate</th>
<th>Neutrophil infiltrate</th>
<th>Intraepidermal microabscesses</th>
<th>Inflammatory cytokines</th>
<th>Putative pathogenesis</th>
<th>Studies of antipsoriatic treatments</th>
<th>Potency of psoriasis phenotype</th>
<th>References</th>
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<tr>
<td><strong>Spontaneous mutations</strong></td>
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<tr>
<td>Aboia (ab)</td>
<td>moderate ortho-hyperkeratosis</td>
<td>no</td>
<td>n.d.</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>n.d.</td>
<td>unclear</td>
<td>limited usefulness</td>
<td>n.d.</td>
<td>Gates and Kunicki, 1965</td>
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<td>Brown and Handley, 1984</td>
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<tr>
<td>chronic psoriatic dematitis (sp)</td>
<td>marked</td>
<td>focal parakeratosis</td>
<td>n.d.</td>
<td>yes</td>
<td>n.d.</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>n.d.</td>
<td>unclear</td>
<td>limited usefulness</td>
<td>n.d.</td>
<td>Rogozinski et al., 1986</td>
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<tr>
<td>flaky skin (fsn)</td>
<td>severe</td>
<td>focal parakeratosis</td>
<td>n.d.</td>
<td>yes</td>
<td>n.d.</td>
<td>stratum-dependent</td>
<td>stratum-dependent</td>
<td>yes</td>
<td>n.d.</td>
<td>unclear</td>
<td>limited usefulness</td>
<td>n.d.</td>
<td>Sundberg et al., 1990</td>
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<td></td>
<td>100%</td>
<td>Sundberg et al., 1994</td>
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<td><strong>Transgenic rodents</strong></td>
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<tr>
<td>K14/IL-1/14a</td>
<td>in severely affected animals of one line</td>
<td>rarely parakeratosis</td>
<td>in severely affected animals</td>
<td>n.d.</td>
<td>n.d.</td>
<td>in severely affected animals</td>
<td>in severely affected animals</td>
<td>IL-1α cytokine</td>
<td>n.d.</td>
<td>lesions only in severely affected animals from one of two lines</td>
<td>n.d.</td>
<td>Tidholm et al., 1992</td>
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<tr>
<td>K14/IL-6</td>
<td>ortho-hyperkeratosis, especially on tail and paws</td>
<td>2.4 to 96-fold increased proliferation</td>
<td>acanthosis and 2-6-fold increased vascularity</td>
<td>mast cells</td>
<td>microabscesses</td>
<td>cytokines</td>
<td>antipsoriatic phenotype</td>
<td>100%</td>
<td>unclear</td>
<td>limited usefulness</td>
<td>n.d.</td>
<td>Gates and Kurasek, 1965</td>
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<tr>
<td>involucrin/IFNγ</td>
<td>yes</td>
<td>n.d.</td>
<td>yes</td>
<td>yes</td>
<td>n.d.</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>n.d.</td>
<td>unclear</td>
<td>limited usefulness</td>
<td>100%</td>
<td>Gates and Kurasek, 1965</td>
</tr>
<tr>
<td>K14/VEGF</td>
<td>no</td>
<td>no</td>
<td>n.d.</td>
<td>yes</td>
<td>yes</td>
<td>n.d.</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>VEGF</td>
<td>cytokine overexpression</td>
<td>n.d.</td>
<td>Guo et al., 1993</td>
</tr>
<tr>
<td>HLA-B27/fibn</td>
<td>marked in some animals</td>
<td>focal</td>
<td>n.d.</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>n.d.</td>
<td>response to IL-1</td>
<td>n.d.</td>
<td>Tidholm et al., 1992</td>
</tr>
<tr>
<td>involucrin/α5, or β1-integrin</td>
<td>acanthosis in 64% of β1 mice, 96% of α5 mice, and 73% of αvβ3 mice</td>
<td>focal parakeratosis</td>
<td>altered differentiation</td>
<td>CAM-1 induction</td>
<td>increased expression</td>
<td>focal parakeratosis</td>
<td>altered differentiation</td>
<td>CAM-1 induction</td>
<td>increased expression</td>
<td>100%</td>
<td>response to UV-B and cyclosporin A</td>
<td>n.d.</td>
<td>Kohler et al., 1992</td>
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<td></td>
<td>100%</td>
</tr>
<tr>
<td>hapten/collegenase</td>
<td>3.5-fold increase in keratinocyte proliferation, acanthosis</td>
<td>n.d.</td>
<td>n.d.</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>n.d.</td>
<td>onset at 4–6 d of age</td>
<td>n.d.</td>
<td>D'Amato et al., 1995</td>
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<td><strong>Knockout rodents</strong></td>
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<td>PL/J/CD18-</td>
<td>marked focal parakeratosis</td>
<td>n.d.</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>n.d.</td>
<td>response to dexamethasone</td>
<td>100%</td>
<td>Ballard et al., 1996</td>
</tr>
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<td>T cell transfer</td>
<td>C3H/THSC3H/J ( scid /) transfer into adult mice</td>
<td>up to 20-fold increased proliferation, acanthosis</td>
<td>altered keratin expression, focal parakeratosis</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>IFN-γ, TNF-α, IL-1, IL-6, GM-CSF</td>
<td>cytokine overexpression</td>
<td>n.d.</td>
<td>100%</td>
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<td>Xenotransplantation models</td>
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<tr>
<td>human tissue onto mice with maintenance of porcine phenotype for &gt;2 mo</td>
<td>yes</td>
<td>n.d.</td>
<td>yes</td>
<td>n.d.</td>
<td>yes</td>
<td>(affinity of both human and murine lymphocytes)</td>
<td>yes</td>
<td>n.d.</td>
<td>maintenance of tissue alterations in porcine lesion; proliferation possibly triggered by infecting mouse T cells</td>
<td>graft persistence in most animals</td>
<td>Briggsman and Wheeler, 1980</td>
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<tr>
<td>human tissue onto scid mice with experimental induction</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>n.d.</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>n.d.</td>
<td>Brinkman et al., 1994</td>
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N.d., not determined
strongly support a primary role of IL-1α as an inducer of cutaneous inflammation, which makes these animals a valuable tool for studying this aspect of the psoriatic pathogenesis.

In contrast, in 5%-20% of involucrin/IFN-γ transgenic mice an up to 10-fold increase in keratinocyte proliferation, hyperproliferative changes of differentiation, induction of MHC class II and ICAM-1, and enlarged dermal capillaries were seen (Carroll et al., 1997). Although there was a dermal infiltrate of T cells and macrophages in severely affected mice, no T cells infiltrated the epidermis, suggesting that IFN-γ does not play a part in T cell epidermotropism observed in human psoriasis. Thus, IFN-γ and IL-1α transgenic mice appear to be somewhat complementary, giving rise to the speculation that synergistic effects of both cytokines might lead to a more psoriasis-like skin phenotype than either cytokine alone. This may also have implications for complementary functions of the two cytokines in the pathogenesis of human psoriasis. It would be interesting to study IL-1α/IFN-γ double-transgens.

Two completely opposite phenotypes were observed in mice expressing K10/BMP-6 (bone morphogenetic protein-6, a member of the TGF-β superfamily) within the epidermis (Blessing et al., 1996). Whereas keratinocyte proliferation was severely reduced in animals with strong and homogeneous expression of the transgene, weaker and patchy expression led to marked hyperproliferation. In addition, an inflammatory infiltrate was seen, and neutrophils accumulated in epidermal microabscesses, a hallmark feature of psoriasis. Although these unexpected observations gave rise to human studies, which revealed elevated expression of BMP-6 in psoriatic lesions (Blessing et al., 1996), the decreased keratinocyte proliferation in transgenics with high expression of BMP-6 suggested dose-dependent alternative responses of keratinocyte proliferation. Thus, a possible role of BMP-6 in the pathogenesis of psoriasis requires further investigation.

The concept of VEGF being an important angiogenic factor in psoriatic skin (Detmar et al., 1994) was strongly supported by transgenic mice with constitutive epidermal K14/VEGF expression, as these animals exhibited dilated and contorted dermal microvessels transgenic mice with constitutive epidermal K14/VEGF expression, between two pathogenic events of psoriasis, angiogenesis and tissue-inflammation. This possible observations, one may speculate that VEGF, as well as its known function was enhanced in VEGF transgenic mice. Based upon these observations, one may speculate that VEGF, as well as its known number of dermal mast cells, and leukocyte adhesion and extravasation was enhanced in VEGF transgenic mice. Based upon these observations, one may speculate that VEGF, as well as its known effects on endothelia, may contribute to mast cell accumulation and influx of inflammatory cells in psoriatic lesions. This possible novel pathogenic role of VEGF may provide a molecular link between two pathogenic events of psoriasis, angiogenesis and tissue-specific leucocyte localization. In addition, upregulation of VEGF receptors on dermal microvessels in VEGF transgenic mice provides strong circumstantial evidence that VEGF is directly involved in upregulating its own receptors in human psoriasis. Thus, VEGF transgenic mice may hint at a broader pathogenic function of this cytokine than previously suspected.

Overall, while important insights into the in vivo action of key cytokines were gained, single cytokines apparently are not sufficient to induce the complex and intertwined tissue alterations seen in psoriasis. This supports the concept of a cytokine network in psoriasis (Nickoloff, 1991). In addition, dynamic changes and mutual interactions of cytokines, which may be involved in pathogenic processes, cannot be mimicked, and the relatively low penetrance of the psoriasiform phenotypes makes some transgenic models somewhat difficult to study. In some animals, such as IL-1α and IL-1β transgenic mice, cutaneous inflammation occurred in animals with high expression levels of the transgene, suggesting that expression beyond a certain threshold level may initiate a cascade of events evoking psoriasiform features. Uniform induction in some transgenic mice of hyperproliferation-associated molecules, such as keratins 6/16 and integrin α4, within the epidermis, support previous hypotheses that these are rather unspecific changes following perturbations of cutaneous homeostasis and/or inflammation.

INVolvement of Adhesion Molecules in the Pathogenesis of Psoriasiform Phenotypes

Tissue-specific localization of immune cells including T cells, granulocytes, and macrophages, is thought to be crucial in the pathogenesis of psoriasis. Therefore, animals overexpressing or lacking certain adhesion molecules are interesting tools for studying pathogenic events.

A role of leukocyte β3 integrins (CD18) such as LFA-1 (αβ, CD11a/CD18) and Mac-1 (αMβ2, CD11b/CD18) was suggested by a hypomorphic mutation of CD18 in the PL/J mouse strain (Bullard et al., 1996). The phenotype of these animals, which was not seen in other genetic backgrounds, comprised chronic skin inflammation, epidermal hyperplasia, hyperkeratosis and parakeratosis, subcorneal microabscesses, and lymphocyte exocytosis. PL/J/CD18-hypomorphic mice provide an example of a psoriasiform skin disorder that apparently has a genetic basis, possibly based on a few (if not a single) modifying genes. The pathogenesis of this disorder, however, remains largely obscure. It is difficult to propose mechanisms by which decreased expression of a receptor, which participates in cutaneous localization of immune cells, results in extravasation or microabscess formation. It would be interesting to study potential compensatory changes of other adhesion molecules in PL/J/CD18 hypomorphic mice, which may mediate these events.

When mice with suprabasal epidermal (involucrin promoter-driven) expression of human β1, αββ1, or αββ2, integrins were studied, psoriasiform lesions were observed in addition to developmental abnormalities (Carroll et al., 1995). Epidermal hyperplasia was seen in 64%-89%, and inflammatory infiltrates in 36%-68% of transgenic mice. Thus, keratinocyte hyperproliferation must have occurred in the absence of infiltrating leukocytes in some cases. This raises the interesting hypothesis that suprabasal expression of β1 integrins in psoriasis contributes to the Maintenance of a hyperproliferative state. It would be interesting to study whether epidermal overexpression of β1 integrins in developing psoriatic lesions precedes or follows keratinocyte hyperproliferation. In addition, β1 integrin-transgenic mice suggest mechanisms of integrin regulation in psoriatic lesions downstream from the induction by immune cells, as suprabasal expression of the β1 chain induces the αc chain, which is also upregulated in psoriasis (Kellner et al., 1992).

T CELL-BASED IMMUNOPATHOGENESIS OF PSORIASIFORM LESIONS IN T CELL TRANSFER MODELS

When scid/scid mice were reconstituted with MHC-matched, but minor histocompatibility mismatched CD44+CD45RBhi T lymphocytes, 100% of the animals developed skin lesions strikingly similar to human psoriasis within 4-8 wk after transfer (Schön et al., 1997). With the exception of the previously reported intestinal inflammation (Morrissey et al., 1993; Powrie et al., 1993), this inflammatory process, a form of graft-versus-host disease, was not generalized. Interestingly, the psoriasiform skin lesions did not develop in recipients of unfractionated splenocytes or CD44+CD45RBhi T cells. In addition, they were alleviated by coinjection of CD44+CD45RBhi and CD44-/CD45RBhi T cells, indicating that T cell dysregulation is the primary pathogenic factor in this model. As in human psoriasis, cutaneous expression of cytokines including IFN-γ, TNF-α, IL-1, IL-6, VEGF, and granulocyte-macrophage colony-stimulating factor, could account for the psoriasiform tissue alterations. In addition, when recipients of CD44+CD45RBhi T cells were treated with either cyclosporine A or ultraviolet B (310 nm) irradiation, the psoriasiform skin lesions were dramatically improved, demonstrating that immunosuppressive therapies are efficacious. Overall, this model directly demonstrated that psoriasiform skin lesions can be induced in vivo activated T cells in the absence of a primary epithelial abnormality. Although it should be used with caution for assessing mechanisms through which T cells are activated within psoriatic lesions, this model appears to be valuable for studying the array of local events.
resulting from the localization of activated T cells within the skin (Schön and Parker, 1997).

Transgenic rats expressing human HLA-B27 and β2m-microglobulin (hβ2m) developed psoriasiform skin changes as part of a multorgan inflammatory disease (Hammer et al., 1990). In the two most severely affected lines, psoriasiform lesions first occurred at about 20 wk of life and were observed in 10%–80% of animals. Males appeared to be more prone to skin changes than females (Taurog et al., 1993). Similar to the pathogenesis postulated for human psoriasis, the major pathogenic factor in HLA-B27 transgenic rats appeared to be T cells (Brebans et al., 1996). This was shown by adoptive transfer of B27 transgenic bone marrow or fetal liver cells, with CD4 cells being more effective in transferring disease than CD8 cells. Thus, although the relatively low penetrance of the cutaneous phenotype and the involvement of various other organ systems limit the use of this model for psoriasis research, HLA-B27 transgenic rats clearly support the concept that dysregulated T cells can induce psoriasiform skin lesions without a primary epithelial abnormality.

In addition, the role of immanocytes for the pathogenesis of psoriasiform skin lesions has also been demonstrated in xenotransplantation models (Nickoloff et al., 1995, Wrone-Smith and Nickoloff, 1996).

HUMAN PSORIATIC SKIN STUDIED IN XENOTRANSPLANTATION MODELS

Xenotransplantation models for psoriasis research are very attractive as they involve the study of human tissue. Initially, investigators focused on human skin grafted on to nude mice. Using this approach, it was shown that psoriatic features could be maintained for more than 2 mo without further manipulations (Fraki et al., 1983). In addition, using these transplantation models, similarities between involved and uninvolved skin from psoriasis patients have been identified (Kruger et al., 1981; Fraki et al., 1982), and an important pathogenic role of (murine) inflammatory cytokines was suggested (Baker et al., 1992). Recent progress in transplantation technology using scid/scid recipients has enabled investigators to establish pathogenic links between T cells isolated from psoriasics and cutaneous alterations characteristic for psoriasis (Nickoloff et al., 1995, Wrone-Smith and Nickoloff, 1996). In another recent study, skin-infiltrating T lymphocytes, but not T cells derived from peripheral blood, maintained the psoriatic phenotype of human skin grafted on to scid/scid mice (Gilhar et al., 1997). In addition, there was circumstantial evidence for a pathogenic role of bacterial superantigens in psoriasis (Boechcke et al., 1996). Thus, xenotransplantation models are clearly appropriate tools for mechanistically studying local events underlying the pathogenesis of psoriasis, including interactions of certain cell types, cytokines, and exogenous factors in an in vivo setting. Dynamic processes involving the entire organism, such as recirculation and cutaneous homing of leukocytes, or roles of regional lymph nodes that may be important for T cell activation in vivo, however, are difficult to study in these models.

CONCLUSIONS AND FUTURE PERSPECTIVES

As seen with BMP-6 and VEGF transgenic mice (Blessing et al., 1996; Detmar et al., 1998), cytokine transgenics sometimes revealed potential pathogenic functions of cytokines that were not discernible from prior human studies. Neither the complete pathogenic cascade nor dynamic changes of cytokines during the development of psoriatic lesions can be mirrored in single cytokine transgenics. Whereas the former problem might be approached by double cytokine transgenics, the latter might be resolved, at least in part, by generating transgenic animals with inducible promoters. In addition, cytokine transgenic animals have great potential value for studies aimed at developing specific cytokine or cytokine receptor antagonists to treat psoriasis and other inflammatory disorders.

Although the immune system appears to play a central part in the pathogenesis of psoriasis, the role of cytokine transgenics in HLA-B27/β2m transgenic rats (Hammer et al., 1990; Breban et al., 1996), its function in most transgenic models remains largely speculative (Bullard et al., 1996; Carroll et al., 1995). An unlikely or at least uncertain contribution of the immune system was seen in spontaneous mouse mutations with a psoriasiform phenotype (Gates and Karasek, 1965; HogenEsch et al., 1994; Sundberg et al., 1994). Thus, both spontaneous mutations and some transgenic animals suggest that psoriasiform features may occur independently from the immune system or represent a rather unspecific reaction pattern of the skin to various stimuli. Along this line, it is unclear whether environmental factors, such as bacterial superantigens or mechanical irritation, may contribute to the pathogenesis in these cases. Besides copy numbers of the transgenes, as yet unidentified environmental factors may offer an explanation to the relatively low penetrance of psoriasiform phenotypes in some transgenic models (Hammer et al., 1990; Carroll et al., 1995, 1997; Groves et al., 1995) (Table I).

In contrast, the CD4+/CD45RB− transfer model (Schön et al., 1997) as well as HLA-B27/hβ2m transgenic rats (Hammer et al., 1990; Breban et al., 1996) demonstrated that subsets of dysregulated and in vivo activated T cells can induce psoriasiform tissue alterations in the absence of a primary epithelial abnormality. These models should also prove useful for assessing events involving the entire organism, such as cutaneous localization and recirculation of leukocytes. Another application would be to test therapeutic strategies interfering with specific steps in the pathogenesis of psoriasiform skin lesions (Table I).

Xenotransplantation models of human psoriasis may be used to study previously activated psoriatic T cells in an in vivo setting, thereby overcoming a limitation of the CD4+/CD45RB− transfer model, whose T cells may be activated through mechanisms distinct from human psoriasis. T cell activation, which may involve regional lymph nodes, and recirculation of leukocytes, however, may be difficult to assess in these “two–species–systems”. In addition, studying short-lived or hard-to-isolate cell types, such as granulocytes, mast cells, or macrophages, may not be practicable. To resolve these limitations, “humanized” scid mice reconstituted with human leukocyte progenitors may be valuable (Garcia et al, 1997; Herz et al., 1997).

Overall, although no single animal model reproduces the complete pathogenesis and phenotype of psoriasis, the currently available models clearly provide a strong handle on many specific phenotypic and pathogenetic aspects of this common disorder.

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