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Wound Repair Studies Reveal New Insights to Psoriasis

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1. Introduction

Psoriasis, a chronic relapsing inflammatory skin disease with a disturbing global incidence of approximately 2%, is an afflicting and disfiguring skin disease with high morbidity (Lomholt, 1964). The disease is characterized by the well-demarcated erythematous plaques with silvery white scales and a predilection for body areas such as the elbows, knees, umbilicus and lumbar area (Schön & Boehncke, 2005). In contrast to normal skin, the dermal vasculature in psoriasis dermis is dramatically increased with large, tortuous blood vessels, accounting for the erythematous appearance or redness of the affected skin regions/psoriatic plaques (Nestle et al, 2009). In addition, the psoriatic epidermis is significantly thickened and acanthotic, due to hyperproliferative keratinocytes with an approximate seven-fold increase in the number of dividing cells in the basal and suprabasal epidermal layers (Castelijns et al, 2000). Keratinocytes of the psoriatic skin are prematurely differentiated, as evident in the incomplete cornification of the stratum corneum, characterized by the retention of nuclei (i.e., parakeratosis) and the loss of the granular layer. The stratum corneum of psoriasiform skin is also thickened (i.e., hyperkeratosis). This heavy disruption of epidermal differentiation and skin barrier homeostasis coupled with altered levels of intercellular adhesion molecules result in the widespread scaling of psoriatic lesions (Christensen et al, 2006). While psoriasis primarily affects the epidermis, the disease has a strong immunopathological basis, with the psoriatic skin being significantly infiltrated with immune cells. Notably, this immune infiltrate has a characteristic distribution and is composed mainly of dendritic cells and macrophages in the dermis, neutrophils in the epidermis and T cells in both layers. Another immunologic feature of the disease is its extracutaneous manifestation of an arthritic condition, which affects approximately 5% of the population and approximately 20% of psoriasis patients (Zachariae et al, 2002; Hueber & McInnes, 2007). However, the direct involvement of the skin and immune system in psoriasiform features complicates and confounds studies of psoriasis. Therefore, despite the detailed documented pathological observations of psoriasis and the vast research efforts aimed at understanding the disease, a key question remains unanswered: is psoriasis provoked by an epidermal or an immunological trigger?

2. Background

It is well accepted that the pathology of psoriasis involves the participation of both the immune system and skin tissue; therefore a rational research approach would include studying the disease from an *in vivo* rather than an *in vitro* perspective. Hence, most psoriasis studies have been in the context of animal models which continue to serve as an invaluable platform for drug testing and development. While there is an absolute need for an *in vivo* platform, an ideal animal model is still lacking as no naturally and frequently occurring animal disease is known to exhibit every complex disease feature of psoriasis (Schön, 1999). Hence the study of psoriasis is narrowly limited to the artificial induction of the disease in laboratory animals. Nevertheless, several animal models have been developed in recent decades to meet the demands of psoriasis research. Study approaches include spontaneous mutants, T cell transfer models and xenografts.

2.1 Spontaneous mutants

The earliest psoriasis models were laboratory-bred mutant mice that were found to manifest skin lesions resembling psoriasis. These animals were spontaneous mutants of known allelic mutations. One such mutant strain was mice carrying the homozygous asebia mutation ($Scd1^{ab}$/ $Scd1^{ab}$). The skin of the asebia mouse is typified by hair loss (i.e., alopecia) and the complete absence of sebaceous glands. Like psoriatic human skin, asebia mouse skin displayed hyperkeratosis, epidermal acanthosis, increased dermal vascularity and an immune cell infiltrate (Gates & Karasek, 1965). However, unlike human psoriatic skin, the leukocytic infiltrate of asebia mouse skin was devoid of neutrophils and T cells. Because the immune system is strongly believed to account for a substantial portion of the pathogenesis of psoriasis, this difference in the inflammatory response in asebia mouse skin reduces the reliability of this disease model. Moreover, lipid metabolism in asebia mouse skin was significantly altered, implying a distinctly different disease mechanism from psoriasis, which further undermined its value as a psoriasis model (Wilkinson & Karasek, 1966). Two other homozygous mouse mutants, chronic proliferative dermatitis (*cpd*) and the flaky skin (*fsn*), also display a hyperproliferative epidermis, increased dermal vascularity and a mixed immune cell infiltrate including neutrophils in micro-abscesses of lesions. These similarities with human psoriatic skin make these animal models slightly superior to the asebia mouse model as disease models for psoriasis (Morita et al, 1995). However, the psoriasiform-like phenotype of both *fsn* and *cpd* critically lack a T cell-based immunopathogenesis. This was demonstrated by the ability of glucocorticosteroid treatment to improve the *fsn* lesions, which targets the innate immune response, but not with cyclosporine A, a licensed psoriasis drug which inhibits T cell-mediated immune responses (Sundberg et al, 1994). Cyclosporin A treatment also did not improve *cpd* skin lesions (HogenEsch et al, 1994). *Fsn* mice that were double homozygous for the severe combined immunodeficiency mutation (*scid/scid*) and lacked mature T and B lymphocytes also developed skin lesions nonetheless (Sundberg et al, 1994). Furthermore, the transfer of hemopoietic T cell precursors from *cpd* to syngeneic recipients did not pass on the psoriasiform condition (HogenEsch et al, 1994). *Cpd* and *fsn* are also far more complex than psoriasis; both involve pathologies that extend to other organ systems. This complexity confounds the study of psoriasis when these models are used. Critically, the psoriasiform-like phenotype of *cpd* and *fsn* could both develop without the participation of T cells, which are known key effectors in psoriasis (HogenEsch et al,

1994; Sundberg et al, 1994). Given these limitations, spontaneous mutants still fall short of being an ideal psoriasis model. The greatest concern about using this type of animal model for psoriasis research is that researchers are essentially deriving conclusions about the causes of psoriasis from diseases with another unknown basis.

2.2 T cell transfer models

The disqualification of the early animal models (i.e., *fsn* and *cpd*) as psoriatic models highlights the strong growing recognition of psoriasis as a T cell-mediated disease. Several clinical observations support this theory, including how psoriasis can be significantly improved with drugs targeting T cell-mediated immunity (Weinshenker et al, 1989). Streptococcal infection of the upper respiratory tract, which is remote from the skin, is known to trigger psoriasis via T cell-mediated responses to bacterial superantigens that mimic keratins. This process initiates a pseudo-autoimmune reaction responsible for the psoriasiform outcome (Prinz et al, 1991; Leung et al, 1995; Valdimarsson et al, 2009). Interestingly, psoriasis was shown to be transferrable when the bone marrow of an affected individual was transplanted into a previously unaffected recipient (Snowden & Heaton, 1997). Conversely, psoriasis in a previously affected individual was completely cured after bone marrow ablation prior to transplant (Eedy et al, 1990). While phagocytic immune cells (i.e., neutrophils, macrophage and dendritic cells) are responsible for indiscriminate immune functions such as the engulfment of pathogens or cellular debris and antigen presentation (Delves & Roitt, 2000), T cells have a more specific molecular recognition role in the immune system. In summary, every cytotoxic CD8 T cell clone possesses antigen specificity, allowing it to recognize a unique antigen presented on the major histocompatibility complex (MHC) of non-immune cells. For example, this antigen could be a viral peptide in the context of an infected cell, a foreign peptide in the context of an allograft, or a self peptide in the event of an autoimmune response. In any of these cases, CD8 T cells would mount a cytotoxic response against the target cell. The CD8 T cells can mediate a necrotic cell killing through the targeted secretion of lytic proteins, perforin and granzyme, onto the target cells. These proteins drastically destabilize the target cell membrane, eventually leading to osmotic stress and colloid osmotic lysis (Delves & Roitt, 2000).

The classic study of tissue graft rejection showed that the adoptive transfer of normal T cells into nude mice *scid* would lead to an immune rejection of the host animal's skin (Roopenian & Anderson, 1988). An experimental proof of T cell pathogenesis for psoriasis would require a T cell-mediated response directed against skin cells. Using principles of tissue graft rejection, MHC compatible naïve CD4+/CD45RB^{Hi} T lymphocytes that were minor histocompatibility complex mismatched were transplanted into *scid/scid* mice. The minor histocompatibility mismatch was aimed at minimizing the severity of the immune response and hence prolonging the rejection process. Without fail, this procedure led to the development of clinically consistent psoriasiform skin within 4-8 weeks. The resulting mouse skin lesions were markedly similar to those of human psoriatic skin; they shared the key histopathological features of acanthosis, parakeratosis, leukocytic infiltrate and dermal angiogenesis. Remarkably, pro-inflammatory cytokine expression in the lesional skin was also similar to that of human psoriatic skin, with elevated expressions of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interferon-γ and granulocyte macrophage colony stimulating factor (GM-CSF). These lesions also responded well to immunosuppressive

treatments such as cyclosporine A and ultraviolet B (310 nm) phototherapy (Schön et al, 1997). Taken together, these features suggest that an epidermal abnormality is unnecessary for the formation of psoriatic lesions and that a T cell-invoked immune response results in psoriasiform skin. However, this model cannot rule out the involvement of an epidermal trigger, as T cells were deliberately mismatched to the host skin cells. Hence, this T cell transfer model can only be used to study cutaneous psoriatic events post-T cell activation and not those processes preceding T cell activation.

2.3 Xenografts

Although animal and T cell transfer models offer a convenient bench approach to studying psoriasis, they still do not reflect the genuine pathogenesis of the disease. Animal models may have typical psoriasiform-like skin lesions but closer analysis has revealed critical cellular differences from the human disease. In addition, T cell transfer models exhibit only the immune aspects of psoriasis after T cell activation, and they lack all aspects of the preliminary events leading to T cell activation. Furthermore, the vast differences between mouse and human skin further complicate the ability to extrapolate animal models to the actual human disease (Gudjonsson et al, 2007). Hence, another approach is to study every *in situ* event of human psoriatic skin *in vivo*. This has been made possible by xenotransplantation, whereby human diseased skin is grafted across species to an immunocompromised murine host. With xenotransplantation, psoriatic features of diseased human skin can be maintained for more than 2 months, providing sufficient study time (Krueger et al, 1975). Apart from T cells originating in the systemic circulation, resident T cells and other immune cells in psoriatic skin may also contribute to pathogenesis, which is not possible using T cell models. Xenotransplantation models circumvent this shortcoming, as all forms of resident immune cells in the transplanted diseased skin may be continually studied post-transplantation (Boehncke & Schön, 2007). Altogether, xenotransplantation models allow the study of *in situ* events in the context of actual human psoriatic skin. This approach has helped elucidate the role of resident T cells in disease pathogenesis and helped identify the molecules involved in the epidermal recruitment of T cells, such as integrin $\alpha_1\beta_1$ (Conrad et al, 2007). Importantly, the xenotransplantation method allows for comparisons between involved and uninvolved skin (Boehncke et al, 1994; Nickoloff et al, 1995). Xenotransplantation models may also be used to study other components of the immune system, such as the role of natural killer cells in psoriasis. The immune background of the host could be modified by cross-breeding mouse strains that carry mutations to different immunity-related genes. For example, non-obese diabetic (NOD) mice with impaired natural killer and antigen presenting cells could be combined with *scid* through cross-breeding to generate a host animal with a modified immune background to enhance the study of natural killer cells in psoriasis (Roder & Duwe, 1979; Shultz et al, 1995). With this concept, many other combinations of immune backgrounds have since been innovated to support novel studies. Regarding drug discovery studies, xenotransplantation models facilitate the testing of human directed antibodies or biologics because of the limited cross-species reactivity (Boehncke, 2005). However, xenotransplantation models do have their own shortcomings and limitations, including the challenge of assessing T cell homing processes since human T cells in the transplanted xenograft may not transit normally to mouse lymph nodes in the hybrid natured "two-species-systems" (Garcia et al, 1997). Also, xenotransplantation is limited by a lack of diseased skin donors. In response to this issue, a

bioengineered skin-humanized mouse model was recently developed. Healthy human skin biopsies were engrafted onto mice and allowed to regenerate. T cells isolated from blood samples of the same donors were cultured *in vitro* and transfected with recombinant IL-17 and IL-22 expression vectors. The regenerated skin graft was then reconstituted with this T cell population through intradermal injections. The stratum corneum surface of the graft was also removed by mild abrasion, which then triggered psoriasiform features. The bioengineered skin was claimed to accurately represent human psoriatic skin (Guerrero-Aspizua et al, 2010).

2.4 Transgenic animal models

With the advent of genetic engineering, another approach using transgenic expression of individual molecules in the mouse epidermis has allowed scientists to identify possible psoriatic triggers. To assess the relevance of a protein factor, researchers induce an overexpression of the factor in the epidermis. By varying the promoter used, scientists can localize and target the epidermal overexpression to either the basal or the suprabasal layer, taking advantage of distinct promoters found in the different skin layers. For example, there is exclusive expression of keratin 14 in the basal layer and involucrin in the suprabasal keratinocytes. Epidermal overexpression helps enhance the presence of the protein of interest in the skin which enables investigations of the effects of the proteins on the immune system (Schön, 2008). To date, most of the proteins shortlisted for studies are related to the immune system or angiogenesis (e.g., TNF-α, IL-1α, IL-6, IL-8, IFN-γ, ICAM-1, VEGF, etc.). Comparatively few proteins studied are of epidermal origin (i.e., TGF-α, KGF, etc.) because previous studies using animal or T cell transfer models have identified a more immunological etiology of psoriasis (Schön, 1999). While the compilation of these studies suggests a strong immunopathogenic basis for psoriasis, an epidermal trigger of psoriasis cannot be completely discounted, as these *in vivo* disease models also involve the immune and cutaneous systems of animal models.

3. New players in psoriasis identified from wound repair studies

While the current evidence suggests that dysregulation of the immune system, particularly abnormal Th1 and Th17 immune responses, is the primary and predominant pathogenic basis for psoriasis, it is still debatable how epidermal barrier dysfunction contributes as a primary and secondary etiological factor in psoriasis. It is noteworthy that psoriasis susceptibility has been linked to a large number of genes, including those involving epidermal and immunological functions. While psoriasis has been associated with key adaptive immune genes like the *PSORS1* MHC locus antigen cluster (Allen et al, 2005), it has also been linked to epidermal proteins like the S100 proteins (Wolf et al, 2010). These genetic associations reinforce the mechanistic complexity of psoriasis, which cannot be reduced simply to either an epidermal or immunological mode of causation. This uneven balance of research attention could also stem from the natural difficulty of studying cutaneous factors in animal models. While immune cells can be studied by their transfer into an *in vivo* system, the same cannot be said for keratinocytes. Moreover, immune responses are always obligate and inseparable from the *in vivo* context of an animal model. Skin grafting, for example, inevitably leads to wounding and subsequent inflammation in the grafted skin region. In every study performed on an animal host, immune responses are inevitable after

manipulation or perturbation of the epidermal barrier. The heavy influx of immune responses and their corresponding mediators would obscure any genuine causal triggers, especially if the cause may be of a subtle epidermal origin. A similar obfuscation of epidermal causes could happen in the actual human disease, confounding the continual search for an initiating factor. Moreover, the concept of skin as a immunological tissue has gradually gained importance over the last two decades, supported by the notion of skin-associated lymphoid tissue (SALT) that was conceptualized in the early eighties. This SALT concept supports a specialized exclusive circulation of immune cells between the skin, the draining lymph nodes and the systemic circulation, which facilitates the priming of the T cell-mediated response in the skin (Streilein, 1983; Streilein, 1989). This helps highlight the importance of the adaptive immune response in psoriasis. Furthermore, to effectively safeguard the extensive cutaneous barrier against the external environment, immunosurveillance of the skin cannot rely solely on skin-residing immune scavenger cells (i.e., Langerhans cell). Rather, the average keratinocyte can capably assume the versatile role of an immune sentinel in the epidermis (Nestle et al, 2009). Armed with Toll-like receptors (TLRs) on their surfaces, keratinocytes recognize pathogen-associated molecular patterns on invading microorganisms and activate both cell-mediated immune responses and the production of type I interferons (IFNs) (Baker et al, 2003; Mempel et al, 2003; Pivarcsi et al, 2004). Keratinocytes are also constitutive producers of pro-inflammatory cytokines (i.e., IL-1, TNF-α, IL-6, IL-10, etc.) (Pivarcsi et al, 2004; Nestle et al, 2009) and can express MHC class II molecules (Nickoloff & Turka, 1994). It is thus feasible for keratinocytes to serve as adjunct antigen-presenting cells (Nickoloff & Turka, 1994). As such, the keratinocyte, despite being a non immune cell, can trigger both the innate and adaptive immune responses, suggesting that it can act as a peripheral extension of the immune system. Importantly, the role of epidermal barrier dysfunction in psoriasis should not be overlooked given the inextricable relationship between the skin and the immune system.

3.1 A neglected aspect of psoriasis research: The relevance of wound healing

3.1.1 Koebner phenomenon

Although psoriasis is strongly believed to have an underlying genetic predisposition, psoriatic plaque formation is demarcated and usually does not cover or affect the patient's entire skin area (Schön & Boehncke, 2005). The unexpected outbreak of psoriatic lesions in most patients gives the impression of an unpredictable skin condition and has greatly complicated the study of psoriasis. With an unknown trigger for psoriasis, it is difficult to rationally attribute a direct or indirect causation to either the epidermal or the immune systems. Thus, to understand the epidermal role in psoriasis, it is advantageous to trigger psoriatic plaque formation on uninvolved skin with a specific epidermal perturbation and subsequently study the molecular changes in keratinocytes corresponding to the known perturbation. This is, however, impossible in animal models in which psoriasis does not naturally occur (Schön, 1999).

The Koebner phenomenon is a well recognized clinical finding in psoriasis, whereby new psoriastic lesions can be induced in previously uninvolved skin after skin wounding or trauma. Such psoriatic lesions usually form within 10-20 days of the wounding event, coinciding with the duration of the wound healing phase. This strongly suggests that skin in predisposed individuals may still develop normally until substantial triggering by key

epidermal perturbations (Weiss et al, 2002). Wounding stands out as the only known epidermal perturbation with the predictable ability to trigger psoriasis, thus offering a unique opportunity to study pathogenetic mechanisms in psoriasis. While the molecular basis for koebnerized psoriasis remains largely unexamined (Weiss et al, 2002), wound healing studies have been comparatively well established. Considering the obligate coincidence and connection between wounding and psoriasis, an adequate understanding of koebnerized psoriasis requires a solid understanding of wound healing. The Koebner phenomenon was initially described after animal bite wounds and incision wounds. However, with accumulated observation and documentation, the Koebner phenomenon was later broadened to more accurately and extensively include psoriasis arising from all other forms of skin injury such as insect bites, friction, pressure wounds, excoriations, burns, contact dermatitis, chemical irritation, infections, tattoo and sunburns (Sagi & Trau, 2011). Some interesting exceptions were also made and accordingly, not every form of trauma resulted in koebnerization. Some interesting exceptions have been observed that did not result in koebnerization, such as experimentally inflicted knife blade injury to the dermis that did not produce psoriatic lesions on the overlying epidermis above the wounded dermal portion, but only at the incisional point where the epidermis was damaged (Farber et al, 1965). Likewise, the dermal injection of potent inflammatory stimulators like hyaluronidase and chymotrypsin did not initiate a Koebner response (Farber et al, 1965). The key conclusion from both experiments was that koebnerization must involve epidermal traumatic damage (Farber et al, 1965). This finding was further confirmed by suction blistering experiments, resulting in epidermal and dermal separation without epidermal rupture, which did not induce koebnerization (Miller, 1982; Pedace et al, 1969). The criterion of an epidermal rupture needed for koebnerization is crucial and on a microscopic level, necrotic damage of keratinocytes will activate the innate inflammatory cascade leading to psoriasis (Chen et al, 2007). Thus, it is conceivable that some forms of wounds, perturbations and traumas to the skin are not as visibly obvious as others. These subtle forms of epidermal injuries could lead to koebnerized psoriasis but still display the misleading outward appearance and impression of a spontaneous psoriatic outbreak. This revelation will shed light on many of our clinical and scientific observations concerning psoriasis. As mentioned earlier, adoptive T cell transfer experiments in *scid* mice have demonstrated the independent ability of T cells to promote the complex pathogenesis of psoriasis (Schön et al, 1997). It is likely that transplanted minor histocompatibility complex mismatched T cells would direct a T cell-mediated cytotoxic response against host keratinocyte cells leading to widespread necrotic epidermal damage, hence fueling the onset of koebnerized psoriasis. Furthermore, the injured epidermis may expose putative self antigens to the adaptive immune system, triggering an autoimmune inflammatory reaction. The importance of undetected, insidious micro-trauma to the skin as a possible initiating and aggravating factor in psoriasis cannot be over-emphasized and may explain the predilection for psoriasis over sites of frequent trauma such as the knees and elbows (Schön & Boehncke, 2005). Recent advances in wound healing research has enhanced our understanding and allowed better insight into the role of wound healing in the pathogenesis of psoriasis.

3.2 Events in wounding

Wounding or skin injury results in keratinocyte disruption leading to an epidermal gap that may expose the dermis if sufficiently large or deep. With the epidermal barrier being the key

protective barrier against various insults of the external environment, re-epithelialization of the breached epidermis is an urgent priority to close the wound gap and restore epidermal integrity. Keratinocytes at the edge of the wound are required to proliferate and migrate to fill up the epidermal gap to effectively seal it (Stadelmann et al, 1998).

The wound and psoriatic lesional microenvironment in the initial stages appear to be largely similar in terms of the abundant production of pro-inflammatory cytokines, such as TNF-α, IFN-γ and IL-1 (Nickoloff et al, 2006). Keratinocytes in wound sites and psoriatic lesions are also similarly differentiated; both express keratin 6 (K6), keratin 16 (K16) and keratin 17 (K17) instead of the standard keratin 1 (K1) and keratin 10 (K10) expressed by normal differentiating suprabasal keratinocytes (de Jong et al, 1991; Mommers et al, 2000; Wang & Chang, 2003). This suggests that transcriptional regulation responsible for both wound healing and psoriasis are similar. It is thus relevant to identify the key transcriptional regulators responsible for wound healing to evaluate its impact on psoriatic skin.

3.3 Nuclear hormone receptors as prospective transcriptional regulators in wounded skin

Among transcriptional regulators, nuclear hormone receptors are of particular interest. Nuclear hormone receptors (NRs), such as the retinoid acid receptors, are one of the largest known classes of transcription factors, several have significant transcriptional activities in the skin and are responsible for skin homeostasis (Redfern & Todd, 1992). In humans, this superfamily comprises 48 ligand-dependent or "orphan" transcription factors (Robinson-Rechavi et al, 2003). Unlike conventional transmembrane receptors, NRs are intracellular and locked in an inactive conformation by means of a bound chaperone (i.e., heat shock proteins, immunophilins) (Young & Hartl, 2002). Upon ligand binding in the cytosol, the chaperone is displaced, and the nuclear receptor is freed to undergo an active conformation, enabling its translocation into the nucleus where it subsequently binds specific DNA recognition elements present in the promoter sequence of target genes, inducing their transcription (Gronemeyer et al, 2004). As such, NRs are dual functional, serving as both a receptor and a transcription factor. The active conformation of NRs possesses a hydrophobic pocket as the ligand-binding site (Gronemeyer et al, 2004). Hence, ligands of NRs are necessarily small hydrophobic molecules (e.g., fatty acids, steroid hormones, thyroid hormones, vitamin D, retinoids, etc.), which eases their diffusion-based passage through the hydrophobic cell membrane and their subsequent binding to intracellular receptors (Friedmann et al, 2005). Furthermore, the skin is increasingly recognized as an endocrine tissue because it synthesizes and modifies steroidal hormones, which subsequently has autocrine, paracrine or endocrine signaling functions (Zouboulis, 2009). As such, significant research attention has been paid to NRs and their transcriptional regulatory role in the skin. Agonist and antagonist drugs that target the NR family constitute one of the largest and most potent groups of pharmaceuticals currently in use, and thus hold great potential for use in improved wound treatment strategies (Sladek, 2003).

3.3.1 PPARβ/δ as wound healing transcription regulator and psoriasis trigger

Recent research by various groups including our laboratory has highlighted the crucial role of a distinct member group of the NR superfamily, the peroxisome proliferator-activated receptors (PPARs), in wound healing (Tan et al, 2004). PPARs consist of three isotypes,

namely α, β/δ and γ (Tan et al, 2004). Specifically, studies of adult murine skin wounds have shown that wounding rapidly elevates the expression of PPAR β/δ from an initially undetectable range to very high levels in wound-edge keratinocytes located at the interfollicular regions of the epidermis (Tan et al, 2004). Apart from the epidermis, dermal PPAR β/δ levels were also up-regulated (Tan et al, 2004). In addition to wounding, the up-regulation of PPAR β/δ in interfollicular keratinocytes was also observed upon hair plucking and treatment with chemical irritants like phorbol esters, which can induce skin inflammation, epidermal hyperplasia and act as tumor promoting agents (TPAs) (Fürstenberger et al, 1981; Tan et al, 2003). The common underlying theme of these three skin perturbation events is that they all involve a preliminary phase of inflammation followed by epidermal proliferation. Wounding and hair plucking which are examples of koebnerization, both involve damage to the epidermis that initiate inflammation, followed by keratinocyte proliferation in order to re-epithelialize the breached epidermis. Inflammation and a hyperproliferative epidermis are also hallmark features of psoriasis, thus suggesting the possible involvement of PPAR β/δ in the transcription regulatory process of psoriasis. We conducted *in vitro* studies on mouse primary keratinocytes to evaluate the means of PPAR β/δ up-regulation during wounding. A mixed leukocyte reactions (MLR) procedure was used to mimic the inflammatory environment in the wound. MLR involves exposing immature bone marrow-derived dendritic cells (DCs) and T cells to a necrotic cellular mixture of minced skin. DCs activated by the necrotic cellular mixture will induce T cells to synergistically produce pro-inflammatory cytokines equivalent to those produced in a wound environment (i.e., TNF-α, IFN-γ, IL-1, etc.). Incubation of keratinocytes with the conditioned MLR media led to the up-regulation of PPAR β/δ. In fact, TNF-α and IFN-γ were confirmed to be the signaling inducers responsible for this PPAR β/δ up-regulation. TNF-α and IFN-γ were also found to up-regulate the endogenous ligand of PPAR β/δ, hence enhancing the transcriptional activity of PPAR β/δ in the wounded skin. Without this production of the ligand, transcription through PPAR β/δ would have been futile despite a deliberate overexpression of PPAR β/δ (Tan et al, 2001).

In summary, wounding and skin injury lead to epidermal damage, which trigger innate skin inflammation. Excessive pro-inflammatory cytokines in the inflamed skin induce the up-regulation of PPAR β/δ and its endogenous ligand, which subsequently counter the apoptotic consequences of inflammation, favoring epidermal hyperproliferation (Tan et al, 2001). This relationship was first established in wounding studies and bears clear resemblances to the pathological manifestation of psoriasis. This insight into PPAR β/δ's involvement in wound healing prompted further investigation into its probable role in psoriasis. Immunohistochemistry and expression profiling studies have revealed that PPAR β/δ is overexpressed in the psoriatic lesions of most patients (Romanowska et al, 2010). The overexpression of PPAR β/δ in mouse skin also resulted in an inflammatory skin disease that was phenotypically similar to psoriasis (Romanowska et al, 2010).

Other epidermal factors have also been linked to psoriasis. One emerging area of interest is the S100 proteins, a multigene family of low molecular weight calcium binding proteins encoded within a well known psoriasis susceptibility locus (PSOR4) on chromosome 1q21 (Semprini et al, 2002). S100A7 (psoriasin) and S100A15 (koebnerisin), prominent members of this protein family, are up-regulated in skin inflammation and psoriasis (Semprini et al, 2002). Uninvolved psoriatic skin was found to have more constitutively enhanced S100A7/A15 expression than healthy skin (Wolf et al, 2010). In lesional psoriatic skin, the

level of S100A7/A15 was further elevated, suggesting its significant role in the disease. This up-regulated S100A7/A15 expression was also retained when psoriatic keratinocytes were isolated and cultured *in vitro* (Wolf et al, 2010). S100A7/A15 was found to prime psoriatic keratinocytes, thereby increasing their susceptibility to inflammation (Wolf et al, 2010). This has been largely attributed to its autocrine effect on keratinocytes with recent studies confirming the intracellular presence of S100A7 (Broome et al, 2003). Moreover, S100A7 expression was also correlated with epidermal fatty acid binding protein (E-FABP), a keratinocyte protein that is distinctly up-regulated in psoriasis (Ruse et al, 2003). As it is difficult for lipophilic ligands to traverse through the hydrophilic cytosolic environment enroute the nucleus, E-FABP eases this transition by binding the endogenous ligands and transferring them to the PPAR β/δ receptor (Kannan-Thulasiraman et al, 2010). Notably, S100A7 has been found to bind and co-localize with E-FABP in keratinocytes (Broome et al, 2003). This interaction effectually stabilizes intracellular E-FABP levels (Broome et al, 2003). Hence, E-FABP is necessary for PPAR β/δ to stabilize and function effectively as a nuclear receptor (Kannan-Thulasiraman et al, 2010). This relationship explains how increased levels of S100A7 predisposes keratinocytes to inflammation and psoriasis, possibly via the stabilization of PPAR β/δ receptors for their relevant transcriptional activity. As S100 proteins interact with their target proteins in a calcium-dependent manner, it is also possible that calcium released from the endoplasmic reticulum during inflammation activates S100A7 which acts together with PPAR β/δ to induce transcription of anti-apoptotic features in psoriatic keratinocytes. Herein, the role of PPAR β/δ in psoriasis is reinforced.

3.4 ROS-induced oxidative damage of keratinocytes as initiating event of psoriasis

Psoriatic lesions are associated with up-regulated levels of reactive oxygen species (ROS) (Zhou et al, 2009). Using dichlorodihydrofluorescein diacetate (DCF) staining, we assessed levels of intracellular ROS in mouse wounds and found ROS levels in wound epithelial tissue peaking at 3-7 days post-injury (Lam et al, 2011). This ROS up-regulation is likely secondary to the strong pro-inflammatory wound microenvironment, supported by TNF-α, which can up-regulate cellular ROS (Kim et al, 2010). ROS-induced oxidative damage can trigger both apoptotic and necrotic cell death through multiple mechanisms including DNA fragmentation (Higuchi, 2003) and mitochondria cytochrome c release (Kirkland & Franklin, 2001). While all previously mentioned forms of skin trauma involve external perturbation to the epidermis, this endogenous ROS-triggered necrotic cell death secondary to epidermal trauma may theoretically be the initializing cause of koebnerized psoriasis. Such an ROS-triggered skin trauma could arise in apparently unwounded psoriatic skin based on intracellular signaling dysregulation and could help explain the spontaneous occurrence of psoriatic lesions. However, key questions remain as to how this death-promoting ROS signal is regulated.

Interestingly, we have found that the wound expression of transforming growth factor-β (TGF-β) activated kinase 1 (TAK1), a downstream signaling player of TNF-α, coincides with the pattern of ROS production, with peak expression also at 3-7 days post-injury (Lam et al, 2011). Like PPARβ/δ, TAK1 activity is most likely affected by TNF-α induction in wounding. A known signal transducer in the innate immune response, TAK1 in keratinocytes may serve as both an epidermal and an immune factor responsible for the pathogenesis of psoriasis. Another separate study reported that mice with an epidermal specific deletion of TAK1 suffered massive keratinocyte death attributed to elevated ROS

levels which subsequently resulted in severe psoriasiform-like skin inflammation (Omori et al, 2008). These findings strongly suggest that the dysregulation of epidermal homeostasis could trigger inflammation and initiate/sustain psoriasis of the skin and death by the 7th post-natal day (Omori et al, 2008). This precise role of TAK1 in psoriasis needs further elucidation.

To circumvent the limitations of *in vivo* models, we generated lentiviral-mediated TAK1 knockdown (TAK1 kd) human keratinocytes and cultured them in organotypic co-cultures (OTC). OTC consists of seeded keratinocytes cultured on a dermal-like fibroblast embedded collagen layer. The bottom fibroblast/collagen dermal layer contacts the OTC medium, while the top keratinocyte layer is exposed to the air. This mimics the *in vivo* positions of keratinocytes and fibroblasts in the intact skin, whereby nutrients are solely supplied to the dermis through the dermal blood circulation with nutrients reaching the epidermal layer only through diffusion (Stark et al, 2004). The advantage of using OTC models in the study of psoriasis is that it allows us to study the behavior and development of keratinocytes at the tissue level without the confounding influences of the immune system. This is especially useful in psoriasis research so that epidermal factors can be isolated and studied alone, without any immune related effects. Using this setup, we found that TAK1 kd OTC epidermis displayed significantly higher ROS levels with an increased incidence of keratinocyte cell death (Lam et al, 2011). This suggests that TAK1 kd keratinocytes succumbed to ROS-induced keratinocyte death even in normal tissue development. A unique feature of keratinocytes is that they are naturally subjected to anoikis-induced death after detachment from the basement membrane during skin homeostasis. Through flow cytometric analyses of DCF and annexin V staining, we found that either TNF-α induction or anoikis could enhance ROS production and subsequently induce cell death in TAK1 kd keratinocytes (Lam et al, 2011).

Importantly, we found that TAK1 protects healthy keratinocytes from ROS-mediated death by inducing epidermal expression of stem cell factor (SCF) through transcription factor c-Jun. SCF is secreted in an autocrine manner to bind and activate its c-Kit receptor on neighboring keratinocytes (Lam et al, 2011). The activation of c-Kit further leads to the activation of phosphoinositide-3 kinase (PI3K)/protein kinase B (PKB)α to initiate cell survival and anti-apoptotic effects (Lam et al, 2011). Incidentally, epidermal deletion of c-Jun in mice has been shown to produce a realistic psoriatic model (Zenz et al, 2005), further substantiating the role of TAK1 in psoriasis pathogenesis. As the skin is frequently exposed to oxidative stress from the external environment (Zhou et al, 2009), additional protection of keratinocytes is necessary to ensure that epidermal cells do not succumb to a fatal, massive cell death fate, similar to mice with epidermal specific TAK 1 deletion (Omori et al, 2008). Likewise, the constant microbial insults the skin confronts may lead to inflammatory responses like TNF-α induction, which will enhance ROS production in keratinocytes (Omori et al, 2008). Without the protective effects of TAK1, the epidermis may undergo necrotic degeneration especially during episodes of skin infection. We postulate that the pathogenesis of psoriasis may involve the suppression of TAK1 mediated protective mechanisms against ROS in psoriatic keratinocytes, leading to keratinocyte death and inflammation. The degree of this suppression may vary with the severity of psoriasis, with mild cases having lower levels of suppression compared to severe cases. Keratinocytes with strong suppression would undergo anoikis-triggered ROS elevation and necrotic cell death, triggering psoriasis even without any external wounding. Several clinically approved

psoriasis drugs have been found to have a therapeutic effect on ROS-induced oxidative stress, further favoring the ROS aspect of psoriasis pathogenesis (Zhou et al, 2009). A primary example is dimethylfumarate (DMF), which is known to up-regulate glutathione (Ghashghaeinia et al, 2010) and the induction of NADPH:quinine oxidoreductase 1 (NQO1) (Begleiter et al, 2004), two antioxidative pathways in the cell. Vitamin D analogues also increase the production and activity of glucose-6-phosphate dehydrogenase (G6PD), which reduces ROS-induced oxidative stress (Bao et al, 2008).

4. Conclusion

Chronic psoriasis has a complex pathogenesis, involving both epidermal barrier and immune mediated dysfunction. While much of the recent advances have been in the area of the immunopathogenesis of psoriasis, the role of epidermal disruption as an initiating event and perpetuating cause of psoriasis certainly warrants further investigation and understanding. In this chapter, we have highlighted wound healing studies that support the key role of epidermal dysfunction in psoriasis and the koebner phenomenon. In particular, the role of nuclear receptor S100 proteins and the protective role of TAK1 against ROS induced stress were highlighted and discussed. It is noteworthy that the wound healing studies using novel organotypic skin cocultures have been crucial in further enhancing our understanding of the epidermal dysfunction in psoriasis and complementing existing *in vivo* models.

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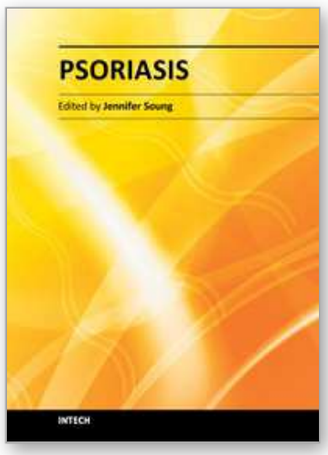

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We hope you enjoy and find the information provided in this book useful in your research or practice. We urge that you continue to keep abreast of the new developments in psoriasis and share your knowledge so that we may advance treatment and cures of psoriasis.

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