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In vivo and In vitro Models of Psoriasis

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1. Introduction

1.1 Skin

The evolution of life in the terrestrial environment required the development of a waterproof integument: the skin (Loden and Maibach, 2006). Skin is an extensive organ covering the entire exterior of the body (Stevens and Lowe, 2005). It provides the primary barrier against chemical and biological external agents and water loss (Hadgraft, 2001). The skin also plays an important role in thermoregulation, sensory perception and vitamin D metabolism (McKay and Leigh, 1995).

The skin is composed of three main layers: the epidermis, the dermis and the hypodermis. The epidermis is the protective skin layer in contact with the external environment (Stevens and Lowe, 2005). This skin layer consists mainly of a stratified squamous keratinized epithelium (Junqueira and Carneiro, 2005). The epidermis cells, the keratinocytes, divide in the basal layer and differentiate throughout their migration to the surface. The epidermis is divided in 5 different layers (stratum basale, stratum spinosum, stratum granulosum, stratum lucidum and stratum corneum). The dermis is the feeder layer of the epidermis and provides most of the skin's mechanical resistance and elasticity. It is mainly composed of fibroblasts, epidermal appendages, blood vessels, nerves and nerve endings (Stevens and Lowe, 2005). Finally, the hypodermis is the deepest layer of the skin. It varies in size and content, but is usually composed of adipocytes which form the adipose tissue (Stevens and Lowe, 2005). Many severe skin diseases can be observed in human beings such as psoriasis.

1.2 Psoriasis

Epidemiology

Psoriasis is an ancient chronic skin disease (Nickoloff and Nestle, 2004). Uncommon under the age of 10 years, it appears between the ages of 15 and 30 years affecting men and women (Fitzpatrick and Wolff, 2008). Psoriasis is universal in occurrence, but its prevalence in different populations varies from 0.1% to 11.8% (Raychaudhuri and Farber, 2001). In fact, this pathology shows a significant geographical variability with the lowest incidence seen at the equator and increasing frequency towards the poles (Kormeili et al., 2004). Psoriasis affects about 25 million people in North America and Europe (Lowes et al., 2007).

Characteristics

Psoriasis is characterized by red and scaly plaques on the skin with a predilection for certain areas (elbows, knees and scalp) (Chapman et al., 1990; Lowes, et al., 2007). There are five clinical variants of psoriasis: guttate, erythrodermic, pustular, inverse and psoriasis vulgaris, the last of wich is the most common type seen in approximately 90% of patients (Fitzpatrick and Wolff, 2008). The severity can be divided into benign, moderate and severe psoriasis. Histological appearance of lesions shows elongation of the rete ridges, disappearance of the granular layer and persistence of the keratinocytes nuclei in the stratum corneum of the epidermis (Danilenko, 2008). In psoriasis, epidermal hyperproliferation, abnormal keratinocyte differentiation, angiogenesis with blood vessel dilatation and excess Th-1 and Th-17 inflammation can be observed (Azfar and Gelfand, 2008). However, although genetic, immunological and environmental factors seem implied, the exact cause is not yet known and even today, psoriasis is not well understood (Bowcock, 2005).

Treatments

A broad spectrum of anti-psoriatic treatments, both topical and systemic, is available for the management of psoriasis (Fitzpatrick and Wolff, 2008). However, it is often resistant to treatment or, else, frequently relapses upon cessation of medication after partial or acceptable clearance is obtained (Kormeili, et al., 2004). The severity of the disease usually determines the therapeutic approach. Among the treatments, there are topical, phototherapy, biologic and systemic treatments (Table 1). Approximately, 70 to 80% of all patients with psoriasis can be treated adequately with topical therapy (Schon and Boehncke, 2005). For others, phototherapy and systemic treatments are effective; however, the duration of a treatment is restricted because of the cumulative toxicity potential of an individual therapy (Kormeili, et al., 2004). For example, some treatments may increase the risk of cancer (phototherapy) while others can induce disorders in the liver (methotrexate) (Dubertret, 2004). Sometimes, treatment efficacy may diminish with time and it must be replaced by another therapy (Fitzpatrick and Wolff, 2008). At the present time, there is still no curative treatment for psoriasis.

Topical	**Phototherapy**	**Biologic**	**Systemic**
Corticosteroids	Narrowband UVB	Alefacept	Cyclosporine A
Vitamin D analogues	Broadband UVB	Efalizumab	Methotrexate
Tazarotene	Psoralen-UVA	Etanercept	Acitretin
Calcineurin inhibitors	Excimer laser	Infliximab	Fumaric acid esters
		Adalimumab	Sulfasalazine
			Mycophenolate mofetil
			6-Thioguanine
			Hydroxyurea

Table 1. Anti-psoriatic treatments

2. Tissue engineering

Although conventional approaches for organ replacement, such as transplantation, autografts and implantation of engineered prostheses, are extensively used, the process by which a patient can regenerate a lost organ is more attractive (Yannas, 2004). Recent biotechnological progress in the tissue engineering field allows us to conceive, develop and

produce biomaterials which can replace tissues or organs (Bernard et al., 2007). It has been demonstrated that tissue reconstruction can be applied to several different tissues such as skin, blood vessels, cartilage, bones and corneas (Arosarena, 2005). Tissue engineering can be used in experimental and clinical applications (Auger et al., 2004).

3. In vivo and in vitro models versus pharmaceutical researches

3.1 Development of drugs

The development of a new drug takes approximately 20 years. During this period of time, pharmaceutical industries spend millions of dollars on the research for new, more effective drugs. The cost of bringing new drugs to the market has recently increased and today, it costs approximately 1 billion US dollars to bring a new medicine to the market. A large amount of research is devoted every year to the discovery of new pharmacologically effective substances and many molecules reach the level of pre-clinical and clinical phase trials. However, attrition rates in clinical development are still very high and up to 90 % of new compounds fail in clinical phases I-III (Zollner et al., 2004). Late-stage clinical failure can be, to a great extent, attributed to a lack of clinical efficacy, indicating a strong need for highly predictive in vivo and in vitro models. Consequently, the pharmaceutical industry stays alert for the development of more relevant pathological in vivo and in vitro models to improve the success rate of new drugs (Zollner, et al., 2004). Highly predictive models can easily translate into significant savings of time and money for the pharmacological industry.

3.2 Experiments on psoriatic models

Some models have already been used to evaluate the effect of various molecules on psoriasis. For example, a team tested an antibody directed against interleukin 15 that was known to inhibit the production of T lymphocytes as well as the liberation of TNF-α in vitro (Krueger and Bowcock, 2005). Application of this antibody on severe combined immunodeficient mice (SCID) led to the disappearance of psoriatic characteristics. This suggested that the molecule could be targeted for future studies to develop a new anti-psoriatic treatment.

4. In vivo models

Animal models are very popular for the study of psoriasis. Many approaches are currently followed in order to obtain a representative animal model of the disease with all the characteristics of the human pathology. Many immunological and genetic models have been developed to date. However none of these models show all the characteristics of psoriasis. Researchers look for a perfect animal model which would have many genetic, histological and morphological similitudes with human beings and react to treatments in a similar way (Zollner, et al., 2004). Furthermore, the models must be easily reproducible, inexpensive and ethical.

4.1 Spontaneous mutations

Over the years, many mutations were described as being responsible for abnormal changes in the skin or hair of mice (Sundberg et al., 1990). Among these mutations, some were

studied for their psoriasis-like characteristics such as thickening of the skin and the formation of scales (Mizutani et al., 2003). However, the resulting mutants do not closely mimic the disease enough to be considered as good models of psoriasis. They must rather be used to compare local pathogenic events such hyperkeratosis, regulation of neutrophil infiltration and microabscess formation or dermal angiogenesis (Schon, 2008). Nearly a hundred mouse mutations that lead to psoriasiform phenotypes have been documented (Sundberg, et al., 1990).

Homozygous asebia ($Scd1^{ab}/Scd1^{ab}$)

The asebia mouse mutation was one of the first in vivo models used to study therapies directed at hyperkeratotic disorders (Schon, 2008). These homozygous asebia mutant mice are characterized by a hypoplasia of the sebaceous glands resulting from a defect in the stearoyl coenzyme A desaturase-1 (Scd1) gene (Zheng et al., 1999). This model exhibits moderate epidermal acanthosis, increased dermal vascularization, a dermal infiltrate composed of macrophages and mast cells, but neither T cells nor neutrophils (Schon, 2008). This lack of T cells and neutrophils do not mirror psoriatic lesions. Moreover, alterations of the cutaneous lipid metabolism seem different from psoriasis.

Flaky skin mice (Ttc^{fsn}/Ttc^{fsn})

The spontaneous chronic proliferative dermatitis mutation ($Sharpin^{cpdm}/Sharpin^{cpdm}$) (HogenEsch et al., 1993) and the flaky skin (Sundberg, et al., 1990) mice show a more interesting psoriatic phenotype than homozygous asebia mice. The flaky skin mice are probably the best spontaneous model of psoriasis described (Danilenko, 2008). Its spontaneous mutation induces proliferation and hyperkeratosis of stratified squamous epithelia including the nonglandular forestomach (Stratis et al., 2006). Previous studies have shown a positive Koebner reaction after tape-stripping, which resolves after 6 weeks of treatment with oral, but not topical, cyclosporine A, topical EGF, or UVB exposure (Sundberg et al., 1994). The flaky skin phenotype is very complex and comprises aspects not present in psoriasis. To verify if plaques had an inflammatory origin, the mice were treated with cyclosporine. The results showed that immunosuppressive treatment had no effect on the psoriatic lesions of those mice. This observation demonstrated that such models are not complete because they lack the immunological side of the pathology (Schon, 1999).

Spontaneous chronic proliferative dermatitis mutation

The spontaneous chronic proliferative dermatitis mutation shows various characteristics found in psoriasis such as hyperproliferative skin, infiltration of inflammatory cells in the skin and dilation of blood vessels in the dermis (Schon, 1999). However, as with the flaky skin mice, the value of the spontaneous chronic proliferative dermatitis mutation for psoriasis research is limited by the lack of a T cell based immunopathogenesis. Moreover, as immunosuppressive therapeutic regimens used to treat psoriasis fail to improve skin lesions with these mutations, it appears uncertain whether they can be used to test potential therapeutic compounds (Schon, 1999).

4.2 Genetically engineered models

Genetically engineered mice represent the largest category of psoriasis models. These include the transgenic and knockout models. In this section, some of these models will be discussed. The complete list of in vivo psoriatic skin models can be seen in table 2.

HLA-B27 rat

The human leukocyte antigen B27 (HLA-B27) transgenic rats are normal at birth but develop chronic inflammation of multiple organ systems as they age (Keith et al., 2005). In this model, the human HLA-B27 and β_2-microglobulin proteins are overexpressed and an epidermal acanthosis with epidermal infiltration of both CD4+ and CD8+ T cells, as well as immune-mediated arthritis and inflammatory bowel disease, which seem similar to the spondyloarthropathies in humans that have been associated with the HLA-B27 and β_2-microglobulin genes, such as acanthosis can be observed (Breban et al., 1996; Keith, et al., 2005; Taurog et al., 1993; Yanagisawa et al., 1995). The HLA-B27 transgenic rat model has been used for several years to evaluate the activity and mechanisms of action of anti-inflammatory molecules (Chadwick et al., 2005; Harnish et al., 2004; Peterson et al., 2002). Results show that broad-spectrum antibiotic therapy can produce significant remissions of inflammatory lesions, but relapse occurs when antibiotic therapy stops (Keith, et al., 2005). In this model, the occurrence of psoriatic skin lesions is less consistent than is the occurrence of the other immune-mediated disorders and there are no published reports of therapeutic efficacy testing for the psoriatic lesions (Danilenko, 2008; Taurog, et al., 1993; Yanagisawa, et al., 1995).

CD18 hypomorphic

The CD18 hypomorphic mice model targets leukocytes (Bullard et al., 1996). This model shows a decreased expression of the common β_2 chain of the leukointegrin adhesion molecule complex (Danilenko, 2008). Beta2 integrins are leukocyte adhesion molecules exclusively expressed on hematopoietic cells and are responsible for cell-cell contacts in a variety of inflammatory interactions (Kess et al., 2003). When the CD18 mutation was crossed onto the PL/J strain of mice, it developed a psoriasiform inflammatory skin condition with a predominantly lymphocyte infiltration (Bullard, et al., 1996). However, these mice exhibit nonpsoriasiform characteristics such as the absence of hyperproliferation markers.

K14/VEGF and Tie2

Mice overexpressing VEGF in epidermis via a keratin 14 promoter develop a phenotype very similar to psoriasis with an epidermal acanthosis, abnormal differentiation, inflammatory infiltrate and inflamed dermal blood vessels (Kunstfeld et al., 2004; Xia et al., 2003). Even if this model has many immunological, vascular and epidermal resemblances with psoriasis, the lesions appear to be vascular-based and there is the presence of a major dermal infiltration of mast cells (Danilenko, 2008). Similar elements were observed in the Tie2 transgenic mice. With the activation of the transgene, the mice develop erythema with silver-white scaling, acanthosis, elongation of the rete ridges, hyperkeratosis, parakeratosis, increase in blood capillaries, infiltration of inflammatory cells and neutrophilic microabscess (Gudjonsson et al., 2007; Voskas et al., 2005). This model also reacts to cyclosporine A when used as a psoriatic therapy.

K14/TGF-α, K5/TGF-β_1, K14/KGF and K14/IL-20

Many transgenic mice models were produced to target, via the keratin 5 or keratin 14 promoter, the expression of epithelial growth factors such as TGF-α (Vassar and Fuchs, 1991), TGF-β_1 (Li et al., 2004) and KGF (Guo et al., 1993) into the basal layer. In each model, psoriasiform phenotype can be observed such as acanthosis, but no cutaneous inflammation is displayed into any of them. In the K14/IL-20 model, the expression of IL-20 was targeted to the basal layer under the control of a keratin 14 promoter (Blumberg et al., 2001). In this

model, some psoriatic characteristics can be observed such as abnormal keratinocyte differentiation and an expression of the keratin 6, a hyperproliferation marker (Blumberg, et al., 2001). However, the lack of inflammatory components is a severe drawback of this model, as it is for K14/TGF-α, K5/TGF-β_1, K14/KGF models.

IKK2 and JunB/c-Jun

The immunological theory of psoriasis was challenged by more recent studies using animal models, including the IKK2 (Pasparakis et al., 2002) and JunB/c-Jun transgenic mice (Zenz et al., 2005). Results obtained with these two models have suggested revisiting the primary pathogenic role for epidermal keratinocytes. In the IKK2 knockout mice model, the deletion of the IKK2 catalytic subunit of the IκB kinase complex caused mice to develop a psoriasiform cutaneous inflammation (Pasparakis, et al., 2002). This model displays many features of psoriasis, including dependence on the dermal expression of TNF-α, acanthosis and abnormal differentiation. However, some characteristics of this model, such as T-cell-independent inflammation, keratinocyte apoptosis and early death are not found in psoriasis (Pasparakis, et al., 2002; Stratis, et al., 2006). In the JunB/c-Jun mice model, JunB and c-Jun are knocked out in the epidermis of postnatal mice with $Junb^{tm3Wag}$ or Jun^{tm4Wag}, or both (Zenz, et al., 2005). In this model, affected skin areas showed infiltration of neutrophils and lymphocytes with upregulation of several cytokines and chemokines typical of psoriasis. However, other factors such as INF-γ were only slightly upregulated while IL-12 or IL-18 were absent (Gudjonsson, et al., 2007). In this model, cutanous inflammation is not dependant on T cells nor is it independent of TNF signalling (Zenz, et al., 2005).

K5.Stat3C

The K5.Stat3C mice model is characterized by the activation of the signal transducer and activator of transcription 3 (Stat3) in basal keratinocytes under the control of the keratin 5 promoter (Sano et al., 2005). Stat3 plays an important role in various biological activities including cell proliferation, survival and migration (Hirano et al., 2000). These mice developed psoriatic-like skin lesions characterized by a keratinocyte hyperplasia, a loss of the granular layer and parakeratosis. The presence of many dilated blood vessels and a leukocytic infiltration of lymphocytes and neutrophils were observed (Sano, et al., 2005). To generate a psoriatic phenotype in transplanted SCID mice, the injection of activated lymphocytes and the Stat3 transgenic skin are necessary. These results allow to establish a link between keratinocytes and CD4+ T lymphocytes in psoriasis (Danilenko, 2008).

K14/IL-6 and K14/IL-1α

A human keratin 14 promoter was used to express IL-6 in the basal cells of epidermal mice (Turksen et al., 1992). IL-6 expression did not lead to enhanced epidermal proliferation, but it did result in a thicker stratum corneum with an otherwise seemingly normal differentiation program. However, IL-6 expression did not lead to leukocytic infiltration (Turksen, et al., 1992). In 1995, Groves et al., observed characteristics of psoriasis in a transgenic mouse model that expresses high levels of interleukin 1α in basal epidermis. This model displayed many characteristics of psoriasis. Uninvolved skin of these animals was characterized by hyperkeratosis and dermal mononuclear cell infiltrate of macrophage/monocyte lineage (Groves et al., 1995). Inflammatory lesions were marked by a mixed cellular infiltrate, acanthosis and parakeratosis in some cases. These results strongly indicate that IL-1 is a cytokine which plays an important role in psoriasis and that it is capable of inducing an inflammatory reaction (Groves, et al., 1995). Murine transgenic

models can provide representative models of the disease, but they can also target or confirm if a cytokine such as interleukin 1 or 6 has a role to play in psoriasis.

Chymotryptic enzyme

In 2002, Hansson et al., developed a transgenic mouse strain that overexpresses the chymotryptic enzyme, which is also overexpressed in the stratum corneum of psoriatic skin. This model allows to observe pathological characteristics of psoriasis such as an increase of epidermal thickness, hyperkeratosis, severe pruritus and an inflammation of the dermis (Hansson et al., 2002).

4.3 Xenotransplantation

Animal models based on transgenic technology have been used extensively to study the pathogenesis of various diseases, including psoriasis (Raychaudhuri et al., 2001). Xenotransplantation experiments were performed in which a skin biopsy from a patient or a skin equivalent produced in vitro was transplanted on mice from spontaneously mutated or genetically modified strains.

Athymic nude mouse

Athymic nude mouse have no thymus and therefore no T cells (Raychaudhuri, et al., 2001). This model has been used in laboratory to gain insights into the immune system and autoimmune diseases. The absence of a functional humoral immune system allows transplantation from another species without graft rejection. However, psoriatic skin transplanted on athymic mice develops certain histological changes that are not typical of psoriasis, such as the absence of parakeratosis and the presence of a granular layer (Raychaudhuri, et al., 2001). In past years, athymic nude mice were mainly used to verify if there was a difference between involved and uninvolved psoriatic skin (Fraki et al., 1983; Krueger et al., 1981). The results showed that involved psoriatic skin maintains its psoriasiform histology when transplanted onto nude athymic mice such as epidermal thickness and papillomatosis (Fraki, et al., 1983). However, not all the characteristics of the pathology were preserved. In fact, psoriatic epidermis did not contain polymorphonuclear leucocytes after grafting on athymic nude mice. In this study, uninvolved psoriatic epidermis from psoriatic patients seemed to be able to display markers of involved psoriatic epidermis independently from the psoriatic host. The authors suggested that the skin itself could be the primary cause of psoriasis. However, some years later, other results obtained in a new mouse model, the severe combined immunodeficient mice, suggested that psoriasis is a T-cell-mediated disease (Fraki, et al., 1983).

Severe combined immunodeficient mice (SCID)

The severe combined immunodeficient mouse model shows a lack of T and B cells, but it contains functional neutrophil and mature natural killer (NK) cells with normal cell activity (Gudjonsson, et al., 2007). This model has a mutation in the DNA-dependant protein kinase gene that is required for successful T-cell and B-cell development (Gudjonsson, et al., 2007). It is probably the most widely used relevant model for psoriasis, but the presence of NK which are involved in rejection of xenogeneic tissue is a severe inconvenience (Gourlay et al., 1998). In fact, single-cell suspensions are rapidly recognized and lysed by mice NK cells (Meyerrose et al., 2003). However, in SCID mice, grafts of solid tissues are well tolerated and psoriatic characteristics are maintained for several months in the transplantations involving psoriatic skin (Raychaudhuri, et al., 2001; Takizawa et al., 1995). Raychaudhuri et al., noticed that clinical, histological and immunological features of psoriasis could be maintained for

durations of 12-16 weeks, while Sugai et al. conserved the human psoriatic skin transplant for up to 22 weeks (Sugai et al., 1998). In this latter study, the psoriatic phenotype was well maintained but the histological and immunohistochemical characteristics gradually disappeared as lymphocytic infiltration of the psoriatic lesion declined. However, Ghilhar et al. showed that injection of T cells from psoriatic plaques in SCID mouse could maintain the pathological characteristics longer than in the absence of T cells (Gilhar et al., 1997). These results show that the presence of inflammatory cells is necessary to maintain the psoriatic phenotype in the SCID model and suggest a role of inflammatory cells in the appearance of psoriasis (Gilhar, et al., 1997).

Spontaneous AGR129 model

A new model, the AGR129 mice, shows a lack of T and B cells but, contrary to the severe combined immunodeficient mice, it has immature NK (Boyman et al., 2004). While the natural killer cells are recognized to have a role in transplant rejection (Gourlay, et al., 1998), the AGR129 model tolerates xenogenic grafts better than the SCID model. The AGR129 mice are deficient in type I(A) and type II(G) IFN receptors in addition to being RAG-2$^{-/-}$. Disruption of both IFN receptors has been previously shown to lead to decreased NK cytotoxic activity in vitro and in vivo (Lee et al., 2000). Such deficiencies imply that these mice possess immature NK cells which are much less cytotoxic than mature ones (Boyman, et al., 2004). Thus, transplant rejection is reduced in this type of mice. Boyman et al. demonstrated that human uninvolved psoriatic skin grafted onto AGR129 mice spontaneously developed psoriatic plaques without injection of activated immune cells or any other exogenous factor. In fact, skin grafts developed a psoriatic phenotype in 28 of 31 (90 %) grafted mice (Gudjonsson, et al., 2007). Histology of developed plaques was comparable to psoriatic lesion biopsies from the same patient. Boyman's team also noticed that when they injected an inhibitor of T cells (monoclonal anti-CD3), the psoriatic phenotype disappeared. The same phenomenon occurred when they injected an inhibitor of TNF-α. Furthermore, in this model, the normal control skin did not develop a psoriasis-like phenotype. These observations indicate that activation and proliferation of resident T cells are necessary and sufficient to drive psoriasis formation, underlining an essential role for immune cells residing within symptomless pre-psoriatic skin (Conrad and Nestle, 2006).

Model	Epidermal thickness	Abnormal differentiation	Increased vascularization	Epidermal T-cell infiltration	References
Spontaneous mutation					
Homozygous asebia	+	-	+	-	(Brown and Hardy, 1988; Brown and Hardy, 1989)
Flaky skin	+	+	+	-	(Sundberg, et al., 1994; Sundberg et al., 1997)
Chronic proliferative dermatitis	+	+	+	-	(HogenEsch, et al., 1993)
Genetically engineered models					

Targeting the immune system					
HLA-B27/β2 microglobulin rat	+	+	+	+	(Breban, et al., 1996; Keith, et al., 2005)
Hypomorphic CD18	+	+	+	+	(Bullard, et al., 1996; Kess, et al., 2003)
αE (CD103)	+	+	?	+	(Schon et al., 2000)
K14/p40	+	?	?	+	(Kopp et al., 2001)
Targeting vascular endothelium					
pTek-*tTA*/Tie2	+	+	+	+	(Voskas, et al., 2005)
K14/VEGF	+	+	+	+	(Xia, et al., 2003)
Targeting epidermal proteins					
K5/Stat3C	+	+	+	+	(Sano, et al., 2005)
IKK2	+	+	?	-	(Pasparakis, et al., 2002)
c-Jun/JunB	+	+	+	+	(Zenz, et al., 2005)
K14/KGF	+	+	+	-	(Guo, et al., 1993)
K14/TGF-α	+	+	?	Some animals	(Vassar and Fuchs, 1991)
K14/IL-20	+	+	-	-	(Blumberg, et al., 2001)
K14/amphiregulin	+	+	+	+	(Cook et al., 1997)
K14/IL-1α	+	+	-	?	(Groves, et al., 1995)
K14/IL-6	+	-	-	-	(Turksen, et al., 1992)
K10/BMP-6	+	+	+	+	(Blessing et al., 1996)
Involucrin/integrins	+	+	+	+	(Carroll et al., 1995)
Involucrin/MEK1	+	+	?	+	(Hobbs et al., 2004)
Involucrin/amphiregulin	+	+	+	+	(Cook et al., 2004)
Involucrin/IFN-γ	+	+	+	-	(Carroll et al., 1997)
Chymotryptic enzyme	+	+	?	+	(Hansson, et al., 2002)
Xenotransplantation					
Athymic nude mouse	+	+	?	-	(Fraki, et al., 1983; Krueger, et al., 1981)
SCID	+	+	+	+	(Boehncke et al., 1994; Gilhar, et al., 1997; Nickoloff et al., 1995; Raychaudhuri, et al., 2001; Sugai, et al., 1998; Takizawa, et al., 1995)
AGR129	+	+	+	+	(Boyman, et al., 2004)

Table 2. In vivo models of psoriasis

5. In vitro Models

Contrary to in vivo models, in vitro models are generally characterized by a lack of inflammatory cells. Since psoriasis has been described to be an autoimmune disease (Bowcock, 2005; Krueger and Bowcock, 2005; Lowes, et al., 2007; Schon and Boehncke, 2005), the pertinence of these models has been discussed. It is important to note that (1) inflammatory cells can be included in most of the in vitro models, (2) these models allow to dissect step by step the mechanisms of psoriasis by isolating or combining the cell types and (3) recent studies using animal models, including the IKK2 (Pasparakis, et al., 2002) and JunB/c-Jun transgenic mice (Zenz, et al., 2005) are challenging the immunological theory of psoriasis.

5.1 Monolayer

Monolayer models allow, from a small biopsy of pathological skin, the generation of a large number of cells sufficient for multiple experiments. In monolayer models, only one cell type is considered at a time. Thus, either keratinocytes or fibroblasts will be used to test different conditions or observe various characteristics of the disease, such as cell proliferation or differentiation. These models allow the isolation of a normal or pathological cell type to better understand its specific role. However, they preclude the study of interactions among many cellular types (e.g. interactions between the dermis and the epidermis).

Despite the absence of interaction between the different cell types, monolayer models have helped in the discovery of several interesting facts about psoriasis and a better understanding of the disease. For example, monolayer cell cultures have helped to realize that TGF-α regulates VEGF expression in psoriasis through an autocrine mechanism, leading to vascular hyperpermeability and angiogenesis (Detmar et al., 1994). In other experiments, van Ruissen et al. found that psoriatic keratinocytes display a lower number of cells in S-phase and a shorter duration of G1 compared to normal keratinocytes (van Ruissen et al., 1996). Monolayer cultures are widely used and have led to many critical observations (Table 3).

5.2 De-epidermized dermis

Organ culture on de-epidermized dermis

Mils et al. developed a reconstructed epidermal model with a de-epidermized dermis. A psoriatic or normal biopsy was placed dermal side down on the epidermal surface of non viable de-epidermized dermis, thus in contact with the remnant basement membrane component (Mils et al., 1994). The dead de-epidermized dermis was maintained at the air-liquid interface on a metallic support. In approximately 15 days, the epidermal layer grew out from the punch biopsy to cover the entire de-epidermized dermis. In this model, the psoriatic substitutes did not differ significantly from normal substitutes. The only observed difference was in LH8 labelling between normal and psoriatic substitutes (Mils, et al., 1994). No distinguishing histological or biochemical criteria could be established between normal and psoriatic equivalents.

Keratinocytes on de-epidermized dermis

Another reconstructed epidermal model was developed with normal adult human keratinocytes seeded on de-epidermized dermis (Tjabringa et al., 2008). This model allowed controlled induction of psoriasis-associated features and gene expression by the addition of

relevant pro-inflammatory cytokines (TNF-α, IL-1α, IL-6 and IL-22) and primary keratinocytes obtained from donors without history of psoriasis. To produce this model, a hollow metal ring was placed on de-epidermized dermis and keratinocytes were seeded within the ring (Tjabringa, et al., 2008). Results showed that after the addition of a pro-inflammatory cytokine mixture, the expression of psoriasis-associated proteins hBD-2 and SKALP/elafin for the pro-inflammatory cytokines IL-8 and of TNF-α were increased in the skin equivalent, as well as keratinocyte hyperproliferation cells. Tjabringa et al. also showed that the addition of all-trans retinoic acid inhibits the expression of psoriasis-associated proteins hBD-2 and SKALP/elafin in cytokine-stimulated skin equivalents and reduces expression of the normal differentiation marker: keratin 10, as such as acanthosis can be observed in psoriatic skin in vivo (Tjabringa, et al., 2008).

5.3 Collagen gels

Organ culture

To observe cell proliferation, some studies were done by making a small full-thickness punch biopsy into a dermal equivalent, which itself originated from the contraction of a collagen gel by dermal fibroblasts (Saiag et al., 1985). The total surface area covered by the keratinocytes was used to calculate the cell proliferation percentage. Higher keratinocyte proliferation values were obtained in the presence of psoriatic fibroblasts (Saiag, et al., 1985). Furthermore, this model led to the conclusion that normal fibroblasts are unable to suppress the hyperproliferative growth of psoriatic keratinocytes and that hyperproliferation of normal epidermis can be induced both by uninvolved and involved psoriatic fibroblasts (Saiag, et al., 1985).

Models using many cellular types

Other teams developed skin equivalents composed of two or more cell types to better understand cell interactions such as those between keratinocytes and fibroblasts. In general, these models imply the isolation of cells from biopsies of normal or affected persons. Fibroblasts are extracted from the dermis, expanded and embedded in a collagen gel. Keratinocytes are extracted from the epidermis, expanded and plated on top of a collagen gel containing fibroblasts.

Konstantinova et al. have presented a psoriatic collagen gel model which showed a psoriasiform phenotype. In fact, in this model, the psoriatic skin equivalent showed a thicker epidermis and a loss of filaggrin (Konstantinova et al., 1996). These models enabled to examine the effects of normal and psoriatic (involved and uninvolved) fibroblasts on epidermal differentiation and cytokine expression. This model led to a number of interesting conclusions, such as the confirmation that involved and uninvolved fibroblasts induce higher amounts of IL-8 than normal fibroblasts (Konstantinova, et al., 1996). This model allowed the observation of interactions between fibroblasts and keratinocytes, but contained exogenous material. As previously described, the collagen gel can be very useful for rapid production of skin substitutes (Bell et al., 1981a; Bell et al., 1981b; Bell et al., 1979) but, the presence of an exogenous scaffold can be disadvantageous for mechanical studies of the extracellular matrix and a severe surface reduction of dermal substitutes can be observed (Auger et al., 1998; Germain and Auger, 1995). Contraction can be prevented using anchorage methods in vitro (Eckes et al., 1995; Germain and Auger, 1995; Grinnell and Lamke, 1984; Parenteau et al., 1991; Xu et al., 1996). However, these anchoraged models are often fragile and difficult to handle.

Other studies have used similar in vitro models. In 2004, Barker et al. developed and characterized a new psoriatic skin model in vitro using collagen gels. In this model, psoriatic skin substitutes maintained many characteristics of psoriasis such as hyperproliferation, overexpression of chemokine receptor CXCR2 and pro-inflammatory genes (TNF-α, INF-γ and IL-8) and also increased levels of pro-inflammatory cytokines IL-6 and IL-8 (Barker et al., 2004). The substitutes derived from uninvolved psoriatic skin showed the same gene expression profile as those derived from involved skin substitutes with an increased proliferation rate when compared to normal substitutes. This model suggests that psoriatic individuals possess an inherent predisposition to develop the disease phenotype even in the absence of T cells (Barker, et al., 2004). As with the model proposed by Konstantinova et al., this model contains exogenous material.

Models	Epidermal thickness	Abnormal differentiation	Increased vascularization	Epidermal T-cell infiltration	References
Monolayer					
IL-15	?	?	?	?	(Krueger and Bowcock, 2005)
TGF-α regulates VEGF	?	?	?	?	(Detmar, et al., 1994)
S-phase	?	?	?	?	(van Ruissen, et al., 1996)
De-epidermized dermis					
Organ culture	-	-	?	-	(Mils, et al., 1994)
Keratinocytes	+	+	?	-	(Tjabringa, et al., 2008)
Collagen gel					
Organ culture	?	+	?	?	(Saiag, et al., 1985)
Skin substitutes	+	+	?	-	(Barker, et al., 2004; Konstantinova, et al., 1996)
Self-assembly					
Skin substitutes	+	+	-	-	(Bernard, et al., 2007; Jean et al., 2009)

Table 3. In vitro models of psoriasis

6. A new in vitro psoriatic skin model

In pharmaceutical sciences, pathological skin substitutes can be very useful for toxicity or for cutaneous cellular and molecular biology studies. To be effective, a pathological substitute must mimic as closely as possible, morphological and ultrastructural characteristics of the pathology. At the present time, although some in vitro and in vivo models of psoriasis have been reported to replicate some aspects of the disease, research into

psoriasis and the subsequent development of therapeutic strategies have been hindered by the absence of more relevant models (Jean, et al., 2009).
As previously shown, a number of teams have carried out in vitro monolayer and stratified keratinocyte culture studies to better understand the behaviour of cell types both in an individual way, but also to study the interactions between cells with co-culture and conditioned media techniques (Mils, et al., 1994; Saiag, et al., 1985; van Ruissen, et al., 1996). Some of these studies have shown the importance of the interaction between fibroblasts and keratinocytes in psoriatic models. Amongst in vivo models (Gudjonsson et al., 2004), there are animal models primarily consisting of grafting a psoriatic skin athymic (Fraki, et al., 1983) or on severe combined immunodeficient mice (Raychaudhuri, et al., 2001). While the clinical and histological characteristics of psoriasis can be maintained for a sufficient period of time to test pharmacological drugs, mouse skin is not like human skin. The graft of human psoriatic plaques on mice might cause in those animal models an immune response that differs from that in humans. Mice used for xenografts are immunocompromised to prevent rejection or graft shrinkage; there is no organized lymphatic system to drain the grafted skin and a lack of lymphocyte recirculation.

7. Self-assembly method

7.1 Introduction

Our team has developed a new psoriatic skin model produced by the self-assembly method. This tissue engineered approach is based on the capacity of fibroblasts to create their own extracellular matrix in vitro, which makes it possible to obtain cell sheets which are easy to handle. A cohesive dermal tissue is obtained by stacking two of these sheets together upon which keratinocytes are seeded. This leads to a complete bilayered skin substitute devoid of exogenous extracellular matrix proteins and synthetic material. This substitute has many histological characteristics close to those of normal human skin (Michel et al., 1999; Pouliot et al., 2002). While previous studies using the self-assembly model only used healthy cells, the present study creates pathological substitutes with cells isolated from psoriatic biopsies. This work strives to develop and characterize a novel in vitro psoriatic skin model produced by tissue engineering, which could be used to investigate the mechanisms of abnormal keratinocyted growth and to study cell-cell interactions. In this section, previously published results will be discussed (Jean, et al., 2009).

7.2 Methods

The psoriatic substitutes were produced using our modified version of the self-assembly method (Fig. 1). The method is, briefly, as follows: human fibroblasts were cultured in the presence of ascorbic acid, thus forming manipulatable sheets, which were superimposed and incubated for 7 days to form the dermal component. After 7 days of culture, keratinocytes were seeded upon this tissue to form the epidermal layer. After another 7 days of culture, the substitutes were raised to the air–liquid interface (Michel, et al., 1999; Pouliot, et al., 2002). Biopsies were taken after 7, 14 and 21 days of culture at the air–liquid interface and analyzed using histological and immunohistochemical techniques. Four different combinations of healthy and/or psoriatic cells were used to produce skin substitutes:
A. Healthy fibroblast/healthy keratinocyte (controls)

B. Psoriatic fibroblast/psoriatic keratinocyte
C. Psoriatic fibroblast/healthy keratinocyte
D. Healthy fibroblast/psoriatic keratinocyte

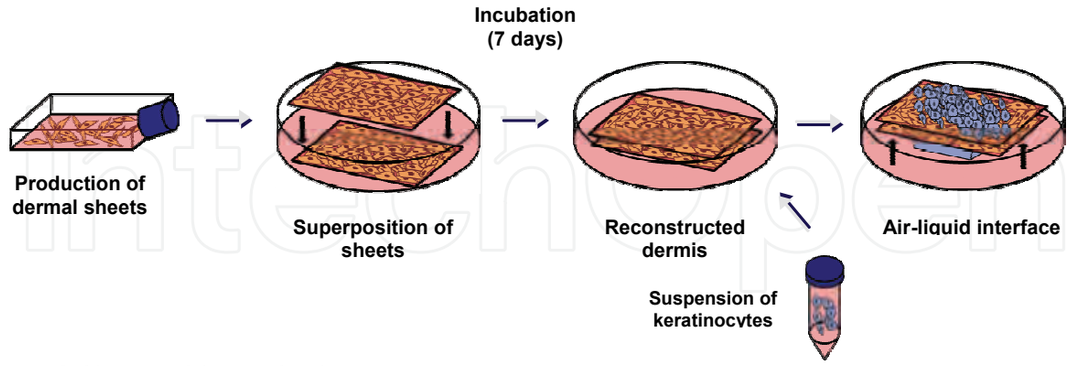

Fig. 1. Self-assembly method

7.3 Results

In the presence of healthy fibroblasts and healthy keratinocytes (controls), the substitutes showed a uniform, smooth and white surface (Fig. 2A). When psoriatic fibroblasts and keratinocytes were used to produce the substitutes, the aspect of the substitutes was less uniform showing a surface that was thick and whitish in some regions and thinner in others (Fig. 2B). The same characteristics were observed with a combination of healthy fibroblasts and psoriatic keratinocytes (Fig. 2D). Skin substitutes produced with psoriatic fibroblasts and healthy keratinocytes showed the presence of some protuberances (Fig. 2C).

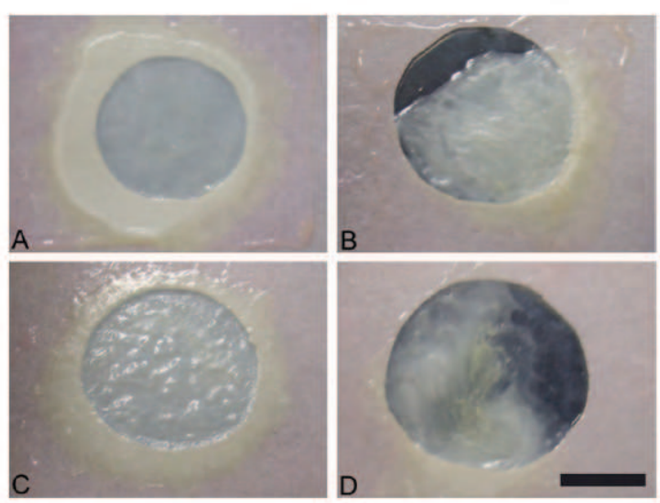

Fig. 2. Macroscopic analysis of skin substitutes produced with healthy fibroblasts and healthy keratinocytes (A), psoriatic fibroblasts and psoriatic keratinocytes (B), psoriatic fibroblasts and healthy keratinocytes (C), and healthy fibroblasts and psoriatic keratinocytes (D). Pictures were taken after 21 days of culture at the air–liquid interface (scale bar = 2.2 cm). Reproduced from Jean et al., 2009 © Journal of Dermatological Science.

Masson's trichrome staining of 5-µm thick biopsies from skin substitutes showed that those produced with psoriatic keratinocytes (Fig. 3B and D) had a significantly thicker epidermis than the controls (Fig. 3A). The basal layer of the epidermis was less organized in psoriatic substitutes (Fig. 3B–D). A compact cornified layer, partly removed during the sectioning process of some constructs (ex; Fig. 3D), was observed in combinations containing psoriatic keratinocytes. No significant histological difference was noticed between the control and the psoriatic fibroblast/healthy keratinocyte combination (Fig. 3A and C), even if the macroscopic appearance of this combination showed some protuberances (Fig. 2C), which could suggest differences in the thickness of the epidermis.

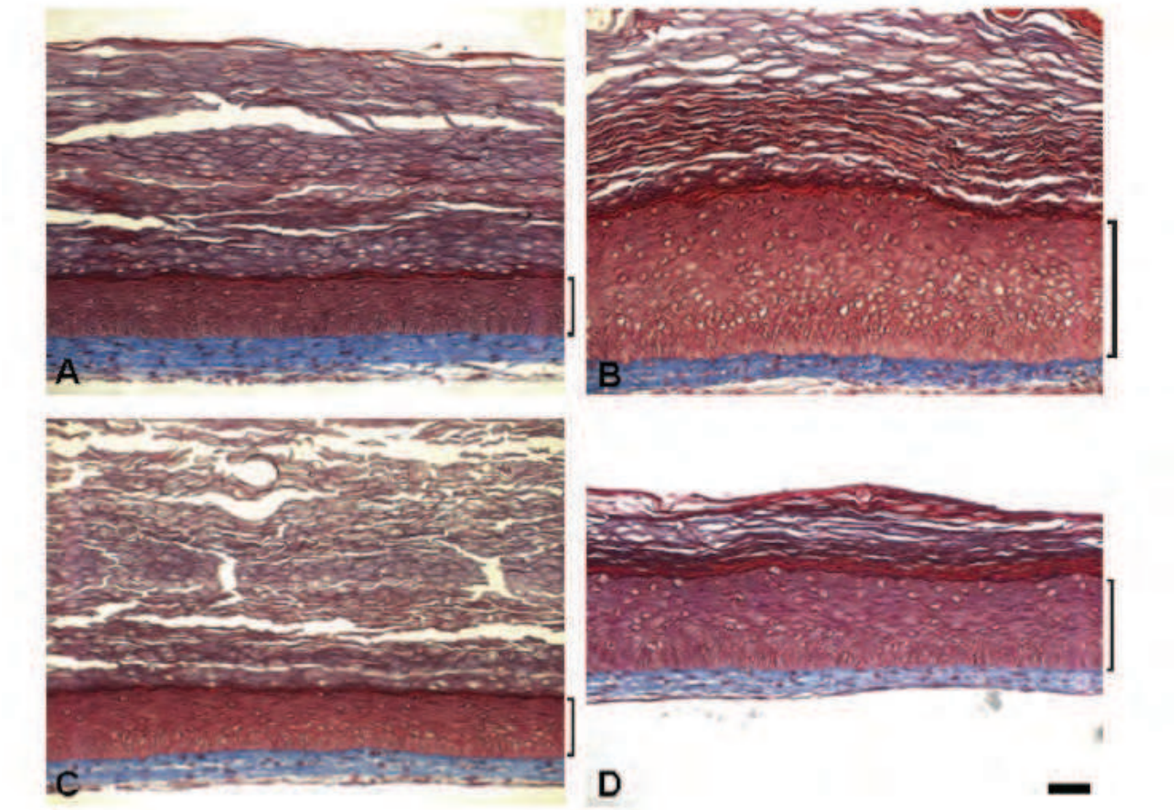

Fig. 3. Histological analysis of skin substitutes produced with healthy fibroblasts and healthy keratinocytes (A), psoriatic fibroblasts and psoriatic keratinocytes (B), psoriatic fibroblasts and healthy keratinocytes (C), and healthy fibroblasts and psoriatic keratinocytes (D) (scale bar = 5 µm). Note: the brackets indicate the measured epidermis. Reproduced from Jean et al., 2009 © Journal of Dermatological Science.

Epidermal differentiation markers, such as involucrin, appeared in deeper epidermal layers of substitutes produced with psoriatic fibroblasts and psoriatic keratinocytes, compared to those produced with healthy fibroblasts and healthy keratinocytes (controls) (Fig. 4). An overexpression of involucrin, relative to the controls was observed in substitutes produced with psoriatic keratinocytes (both combinations). Filaggrin staining showed a diminution or

absence of filaggrin expression in substitutes with psoriatic cells compared to those produced with healthy fibroblasts and healthy keratinocytes (controls), in which filaggrin expression was present from the granular layer (Fig. 4). In the combination of psoriatic fibroblasts and healthy keratinocytes, the expression of loricrin was similar to levels seen in controls but in the presence of psoriatic keratinocytes (both combinations) its expression was partially or completely absent (Fig. 4). In substitutes produced with psoriatic keratinocytes, keratin 10 expression was less intense and appeared in the upper layers of the epidermis compared to those produced with healthy keratinocytes (both combinations) (Fig. 4). Some of our immunohistological results, such as loricrin and filaggrin stainings, showed the presence of blue nuclei stained with Hoechst in the upper layers of the stratum corneum, which is characteristic of parakeratosis.

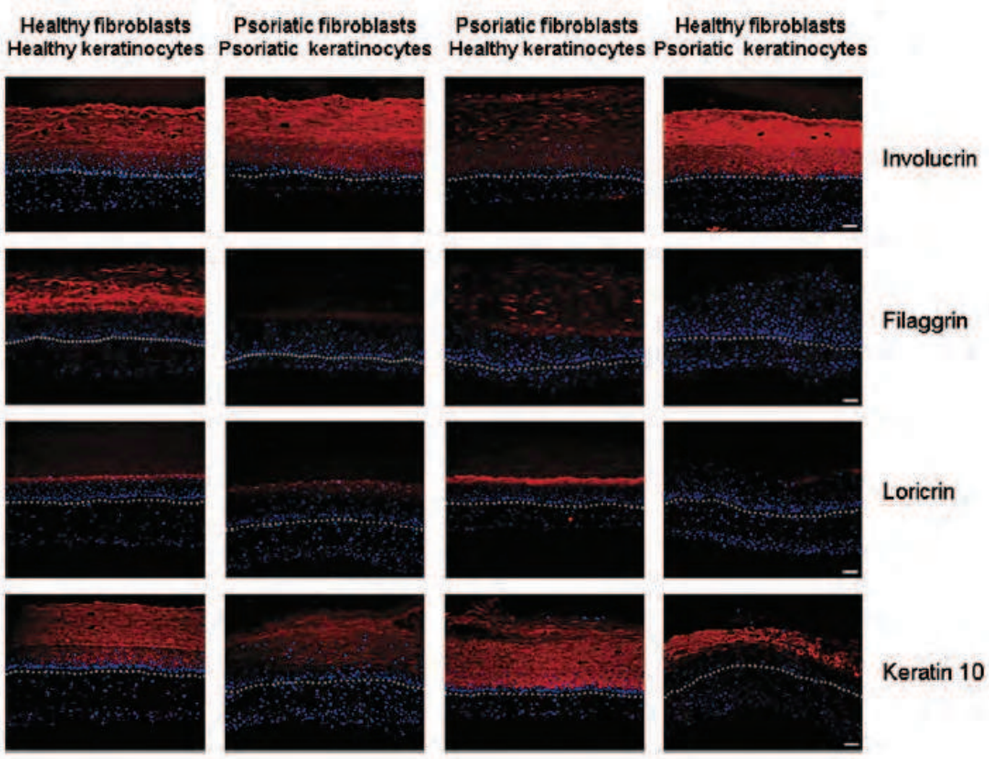

Fig. 4. Markers of keratinocyte differentiation in skin substitutes. Samples were prepared after 21 days of culture at the air–liquid interface (scale bar = 5 μm). The dotted line indicates the dermo-epidermal junction. Reproduced from Jean et al., 2009 © Journal of Dermatological Science.

In previous studies, the organization of the stratum corneum lipids was analyzed by attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FITR) (Bernard, et al., 2007). Results suggested that the stratum corneum of involved psoriatic skin substitutes is less organized than that of normal skin substitutes. Bernard et al., also showed that the properties of uninvolved psoriatic skin may vary with the severity of the disease. In fact, in substitutes made with cells from a patient with 20% of affected body area, the ATR-FITR

results are similar to controls and uninvolved psoriatic substitutes. However, in substitutes made with cells from a patient with an affected body area 40%, the ATR-FITR results of uninvolved psoriatic substitutes are different from those of the control (Bernard, et al., 2007). To summarize, this study showed that psoriatic skin substitutes produced by the self-assembly method have a higher level of lipid disorder and a modification of protein conformation in involved psoriatic stratum corneum layer compared to the stratum corneum of healthy substitutes (Bernard, et al., 2007).

7.4 Discussion

The psoriatic substitutes produced by the self-assembly method maintained many psoriasis-like characteristics such as thicker epidermis, abnormal differentiation, increased proliferation and higher levels of lipid disorganization of the stratum corneum. The four different keratinocyte/fibroblast combinations show different intensities in the expression of the psoriatic phenotype. These combinations allow the observation of interactions between healthy/psoriatic cells and fibroblast/keratinocyte cells. This model could become the basis of a robust technique to better understand the mechanisms involved in psoriasis and an excellent tool for the study of accelerated cellular differentiation of psoriatic keratinocytes. In an effort to resolve this complex skin disease, our research first endeavoured to develop a psoriatic model devoid of complicating elements such as immunocytes, in order to dissect step by step the mechanisms of this pathology. However, this model will be further refined to include elements of the immune system which may help establish the roles of different T cell subsets and cytokines in psoriasis.

8. Future research

A large number of psoriatic models have been developed. However, although many characteristics of the disease are preserved, no model shows all of them. Experts agreed that there was no available model that served all their needs (Zollner, et al., 2004). The choice of the most suitable model must always depend on the particular scientific question. The ultimate purpose of future research is to find the exact causes of psoriasis in order to find specific and effective treatments that will provide a definitive cure for psoriasis with a minimum of side effects. In vitro or in vivo pathological models that faithfully mimic this disease would be of significant help in the research and development of new treatments. For that reason, the development of a more relevant model of psoriasis is a priority for the various research efforts that are targeting this disease and would be an important step towards its cure.

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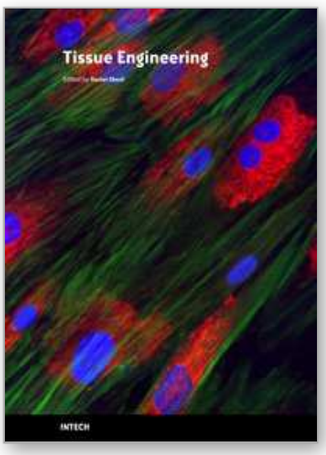

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The Tissue Engineering approach has major advantages over traditional organ transplantation and circumvents the problem of organ shortage. Tissues that closely match the patient's needs can be reconstructed from readily available biopsies and subsequently be implanted with minimal or no immunogenicity. This eventually conquers several limitations encountered in tissue transplantation approaches. This book serves as a good starting point for anyone interested in the application of Tissue Engineering. It offers a colorful mix of topics, which explain the obstacles and possible solutions for TE applications.

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