

Lessons Learned from Psoriatic Plaques Concerning Mechanisms of Tissue Repair, Remodeling, and Inflammation

Brian J. Nickoloff¹, Brian K. Bonish², Deborah J. Marble², Kelleen A. Schriedel², Luisa A. DiPietro³, Kenneth B. Gordon⁴ and Mark W. Lingen⁵

Following injury, skin establishes a balance between too little inflammation increasing risk of infection, and excessive inflammation contributing to delayed wound healing and scarring. Mounting evidence indicates both initiation and termination of inflammation involve active mechanisms. Not only does inflammation itself seem to be a paradox because inflammatory responses are both essential and potentially detrimental, but one chronic inflammatory skin disease (e.g. psoriasis) presents additional paradoxes. While plaques share several factors with wound healing, two understudied and puzzling aspects include why do not inflamed plaques more frequently transform?; and why do not plaques result in scarring? To get at these questions, we review responses involved in wound repair. Oral mucosa was probed because, like fetal skin, wound repair is characterized by its rapidity, low inflammation, and scarless resolution. Active roles for macrophages as both initiators and terminators of inflammation are highlighted. Therapeutic implications are discussed regarding psoriasis and pyoderma gangrenosum. Based on biochemical and immunohistochemical considerations linking psoriatic plaques to hard palate, a novel metaplastic model is presented. We hypothesize saliva and chronic trauma contribute to a constitutive epithelial program where keratinocyte proliferation is more intense prior to differentiation, accompanied by keratin 16 expression in hard palate, thereby resembling plaques. Rather than viewing psoriasis as a nonspecific response to inflammation, we postulate a metaplastic switch by which prepsoriatic skin is converted to a distinct adult tissue type resembling hard palate. In summary, many lessons can be learned by focusing on complex processes involved in regulation of inflammation, tissue repair, and remodeling.

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INTRODUCTION

Psoriatic plaques can be viewed as one of the most common, and yet puzzling, examples in which previously healthy appearing human skin is rapidly and dramatically remodeled in response to a variety of stimuli – both exogenous and endogenous (Nickoloff and Nestle, 2004). The tissue response in psoriasis has been likened to a persistent wounding response in which reparative processes are called into play that ultimately remodel both epidermal and dermal compartments (Mansbridge and Knapp, 1987; Morhenn, 1988; McKay and Leigh, 1995). Despite several decades of intensive basic and clinical scientific studies, many questions remain concerning this cutaneous disorder characterized by chronic inflammation accompanied by alterations in

epidermal keratinocyte proliferation and differentiation, as well as inflammatory and angiogenic tissue responses including vast influxes of T cells, macrophages, and dendritic cells (DC) (Nickoloff, 2000). This multicellular conspiracy generates a “perfect cytokine storm” that complements the cellular infiltrate, and joins together a confederacy of both soluble mediators and cellular constituents, manifesting itself from head to toe in genetically susceptible individuals as red thick scaly plaques (Uyemura *et al.*, 1993; Nickoloff and Nestle, 2004). A better understanding of the inflammatory nature of psoriasis will provide clues to the prevention and treatment of this devastating disease.

Perhaps equally amazing as the genesis of psoriatic lesions is the fact that with appropriate therapy these complex skin

¹Department of Pathology, Cardinal Bernardin Cancer Center, Loyola University Medical Center, Maywood, Illinois, USA; ²Department of Medicine, Division of Dermatology, Cardinal Bernardin Cancer Center, Loyola University Medical Center, Maywood, Illinois, USA; ³Department of Surgery, Cardinal Bernardin Cancer Center, Loyola University Medical Center, Maywood, Illinois, USA; ⁴Division of Dermatology, Evanston Northwestern Healthcare, Skokie, Illinois, USA and ⁵Department of Pathology, University of Chicago, Chicago, Illinois, USA

Correspondence: Dr Brian J. Nickoloff, Skin Cancer Research Program, Cardinal Bernardin Cancer Center, Building 112, Room 301, 2160 S. First Avenue, Maywood, Illinois 60153, USA. E-mail: bnickol@lumc.edu

Abbreviations: DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase; TGF- α , transforming growth factor alpha; TNF α , tumor necrosis factor alpha

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lesions can be reverted back to healthy appearing skin, with little if any evidence of the aforementioned changes in the epidermis and dermis (Schon, 2005). The mechanisms underlying such reversibility has been understudied in the past; but with the advent of new biological agents that target specific cytokines such as tumor necrosis factor alpha (TNF- α) and IL-12/23, new powerful investigative tools are available to explore both passive and active tissue processes underlying the effective treatment response (Kauffman *et al.*, 2004; Gottlieb *et al.*, 2005; Schon and Boehncke, 2005).

We address several important issues relevant to the topic of this symposium, which highlight the biology of skin involved in the molecular mechanisms and clinical challenges associated with wound healing, tissue repair, tissue remodeling, and the reversibility of psoriatic plaques. As will become clear, we have more questions than answers, but by raising these issues and delineating what we do not know, we hope to foster more rapid and insightful progress from both a basic science as well as clinical perspective as we continue to search for the cause and cure of psoriatic lesions. It is likely that discoveries made along this investigative journey will pay dividends for other disease processes as vastly different as skin cancer, wound healing, and tissue re-engineering (Singer and Clark, 1999).

Thus, this review focuses on several important aspects of wound healing and uses for comparison, psoriatic tissue similarities and dissimilarities. We address:

- similarities and differences in wound healing and psoriasis;
- key cellular signaling molecules likely to play a role in both wound healing and psoriasis, including TNF- α , transforming growth factor (TGF)- β , and inflammatory cytokines;
- cellular components key to each of these processes, that is, macrophages and keratinocytes;
- the process of inflammation and scar formation; and
- potential tumor suppressor mechanisms in psoriatic tissue.

In the final section, we propose a new model for psoriasis that incorporates concepts presented herein, whereby cutaneous plaques are viewed from a metaplastic perspective. Thus, it is suggested that the conversion of prepsoriatic skin to psoriatic plaques results from a metaplastic signal in which the skin is reprogrammed to resemble the hard palate in the oral cavity. This hypothesis attempts to address the paradox as to why psoriatic plaques do not transform into cancer, suggesting a paradigm shift from reactive hyperplasia to metaplasia. Rather than continuing to lump psoriatic plaques into the same heap of chronic inflammatory dermatoses, this new “metaplastic theory” points to a distinct biological process (replacement of one adult tissue type with another different adult tissue type) for psoriatic plaques. From this perspective, several key distinguishing features of psoriatic plaque formation and resolution can be re-explored with new investigative opportunities.

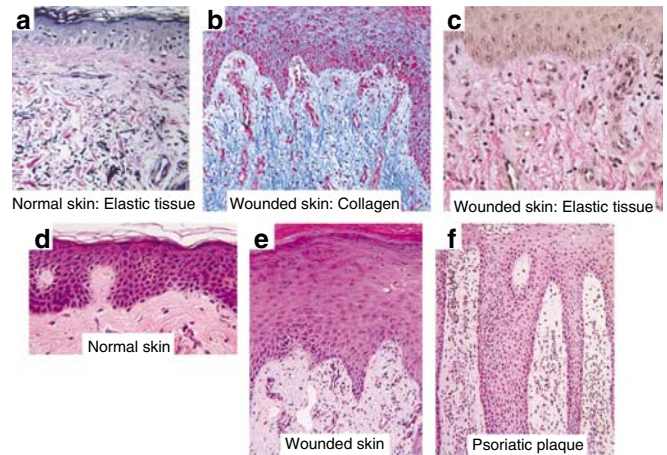


Figure 1. Microscopic appearance of normal human skin, wounded skin, and psoriatic plaques highlights the remarkable tissue remodeling of both epidermal and dermal compartments.

(a) Note in normal adult human skin the presence of elastic tissue fibers (stained black) that are thin and delicate in papillary dermis and thicker in reticular dermis (elastin tissue stain; EVG). (b) Following injury, this 20-day-old wound site (melanoma re-excision following biopsy) reveals irregular acanthosis and prominent collection of clumped collagen bundles (stained blue), accompanied by inflammatory cells and vertically oriented proliferating blood vessels (collagen stain, Trichrome). (c) In wounded skin, there is loss of elastic tissue fibers in the dermis as revealed by the EVG stain. (d) Light microscopic view of normal adult human skin with unremarkable epidermis containing basket weave stratum corneum, granular cell layer, and unremarkable dermis. (e) Light microscopic appearance of skin 20 days following punch biopsy in which the reparative process for this wounded skin reveals hyperkeratosis, irregular acanthosis, underlying dermal fibrosis, dilated blood vessels, and chronic inflammatory cells (Figure 1e). (f) Light microscope view of an active untreated psoriatic plaque with classical histological alterations including parakeratotic scale, loss of granular cell layer, prominent and uniformly elongated rete ridges accompanied by a chronic inflammatory cell infiltrate.

Throughout this presentation, an emphasis will be made to highlight the aforementioned key concept that psoriatic plaques, while sharing some features with wound healing and other inflammatory skin diseases, represents a special, if not a unique, tissue response. Before proceeding further, a pictorial overview of normal human skin, wounded human skin, and psoriatic plaques is portrayed in Figure 1. As can be easily seen, there is prominent tissue remodeling of both epidermal and dermal compartments in both wounded skin and psoriatic plaques. Note the presence of elastic tissue fibers in the dermis of normal skin (Figure 1a), compared to the loss of elastic tissue and prominent collagen deposition in wounded skin (Figure 1b and c). Relative to normal skin (Figure 1d), wounded skin is characterized by irregular acanthosis, and hyperkeratosis with underlying dermal fibrosis, dilated blood vessels, and chronic inflammatory cells (Figure 1e). By contrast to wounded skin, a psoriatic plaque has characteristic uniform and prominent elongation of epidermal rete ridges, with loss of the granular cell layer and a mononuclear cell perivascular infiltrate (Figure 1f). Thus, the highly consistent architectural abnormalities in psoriatic plaques (e.g. uniform elongation of rete ridges) contrast sharply with irregular patterns of acanthosis and

variable architectural changes in wounded skin. In the next section, the cellular and molecular basis for tissue remodeling is reviewed, and similarities between wound healing and psoriasis are discussed.

PARALLELS BETWEEN WOUND HEALING AND PSORIATIC PLAQUE FORMATION

The biological basis of wound healing has been well studied in a wide variety of animal- and human tissue-based experimental models beginning with the pioneering work of Alexis Carrel in 1922, who first demonstrated that leukocytes produced soluble factors capable of stimulating cell proliferation (Carrel, 1922). Each living organism must be capable of responding to injury of its outer protective coat by triggering a repair response to close the wound, thereby preventing blood loss and infection (Singer and Clark, 1999). A well orchestrated series of molecular and cellular events has been defined beginning with creation of a fibrin-rich clot that serves as the initial response, followed by rapid migration of keratinocytes across a provisional matrix composed of fibronectin, vitronectin, type I collagen, and other macromolecules. Further below the skin surface, fibroblasts in the dermis become activated to form a granulation tissue in which a capillary network is created by proliferating endothelial cells (Diegelmann and Evans, 2004). The collagen-rich connective tissue is accompanied by a robust inflammatory response composed of several different constituents of innate immunity such as neutrophils, macrophages, natural killer cells, and lymphocytes (Hunt et al., 1984). All of these cellular events are coordinated by a wide variety of growth factors, cytokines, chemokines, and adhesion molecules.

Among the wound healing related molecules, many are also present in psoriatic plaques including TGF- α , TNF- α , IGF-1, vascular endothelial growth factor, macrophage inhibiting factor, matrix metalloproteinase (e.g. MMP-19), various interleukins (IL-6, IL-8, IL-15), tenascin, and antimicrobial polypeptides (e.g. hCAP-18, hBD-3, SLPI) to name a few (Latijnhouwers et al., 1996; Ashcroft et al., 2000; Gillitzer and Goebeler, 2001; Sadowski et al., 2003; Sorensen et al., 2003; Shimizu, 2005), as well as important shared signaling pathways such as STAT3 (Sano et al., 1999, 2005), and mitogen-activated protein kinase activation (Haase et al., 2001). If the injury to the skin is minor, the inflammatory response tends also to be relatively transient and restores the site to a near normal appearance. However, generally in adult human skin, an inevitable result following skin repair is a scar that represents a disorder fibrotic response in which dermal collagen bundles are more clumped compared to uninjured skin, accompanied by loss of elastic tissue fibers, as depicted in Figure 1b and c. Taken together, there are clearly many cellular and molecular mediators of inflammation shared between the wound healing response and psoriatic plaques. Besides these aforementioned shared properties, in the next section, a further elaboration of links between wound healing and psoriasis is presented.

In normal human skin, there is a confederacy of immunocytes poised to respond to perturbation in the barrier

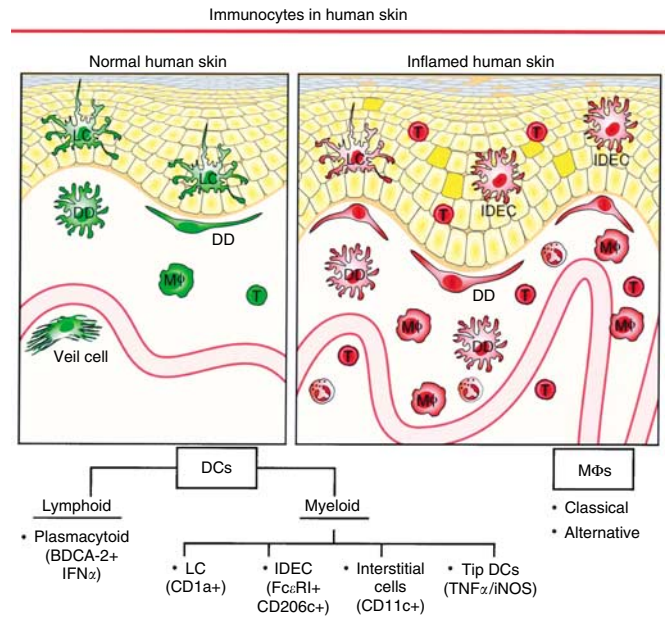


Figure 2. The presence of immunocyte subsets in normal skin (left side panel) and inflamed skin (right side panel) that may contribute to both wound healing and psoriatic plaque formation. Note the confederacy of both lymphoid and myeloid-derived mononuclear cell subsets, including plasmacytoid DCs, Langerhans cells, IDEC, interstitial DCs, TipDC. For each DC subset, a characteristic feature is listed below the subset. As regards macrophages (MΦs), at least two distinct subsets are portrayed as classical and alternatively activated macrophages. In addition to the aforementioned immunocytes, skin also contains T cells admixed with dermal dendrocytes and perivascular veil cells.

involving physical, chemical, or infectious assaults. Besides resident T cells, the mononuclear cells include epidermal Langerhans cells (CD1a+), and dermal dendritic cells of myeloid origin including CD11c+ interstitial DCs, as well as veil cells and macrophages (Figure 2). In inflamed human skin (e.g. during wound healing or in psoriatic plaques), there are both quantitative and qualitative changes in the composition of mononuclear cells. In psoriatic plaques, these changes involve both lymphoid type DCs (e.g. plasmacytoid cells providing IFN- α and expressing the BDCA-2 marker), and myeloid DCs (e.g. Langerhans cells, inflammatory dendritic epidermal cells; IDECs expressing Fc ϵ R1 and CD206; interstitial DCs expressing CD11c, and DCs producing TNF- α and inducible nitric oxide synthase; Tip DCs) (Wollenberg et al., 2002a,b; Tam and Wick, 2004; Nestle et al., 2005). As regards macrophages, both classical and alternatively activated cells are also present (van den Oord and Wolf-Peeters, 1994; Boehncke et al., 1995; Djemadjji-Oudjil et al., 1996; Goerdt and Orfanos, 1999; Nickoloff, 2000), as further illustrated and defined in Figure 3.

If one considers the response of prepsoriatic or clinically symptomless uninvolved skin to trauma, it is clear that all of the aforementioned early wound healing events also take place in the skin. However, significant differences are the exaggerated angiogenic tissue response, the excessive thickening of the epidermis in which proper terminal

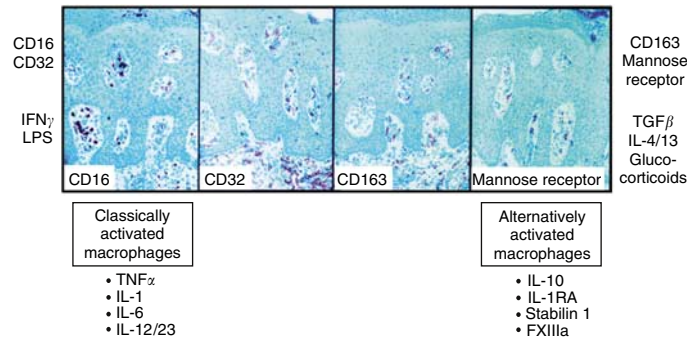


Figure 3. Diversity of macrophage subsets in psoriatic plaques. These include both classically activated macrophages (left side panel) characterized by CD16, CD32, and CD64 expression, which upon IFN- γ or LPS stimulation lead to production of TNF- α , IL-1, IL-6, and IL-12/23; and alternatively activated macrophages (right side panel) characterized by CD163 and mannose receptor expression, which upon TGF- β , IL4/13, or glucocorticoid stimulation produce IL-10, IL-1RA, stabilin 1, and factor XIIIa. Reproduced with permission of the *Journal of Investigative Dermatology* (Nickoloff, 2000).

differentiation of the keratinocytes is altered (Thelu *et al.*, 2002), and the persistent activation of the innate immune system responsible for sustaining the inflammation, perhaps leading to engagement of adaptive immune responses (Sorensen *et al.*, 2003) in psoriatic individuals. Given these histological and clinical parallels, it is not surprising that investigative skin biologists have regarded the pathophysiology of psoriasis as a persistent and hence aberrant wound healing reaction. In 1987, Jonathan Mansbridge suggested that psoriatic plaques were composed of epidermal keratinocytes following a regenerative maturation pathway, providing some of the earliest biochemical evidence for a link between wound healing and psoriatic plaques (Mansbridge and Knapp, 1987). Of course, clinicians have long been aware of the Koebner phenomenon, in which mild trauma to the skin (e.g. scratch, incision) creates psoriatic lesions (rather than normal wound repair) in genetically susceptible individuals (Weiss *et al.*, 2002). As regards the Koebner phenomenon, it is unclear why some psoriatic patients generate a normal wound response to skin injury, while other individuals produce psoriatic plaques at sites of trauma (Boyd and Neldner, 1990). Factors that contribute to the Koebner phenomena include previous Koebner responses and extent of coexisting clinically active psoriatic lesions (Eyre and Krueger, 1982). Further studies are indicated to better define the molecular and genetic elements contributing to the Koebner response.

As regards the Koebner phenomenon in psoriasis, even simple removal of the stratum corneum by repeated tape stripping has provided insights into the immunopathogenesis of psoriasis. Tape stripping of symptomless skin has revealed that such superficial trauma initiates numerous cellular and molecular events. The sequence of events includes rapid (within 2 days) infiltration of the skin by T cells, macrophages, and DCs (Heng *et al.*, 1985). Interestingly, the presence of CD8+ T cells and CD11c+ mononuclear cells on day 7 correlated with the appearance of psoriatic lesions following tape stripping (Paukkonen *et al.*, 1992). Besides induction of inflammatory cells into human tape stripped skin, the loss of barrier function has also been found to initiate a cytokine cascade, with increased mRNA levels

including TNF- α , IFN- γ , and TGF- α present as early as 6 h following tape stripping (Nickoloff and Naidu, 1994). Given the growing interest in the role of innate immunity in psoriasis (Bos *et al.*, 2005), the relative contribution of various components of the innate immune system in normal wound healing and in the Koebner response leading to psoriasis lesion formation will require additional studies. Along this line of inquiry, it has been recently observed that topical application of imiquimod, which stimulates specific toll like receptors (e.g. TLR7 components of innate immunity), on DCs induces plaque formation in psoriatic patients (Gilliet *et al.*, 2004). Engagement of TLR7 on plasmacytoid dendritic cells activates IFN- α production (Goldstein, 2004), and Nestle's group implicated plasmacytoid dendritic cells in psoriasis (Nestle and Gilliet, 2005; Nestle *et al.*, 2005). As regards innate immunity, it should be noted that human beta defensins are overexpressed in psoriatic lesions (Harder *et al.*, 1997; Huh *et al.*, 2002; Sorensen *et al.*, 2003), and defensins are also expressed at high levels in gingival tissue (Mathews *et al.*, 1999; Dunsche *et al.*, 2002; Dale and Fredericks, 2005). We will return to a potential link between psoriatic plaques and oral mucosa further in the last section of this review. Finally, defensins may also serve to recruit DCs that could thereby link innate immunity with adaptive immunity (Yang *et al.*, 1999; Biragyn *et al.*, 2002; Conejo-Garcia *et al.*, 2004).

LINKS BETWEEN WOUND HEALING, CHRONIC INFLAMMATION, AND SKIN CANCER – THE PSORIATIC PARADOXES

The two main paradoxes to be considered surrounding psoriatic plaques are: why is there only rare conversion to malignancy; and why is not there scarring associated with psoriatic plaques? We will address each of these questions in the following sections of this review. During the past few years, a growing body of evidence has emerged in many organ systems linking sites of chronic inflammation and the increased development of cancer at such tissue locations (Coussens and Werb, 2002; Balkwill and Coussens, 2004; Beachy *et al.*, 2004). Frequently cited non-dermatological associations include chronic hepatitis and liver cancer,

chronic inflammation of the intestinal tract with colorectal cancer, and chronic esophagitis with esophageal cancer. From a dermatological perspective, nonhealing ulcers of the skin can predispose to development of squamous cell carcinoma. There are many molecular pathways that have been invoked to explain these associations, including production of DNA damaging free radicals and activation of AP-1 mediated signaling, to name a few (Nickoloff, 2004). Owing to space constraints, we will restrict our focus to the importance of AP-1 activation in wound healing and its role in psoriatic pathogenesis. Since DNA binding by AP-1 family transcription factors regulate a large number of genes associated with cell proliferation and extracellular matrix molecules, numerous studies have implicated AP-1 in the wound healing response (Yates and Rayner, 2002; Florin *et al.*, 2004). One of the key regulatory roles for AP-1 involves TGF- β and collagen production (Li *et al.*, 2005). As will be discussed in later sections, it is also possible that altered AP-1 signaling in psoriatic plaques could contribute to defective TGF- β signaling involving specific isoforms as well, which may explain the persistent inflammation (TGF- β 3 is anti-inflammatory) and lack of scarring (TGF- β 1 and TGF- β 2 are profibrogenic) in psoriatic plaques. AP-1 related signaling alterations in psoriatic plaques may also be relevant to the rarity of squamous cell carcinoma, as described below.

While there is considerable support for a link between chronic inflammation and cancer, one previously overlooked exception is the paucity of skin cancers that develop within psoriatic plaques (Nickoloff *et al.*, 2005). From the current perspective of psoriasis pathogenesis, the presence of immune-mediated chronic inflammation leads to many alterations in the skin that would be expected to significantly predispose the plaques to malignant transformation such as increased proliferation, altered differentiation, increased resistance to apoptosis, and angiogenesis. One possible molecular mechanism to resolve this paradox has been invoked in the past based on the senescent-switch theory (Nickoloff, 2001). In this theory, the cytokines present in the plaque trigger a keratinocyte response in which potent tumor suppressor and cell cycle inhibitors such as p16 are induced to counteract the protumorigenic processes (Chaturvedi *et al.*, 2003; Elias *et al.*, 2004). Another possible insight into this paradox is derived from a recent mouse model of psoriasis in which the investigators observed that a conditional knock-down of both AP-1 components c-Jun and JunB led to an inflammatory skin disease accompanied by an arthritis resembling psoriasis (Zenz *et al.*, 2005). In addition to these mouse-based models, the authors also determined that human psoriatic plaques were characterized by a strong reduction in JunB/c-Jun ratios, which was significantly different from the pattern of these AP-1 components in normal skin (Mehic *et al.*, 2005). If indeed psoriatic plaques are characterized by lesional keratinocytes with reduced AP-1 levels, then the lack of skin cancer in psoriatic plaques may be explained by this defect in a key AP-1 mediated tumorigenic pathway. However, as AP-1 mediated signaling represents a double-edged sword in tumorigenesis, more studies will be necessary to better define the molecular

mechanism by which psoriatic plaques resist transformation and the potential role for either a senescent switch or reduction in AP-1 signaling in such a complex and paradoxical setting. It will also be critically important to determine if the findings involving c-Jun and JunB in the latest transgenic mouse model are truly reflective of the psoriatic phenotype (Nickoloff, 2006).

DIVERSITY OF MACROPHAGE SUBSETS IN PSORIATIC PLAQUES

Returning to the role of mononuclear cells in the pathophysiology of psoriasis, the contribution of specific macrophage subsets is delineated in this section. Cells belonging to the monocyte-macrophage lineage in psoriatic lesions have previously been relatively overlooked because of a primary focus on T cells and DCs. However, psoriatic plaques are characterized by a prominent collection of various types of macrophages (Figure 3) as we previously highlighted in the context of the psoriatic angiogenic tissue response (Nickoloff *et al.*, 2002). One of the difficulties in attempting to link macrophages to the pathogenesis of psoriasis is the heterogeneous make-up and lack of unique lineage specific markers. Currently, it has been proposed to utilize key properties of macrophage activation and polarization in defining four subsets of macrophages (e.g. M1, M2a, M2b, M2c). Table 1 summarizes the features for each major type of macrophage (reviewed by Mantovani *et al.*, 2004).

At first glance the nomenclature appears confusing, but upon further inspection it becomes clear that the heterogeneity among the four major types of macrophages reflects the plasticity and versatility of mononuclear cells required to handle the diverse response to a wide array of environmental and microenvironmental signals. The basic categorization of macrophages essentially falls into two categories (Table 1): a type I response (mediated by M1 macrophages) and a type II response (mediated predominantly by M2 macrophages, including M2a, M2b, and M2c subsets). The M1 or classically activated macrophages are most closely aligned to the phenotype of mononuclear cells in psoriatic lesions in that IFN- γ serves as a stimulus, and psoriatic plaques containing macrophages are characterized by high levels of inducible nitric oxide synthase, reactive oxygen species, and cytokines such as IL-12, IL-23, as well as IL-6 and TNF- α (Figure 3).

In addition to the M1 cells or classical macrophages (surface expression of CD16, CD32), we and others have also identified alternatively activated (surface expression of CD163, mannose receptor), or M2 macrophages, in psoriatic plaques as portrayed in Figure 3 (Djemadji-Oudjijel *et al.*, 1996; Goerdts and Orfanos, 1999; Nickoloff, 2000). Some of the other characteristics of alternatively activated macrophages include IL-10, IL-1 receptor antagonist (IL-1RA), stabilin 1, and factor XIIIa expression (Figure 3). The exact interactions between the classical and alternative macrophages in psoriatic lesions are not clear. Besides these two subsets of macrophages, the other type of macrophage to mention is the M2c type macrophage because this mononuclear cell subset has been linked to extracellular matrix depositions and tissue remodeling via production of TGF- β

Table 1. Diversity of macrophage subsets¹

Macrophage (MΦ) type	M1 MΦ “Classical MΦ”	M2a MΦ “Alternative MΦ”	M2b MΦ “Type II MΦ”	“Deactivated MΦ”
Stimulus	IFN-γ+LPS TNF-α	IL-4+IL-13 —	Toll-like receptor —	IL-10 —
Production profile	Reactive O ₂ species IL-6 IL-12 IL-23 TNF-α	IL-10 IL-1ra — — —	IL-10 TNF-α IL-6 — —	IL-10 TNF-β — — —
Immunobiological function	TH1 responses DTH responses Tumor resistance	Th2 responses Parasite killing —	Th2 activation — —	Matrix deposition Tissue remodeling —

DTH, delayed type hypersensitivity; LPS, lipopolysaccharide; TNF, tumor necrosis factor.
¹Adapted from Mantovani *et al.* (2004, p 677).

(Mantovani *et al.*, 2004). As will be discussed in the next section, given the absence of fibrosis and scarring in psoriatic plaques, we would postulate that the TGF-β producing M2 type macrophages would be conspicuous by their absence, and hence further studies of macrophage subsets are needed in this regard.

Two different groups have described transgenic mouse models that resemble psoriasis in which the skin lesions were found to be independent of a T-cell component (Pasparakis *et al.*, 2002; Zenz *et al.*, 2005). One of these models was previously mentioned involving the conditional knockdown of c-Jun and JunB in epidermal keratinocytes (Zenz *et al.*, 2005), whereas the other model involved loss of IKK2 in keratinocytes creating alterations in NF-κB signaling (Pasparakis *et al.*, 2002). In both of these models, TNF-α was a critically important cytokine for persistence of skin lesions, and since TNF-α is produced by macrophages and DCs (Nickoloff *et al.*, 1991), interest in these mononuclear cells has been rekindled, directing attention somewhat away from the T cells and more toward non-T cells such as keratinocytes, macrophages, and DCs (Nickoloff, 2006).

Another recent report has identified TNF-α and inducible nitric oxide synthase positive mononuclear cells in psoriatic plaques (Lowe *et al.*, 2005). The predominant phenotype for these cells was CD11c positivity and the so-called Tip-DCs (TNF and inducible nitric oxide synthase producing DCs) (Serbina *et al.*, 2003) appear to be derived from monocytes, which are the same cells that give rise to macrophages. While the actual CD14+ macrophages are not as frequent in psoriatic plaques as CD11c+ DCs (Lowe *et al.*, 2005), further studies are clearly required to determine the respective roles for both mononuclear cell subsets as regards the generation and maintenance of chronic inflammation, tumor resistance, and tissue remodeling in psoriatic skin.

REGULATING INFLAMMATION AND FIBROSIS FOLLOWING SKIN INJURY

Once the skin is injured both healthy individuals, as well as psoriatic patients, respond by mounting an acute inflammatory reaction (Figure 4). However, as has been highlighted throughout this review, there are many differences following the onset of acute inflammation that distinguished normal individuals from psoriatic patients. In this section, a brief summary of these differences is highlighted to emphasize both positive and negative feedback loops that regulate and coordinate inflammation and fibrotic tissue responses. Following skin injury in non-psoriatics (e.g. healthy individuals; Figure 4, left side panel), the initial tissue response is portrayed as consisting of both proinflammatory cytokines such as TNF-α and IFN-γ, as well as anti-inflammatory cytokines such as IL-10 and TGF-β1. The IL-10 can function as a negative feedback inhibitor blocking further inflammation, such that the vascular, epidermal, and fibrogenic events (including the absence of TGF-β3) are allowed to proceed in a coordinated fashion to facilitate tissue repair and restoration of normal skin; and not be perturbed by persistent or chronic inflammation.

By contrast, in psoriatic patients (Figure 4, right side panel), the balance between proinflammatory cytokines (IL-10, TGF-β) following acute inflammation is portrayed as being unbalanced or skewed toward excessive pro-inflammatory cytokines. This imbalance alters the vascular, epidermal, and fibrogenic events that become dysregulated and accompanied by chronic inflammation. Such abnormal regulation and perturbed inflammatory conditions give rise to the pathological features of psoriatic plaques, including a prominent angiogenic tissue response as well as altered keratinocyte differentiation and proliferation, but no scar formation. In the remaining portion of this section, we focus on the regulation of fibrosis/scar formation, and highlight

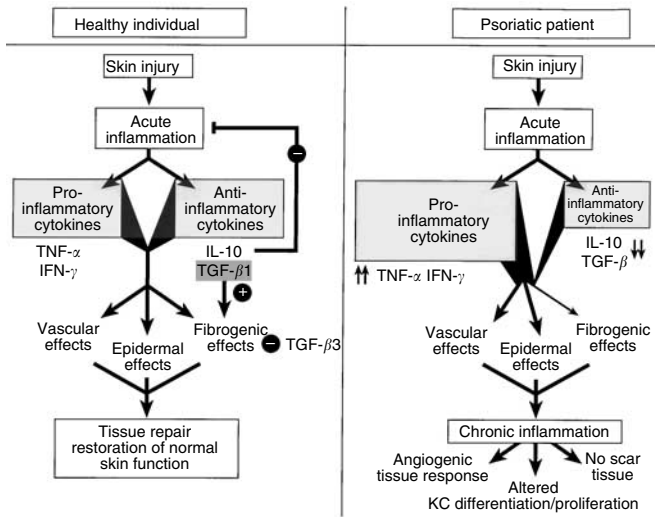


Figure 4. Comparison and contrast in the response to skin injury between healthy individuals (left panel) and psoriatic patients (right panel). While both groups of individuals initially respond to skin injury by acute inflammation, there are significant differences in the relative balance between proinflammatory cytokines and anti-inflammatory cytokines, which differentially influence vascular, epidermal, and fibrogenic effects. Key molecular mediators include TNF- α , IFN- γ , IL-10, and TGF- β isoforms. In normal individuals, there is rapid tissue repair and restoration of skin function, but in psoriatic patients, skin injury may result in chronic inflammation and exaggerated angiogenic tissue response, accompanied by altered differentiation and proliferation of epidermal keratinocytes, but no scar tissue formation. Note that normal wound response is characterized by transient inflammation and scar tissue dependent on TGF- β isoforms. TGF- β 1 isoform is depicted as profibrogenic and anti-inflammatory, whereas TGF- β 3 is depicted as inhibiting scar formation. Note that in psoriasis, it is possible that the persistence of inflammation and lack of fibrosis and scar tissue is related to the absence or dysregulation of TGF- β mediated signals in psoriatic plaques.

roles for TGF- β family members, as well as macrophage subsets, that can contribute to both the maintenance and resolution of skin inflammation.

To address the second paradox associated with psoriatic plaques (e.g. why do not plaques resolve with scar formation?), this section reviews what is known about scarless wound healing and mechanisms responsible for scar formation and resolution of inflammation.

As one considers scarless wound healing, it is important to recognize the critical relationship between inflammation and wound healing (Diegelmann and Evans, 2004). Indeed, we can ask: why does one need an inflammatory reaction at all following skin injury?, and is scar formation the price that is paid for the presence of inflammation? First, since most skin injury occurs in the context of an external environment that is non-sterile and full of infectious agents (in contrast to modern day surgical procedures performed under highly sterile conditions), it is clear that inflammatory cells with all of their antimicrobial properties are essential for wound repair so as to avoid complications such as wound infection and sepsis (Hunt, 1980). On the flip side, there is no question that reduced inflammatory responses lead to a superior wound healing response under certain conditions that is not

accompanied by scar formation. Thus, in fetal wounds there is little to no inflammation and no scar formation (Martin and Parkhurst, 2004). In mice, when neutropenia is induced, there is less inflammation and accelerated rate of wound repair (Dovi et al., 2003). Moreover, using the PU.1 null mouse, which lacks both macrophages and neutrophils, the standard inflammatory response was significantly reduced, and yet the skin wounds were rapidly repaired with reduced fibrosis (Martin and Parkhurst, 2004). When detailed molecular profiling was undertaken in the PU.1 mice, it became clear that a key factor significantly dampened during the wound healing response in this macrophage-less and scarless model was TGF- β (Martin and Parkhurst, 2004; Cooper et al., 2005). The growing body of evidence linking the cytokine TGF- β to scar formation in wound healing reactions includes TGF- β itself, as well as intracellular signaling component Smad 3, and a downstream effector – connective tissue growth factor. The TGF- β family is diverse, including three isoforms in mammals (Millan et al., 1991) that play distinct biological roles depending on the clinical setting (Graycar et al., 1989).

Direct links to TGF- β are derived from experiments using a TGF- β antibody to reduce local tissue levels in adult rats, which produced less scar formation (Shah et al., 1992; Shah et al., 1995). In a mouse model for human scleroderma, anti-TGF- β treatment reduced scar formation in the skin involving a cutaneous graft-versus-host disease reaction (McCormick et al., 1999). When transgenic mice with deletion of the Smad 3 gene were examined, the inability of cells within the wound bed to respond to TGF- β resulted in reduced inflammation and increased re-epithelization almost devoid of scar tissue (Ashcroft et al., 1999). Also, the TGF- β inducible gene connective tissue growth factor has been implicated in inflammation-mediated fibrotic reactions (Igarashi et al., 1996). Another link between TGF- β and wound healing relates to transgenic mice in which SLPI is deleted (Ashcroft et al., 2000). In normal wound healing, SLPI is expressed relatively early and is triggered by TNF- α , and can modulate levels of elastase and TGF- β by its ability to function as a protease inhibitor (Ashcroft et al., 2000) When SLPI is absent, the generated null mice display impaired wound healing with increased inflammation, elastase activity, and local TGF- β levels derived from tissue macrophages. It has been noted that licking of wounds, as is frequently observed in animals, may promote repair because SLPI is present in saliva, which could thereby mediate many beneficial processes such as promoting innate host defense, antiproteolysis, antimicrobial, and anti-inflammatory roles (Ashcroft et al., 2000).

Taken together the aforementioned studies point to roles for inflammation and macrophages, as well as TGF- β isoforms in regulating wound repair and contributing to presence or absence of scar formation. Next, we will briefly review the additional evidence highlighting an important role for TGF- β isoforms in the scarring process. As regards TGF- β isoforms, there appears to be distinct functional influences on the wound healing process, for example, TGF- β 1 has been implicated in various fibrotic diseases (Broekelmann et al.,

1991; Castilla *et al.*, 1991). When either TGF- β 1 or TGF- β 2 has been neutralized, reduced scarring was achieved in cutaneous wound response of adult rodents (Shah *et al.*, 1995). However, the addition of exogenous recombinant TGF- β 3 actually reduced scarring in the same experimental model (Shah *et al.*, 1995). Thus, as one considers the role for TGF- β in wound healing and tissue remodeling, as well as in the regulation of inflammation, it is critical to carefully consider all three family members.

One additional important new viewpoint regarding the regulation and resolution of inflammation focuses on dampening inflammation as an active rather than passive biological process. New evidence has emerged to support the concept that the beginning of inflammation is also linked to the termination of inflammation under physiological conditions. Thus, the traditional viewpoint that resolution of the inflammatory response occurs passively is giving way to the new perspective that resolution of inflammation is an active process. For a complete review of this important topic, interested readers are referred to the series of reviews and perspectives recently appearing in the December 2005 issue of *Nature Immunology* (www.nature.com/ni/focus/inflammation/index.html). Owing to space constraints, a focus on the role of macrophages will be provided herein as cellular mediators of the termination of chronic inflammation in general, with potential links to psoriasis. To complement the role of macrophages as important cellular contributors to the termination of inflammation, a role for the secreted cytokine TGF- β will be included as it clearly possesses both anti-inflammatory as well as profibrogenic roles in the normal wound healing response. Indeed, it is possible to create a model for psoriasis pathophysiology in which alterations in TGF- β (either by its absence or by abnormal signaling events) contribute to our understanding as to the molecular basis for persistent inflammation and lack of fibrogenic scar formation in psoriatic plaques. It should be noted that a connection has been established between oncofetal fibronectin (EDA), prominent in psoriatic lesions, and wound healing in fetal tissue (Ting *et al.*, 2000; Szell *et al.*, 2004).

The evidence that TGF- β signaling is altered in psoriatic plaques is derived from several sources. Before delving into these reports, it is important to remember that there are many complexities associated with TGF- β as it represents a multifunctional cytokine via a heteromeric receptor complex of TGF- β R1 and TGF- β R2 (Miyazono *et al.*, 2001). Moreover, TGF- β 1 is secreted in a latent form that requires further activation, and activated TGF- β 1 can have varied biological effects depending on its levels and duration of expression, location, and timing of exposure in the tissue response (Li *et al.*, 2004). As mentioned earlier, TGF- β isoforms can exert their effects via autocrine or paracrine mechanisms to impact keratinocyte growth, inflammation, and fibrosis. Given these complexities, it should not be too surprising that drawing definitive conclusions on the relationship between TGF- β and psoriasis is difficult at the moment, but some observations indicate reduced TGF- β expression and TGF- β mediated signaling in psoriatic plaques (Kane *et al.*, 1990; Matsuura *et al.*, 1994; Cai *et al.*, 1996; Doi *et al.*, 2003). Besides these

direct measurements using human tissue, targeting TGF- β has also been performed using transgenic mice. When TGF- β signaling is either reduced or eliminated in keratinocytes, the next effect is increased epidermal thickness (Werner *et al.*, 2001; Li *et al.*, 2004). Taken together, all of these results indicate more studies are required to better define the role for TGF- β (Werner *et al.*, 2001; Li *et al.*, 2004) in the pathogenesis of psoriasis.

Returning to macrophages, it should be noted as depicted in Table 1, that not only are there macrophage subsets that can be proinfiltrating (e.g. M1M Φ), by virtue of their production of reactive oxygen species, TNF- α , IL-6, IL-23, etc, but also macrophage subsets that can be anti-inflammatory (e.g. M2a, M2b, M2c, M Φ) by producing IL-10 and TGF- β . Not only can this latter group of macrophage subsets serve as anti-inflammatory agents, they can also support tissue remodeling and healing (Gratchev *et al.*, 2005). Macrophages and neutrophils exhibit cross-talk and the ingestion of neutrophils by macrophages may serve as an anti-inflammatory process (Fadok *et al.*, 1998; Murai *et al.*, 2003; Daley *et al.*, 2005). Another mechanism by which macrophages can actively participate in resolution of inflammation is by producing indoleamine 2,3-dioxygenase (IDO), which triggers apoptosis of T cells by interfering with tryptophan metabolism (Munn *et al.*, 1999). Since IDO functions to degrade tryptophan, T cells, which are very sensitive to external tryptophan levels, undergo apoptosis when local tryptophan levels are depleted (Munn *et al.*, 1999). Interestingly, two inducers of IDO production in macrophages include IFN- γ as well as estrogen. The link to estrogen underlies the importance of IDO in regulating maternal T-cell immunity during pregnancy to block fetal allograft rejection (Munn *et al.*, 1998). The link between IDO and psoriasis resolution may be two-fold. First, it has been observed that psoriatic lesions improve during pregnancy (Murase *et al.*, 2005), and we suspect the increased estrogen levels could enhance macrophage IDO levels in plaques leading to T-cell apoptosis and resolution of lesions (Xiao *et al.*, 2004). Second, we have observed when a TNF- α inhibitor is administered to psoriatic patients (adalimumab), there is prominent enhancement of macrophage IDO expression in the plaques, which correlated with clinical improvement and decreased number of lesional T cells (Gordon *et al.*, 2005). Thus, it is likely that various macrophage subsets are playing both proinflammatory as well as anti-inflammatory roles, and additional studies should be performed to determine the precise mechanistic role macrophages play in resolving inflammation and mediating the scarless healing of psoriatic plaques.

CRITICAL ROLE FOR TNF- α IN PSORIATIC PLAQUES AND IN CHRONIC WOUNDS THAT DO NOT HEAL

In this review, several lines of inquiry have been summarized and the evidence cited demonstrates that for wound repair to occur in which tissue homeostasis is rapidly restored following injury, a delicate balance between too little inflammation versus excessive inflammation must be achieved (Elias *et al.*, 1999). If there is too little inflammation, one may experience a local or generalized infectious

complication following loss of structural integrity of the skin, but if there is excessive inflammation complications include fibrosis and scarring with the loss of function or failure to heal leading to ulcer formation. Experimental evidence demonstrating enhanced wound healing when TNF levels are reduced include rodent and primate related experimental models (Mori *et al.*, 2002; Zhang *et al.*, 2004). Drawing from experience with TNF- α inhibitors in human subjects with psoriasis (Gottlieb *et al.*, 2005), it is possible that use of these biologically engineered inhibitors of the pre-inflammatory cytokine TNF- α , may be of benefit to promote wound repair. For this particular therapeutic approach, it will be critical to achieve the correct balance such that a reduction in the detrimental aspects of inflammation can be accomplished without increasing the risk of local infection (Szpaderska and DiPietro, 2005).

One of the most prominent clinical examples for excessive and dysregulated inflammation, tissue alterations, and definitive wound repair is pyoderma gangrenosum (Brunsting *et al.*, 1930). The pathogenesis of pyoderma gangrenosum has been elusive, and skin lesions represent a noninfectious inflammatory disease culminating in painful ulcers with undermined violaceous borders. In the past, various local and systemic therapies designed to suppress the immune system were utilized with varying success. As pyoderma gangrenosum may be associated with other noncutaneous inflammatory diseases such as Crohn's disease, clinicians began using TNF- α inhibitors to determine if reducing inflammation in pyoderma gangrenosum would promote wound healing. Interestingly, targeting TNF- α did indeed prove highly beneficial in pyoderma gangrenosum (as well as in psoriasis and Crohn's disease) as reported by numerous clinicians (Tan *et al.*, 2001; Grange *et al.*, 2002; Triantafyllidis *et al.*, 2002; Hubbard *et al.*, 2005). Taken together, these observations clearly indicate that excessive inflammation mediated by TNF- α can inhibit wound repair, and dampening inflammation can be safely accomplished without a concurrent increase in infection.

RESOLVING THE CANCERLESS AND SCARLESS PHENOTYPE OF PSORIATIC PLAQUES: A NOVEL MODEL FOCUSING ON A HARD PALATE-LIKE METAPLASTIC THEORY

Rather than viewing psoriatic plaques as the end result of a chronic inflammatory and hyperplastic response, we propose an entirely new model for the generation and maintenance of psoriatic plaques. The primary consideration for this model is to explain why psoriatic plaques do not transform into malignancies, and also to explain why the plaques resolve without scar formation. The essence of this model is that psoriatic plaque formation actually represents a metaplastic switch, rather than a purely reactive hyperplastic process. Thus, rather than a traditional pathological sequence of events such as normal, benign hyperplastic, dysplastic, carcinoma *in situ* and invasive carcinoma, we propose a simple normal to metaplastic switch by which prepsoriatic skin, under the influence of immunocyte-derived cytokines, growth factors, and chemotactic polypeptides, re-program

the skin into a plaque, which resembles the hard palate in the oral cavity. The pathological definition of metaplasia is the replacement of one adult tissue type by an entirely different adult tissue type. If we invoke a metaplastic switch to psoriasis, then the next question is what other adult type tissue is being created and replacing the symptomless, prepsoriatic skin?

By examining the histological, immunophenotypic, biochemical, and clinical features, we propose the metaplasia of the psoriatic skin resembles the hard palate. While at first glance, it may seem absurd to suggest that there is any link between a highly inflamed psoriatic plaque in skin and the hard palate in the oral cavity, this section is devoted to evidence supporting this hypothesis. Before presenting the histological and immunophenotypic similarities between psoriatic plaques and palate, we will first highlight some indirect evidence that is relevant to this viewpoint. First, it has been demonstrated that there is a "privileged repair" of oral mucosal wounds when compared with cutaneous wounds (Szpaderska *et al.*, 2003). DiPietro and her co-workers clearly demonstrated the oral mucosal response to injury is distinguished from skin wound repair mechanisms by its rapidity and lack of scar formation (*ibid*). The underlying mechanism for these differences was suggested to be linked to less inflammation in the oral cavity secondary to lower TGF- β 1 levels; features mentioned earlier in the context of rapidly healing fetal wounds.

A second reason for considering a link between oral mucosa/hard palate and psoriatic plaque is derived from the observation of many investigators that saliva which normally bathes the frequently traumatized hard palate contains a complex mixture of cytokines, growth factors, and protease inhibitors such as SLP1, which may account for the rapid healing without scarring, and lack of necessity for recruiting inflammatory cells (Hutson *et al.*, 1979; Bodner *et al.*, 1993; Zelles *et al.*, 1995; Ashcroft *et al.*, 2000). In other words, in the microenvironment of the hard palate, externally derived saliva provides an assortment of factors necessary for epithelial integrity and rapid response to injury. By contrast, in skin we postulate in the absence of saliva on the surface, when injury occurs, the resident and recruited immunocytes provide the cytokines, growth factors, protease inhibitors, and chemotactic polypeptides responsible for reprogramming the prepsoriatic skin into a psoriatic plaque. Thus, in the hard palate, a driving force for tissue structure is the externally derived saliva, whereas in the psoriatic plaque, the tissue remodeling is derived from an internally driven cytokine network provided by local immunocytes. Since in many cases, the inciting stimulus to provoke psoriatic lesion formation is only minor trauma or inadvertent response to medications (lithium, beta blockers), we have previously speculated that overactive innate immunity may represent a liability or foe, rather than friend, for psoriatic patients (Nickoloff, 1999).

The third reason for linking hard palate with psoriatic plaques is the remarkable light microscopic similarities in the epithelial silhouettes, and their shared expression of cytokeratins (i.e. keratin 16). As portrayed by immunohistochemical

stained sections, both normal hard palate and psoriatic plaques are characterized by numerous microscopic characteristics, including confluent parakeratotic scale, loss of granular cell layer, thick epithelial compartment with prominent elongation of rete ridges, and strong diffuse suprabasal positivity for keratin 16 (Figure 5). Of course,

psoriatic plaques are different from the hard palate tissue sections because the plaques are infiltrated by numerous immunocytes including T cells, macrophages, and DC subsets. Nonetheless, if one were to create a silhouette of the epithelial/epidermal compartments for hard palate and psoriatic plaques, they would be virtually superimposable.

By contrast to normal human skin, which completely lacks keratin 16 expression, psoriatic plaques contain suprabasal layer keratinocytes positive for keratin 16. Using normal keratinocytes, keratin 16 can be induced by several cytokines such as IL-1, TGF- α , and TNF- α (Freedberg *et al.*, 2001). Since growth factors may also influence keratin 16 expression, it will be interesting to determine which factors in saliva or in submucosal tissue are responsible for the constitutive and diffuse keratin 16 expression in hard palate of the oral cavity. It should be noted that when other compartments of the oral cavity were examined such a buccal mucosa, gingiva, and alveolar ridge tissue (for each tissue type, a representative example from five different patients is displayed), the keratin 16 expression was also present in other sites where trauma from mastication is common (gingiva and alveolar ridge), with much less K16 expression by the much less traumatized buccal mucosa (Figure 5). While the alveolar ridge and gingiva could also be considered in the context of the psoriatic metaplastic hypothesis, the hard palate is emphasized in the current setting simply because of space constraints, and clinical observations from our colleagues in dentistry in which biopsy wounds of hard palate have been examined carefully and found to heal rapidly with no scar formation (Marucha *et al.*, 1998). However, by no means do we suggest that the ability of saliva and trauma to influence the tissue response of the alveolar ridge and gingiva be ignored in future studies. Two other interesting aspects of the biology of hard palate are that this distinct tissue site is highly resistant to infection, and it is only rarely involved by malignant transformation.

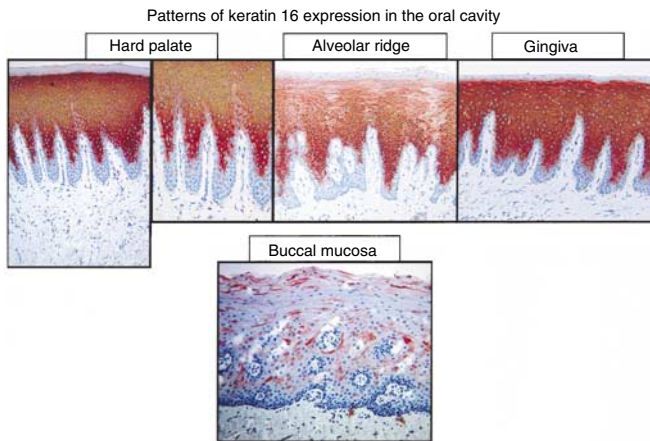


Figure 5. Profile of different tissue sites ($n=5$) within the oral cavity exposed to saliva and varying degrees of mild trauma, including hard palate, alveolar ridge, gingiva, and buccal mucosa. Note prominent suprabasal keratin 16 expression and elongated rete ridges in hard palate and other sites of frequent intraoral trauma from mastication such as alveolar ridge and gingiva, whereas buccal mucosa has only focal keratin 16 expression and more irregular acanthosis. Specimens selected for immunohistochemical analysis consisted of biopsies that did not contain either epithelial pathology or submucosal inflammation that would have altered the epithelial layer (i.e. many cases were derived from amalgam tattoos). Formalin-fixed paraffin-embedded sections were immunostained using a sensitive avidin-biotin kit (Vectastain, Vector Laboratories, Burlingame, CA) with 3-amino ethyl carbazole producing a red chromagen signifying positive staining. Keratin 16 antibody was purchased from Vector Laboratories (catalogue number VPC 412).

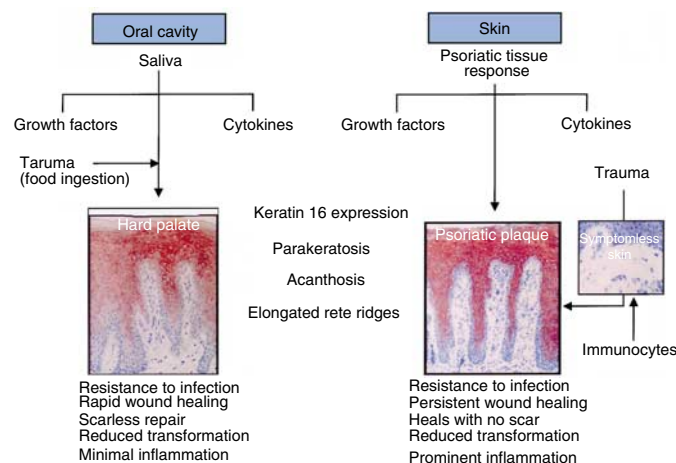


Figure 6. Similarities between hard palate in oral cavity and psoriatic plaques in skin featuring keratin 16 expression. Note the overall epithelial microscopic architecture with parakeratosis, acanthosis, elongation of rete ridges, accompanied by strong diffuse suprabasal layer keratin 16 expression and low or abnormal TGF- β signaling. The main difference is the source of the growth factors, cytokines, and protease inhibitors responsible for tissue architecture: in oral cavity, constituents of saliva are critically important, whereas in psoriatic plaques these driving forces are derived from immunocytes. In both cases, the net biological response is characterized by resistance to infection, and wound healing that is rapid and scar-free.

A summary of the similarities between hard palate in the oral cavity and psoriatic plaques in skin is provided in Figure 6. Of course, we recognize this model is highly simplified and will require extensive and rigorous experimental study in which other variables need to be considered, including the role for specialized mesenchymal elements in skin and oral cavity that may control epithelial/epidermal cell fate determinations (Dimitrakopoulos *et al.*, 1998). It is also necessary to determine why true psoriatic lesions are rare in oral mucosal sites (Richardson *et al.*, 2000; Bockelmann *et al.*, 2001).

SUMMARY AND FUTURE DIRECTIONS

The complex biological process known as inflammation is critically important for the response of the body to injury that normally restores homeostasis following tissue remodeling and repair. When the physiological processes are dysregulated, skin injury can lead to wounds that do not heal properly. Several pathways contributing to the pathophysiology of psoriasis were highlighted, and the viewpoint that psoriasis, like pyoderma gangrenosum, may be considered in a broad sense as representing abnormal wound responses. As reviewed herein, several skin diseases including psoriasis are characterized by excessive and persistent inflammation. By considering the molecular and cellular basis underlying these disorders, new therapeutic insights are derived that can be used to restore homeostasis by manipulating active mechanisms designed to dampen inflammation and prevent scar formation leading to tissue dysfunction. As mentioned at the onset of this presentation, there are clearly more questions than answers at the moment in this field, and considerable challenges facing investigative skin and oral biologists confronting such complex biological processes as inflammation, tissue remodeling, and wound healing. However, by using grafting techniques, animal models of psoriasis, proteomics, and genomics, it is hoped that the questions raised throughout this text will stimulate and provoke new experimental approaches in research activity to resolve unanswered questions surrounding these fascinating tissue responses in skin and oral mucosa.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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REFERENCES

- Ashcroft GS, Lei K, Jin W, Longenecker G, Kulkarni AB, Greenwell-Wild T *et al.* (2000) Secretory leukocyte protease inhibitor mediates non-redundant functions necessary for normal wound healing. *Nat Med* 6:1147-53
- Ashcroft GS, Yang X, Glick AB, Weinstein M, Letterio JL, Mizel DE *et al.* (1999) Mice lacking Smad3 show accelerated wound healing and an impaired local inflammatory response. *Nat Cell Biol* 1:260-6
- Balkwill F, Coussens LM (2004) Cancer: an inflammatory link. *Nature* 431:405-6
- Beachy PA, Karhadkar SS, Berman DM (2004) Mending and malignancy. *Nature* 431:402
- Biragyn A, Ruffini PA, Leifer CA, Klyushnenkova E, Shakhov A, Chertov O *et al.* (2002) Toll-like receptor 4-dependent activation of dendritic cells by beta-defensin 2. *Science* 298:1025-9
- Bockelmann R, Neugebauer P, Paseban ND, Huttemann M, Gollnick H, Bonnekoh B (2001) Suprabasal overexpression of the hsRPB7 gene in psoriatic epidermis as identified by a reverse transcriptase-polymerase chain reaction differential display model comparing psoriasis plaque tissue with peritonsillar mucosa. *Am J Pathol* 158:367-72
- Bodner L, Dayan D, Pinto Y, Hammel I (1993) Characteristics of palatal wound healing in desalivated rats. *Arch Oral Biol* 38:17-21
- Boehncke WH, Wortmann S, Kaufmann R, Mielke V, Sterry W (1995) A subset of macrophages located along the basement membrane ("lining cells") is a characteristic histopathological feature of psoriasis. *Am J Dermatopathol* 17:139-44
- Bos JD, de Rie MA, Teunissen MB, Piskin G (2005) Psoriasis: dysregulation of innate immunity. *Br J Dermatol* 152:1098-107
- Boyd AS, Neldner KH (1990) The isomorphic response of Koebner. *Int J Dermatol* 29:401-10
- Broekelmann TJ, Limper AH, Colby TV, McDonald JA (1991) Transforming growth factor beta 1 is present at sites of extracellular matrix gene expression in human pulmonary fibrosis. *Proc Natl Acad Sci USA* 88:6642-6
- Brunsting LA, Goeckermann WH, O'Leary PA (1930) Pyoderma gangrenosum—clinical and experimental observations in five cases occurring in adults. *Arch Dermatol* 22:655-80
- Cai JP, Falanga V, Taylor JR, Chin YH (1996) Transforming growth factor-beta receptor binding and function are decreased in psoriatic dermal endothelium. *J Invest Dermatol* 106:225-31
- Carrel A (1922) Growth-promoting function of leucocytes. *J Exp Med* 36:385-91
- Castilla A, Prieto J, Fausto N (1991) Transforming growth factors beta 1 and alpha in chronic liver disease. Effects of interferon alfa therapy. *N Engl J Med* 324:933-40
- Chaturvedi V, Cesnjaj M, Bacon P, Panella J, Choubey D, Diaz MO *et al.* (2003) Role of INK4a/Arf locus-encoded senescent checkpoints activated in normal and psoriatic keratinocytes. *Am J Pathol* 162:161-70
- Conejo-Garcia JR, Benencia F, Courreges MC, Kang E, Mohamed-Hadley A, Buckanovich RJ *et al.* (2004) Tumor-infiltrating dendritic cell precursors recruited by a beta-defensin contribute to vasculogenesis under the influence of Vegf-A. *Nat Med* 10:950-8
- Cooper L, Johnson C, Burslem F, Martin P (2005) Wound healing and inflammation genes revealed by array analysis of 'macrophageless' PU.1 null mice. *Genome Biol* 6:R5
- Coussens LM, Werb Z (2002) Inflammation and cancer. *Nature* 420:860-7
- Dale BA, Fredericks LP (2005) Antimicrobial peptides in the oral environment: expression and function in health and disease. *Curr Issues Mol Biol* 7:119-33
- Daley JM, Reichner JS, Mahoney EJ, Manfield L, Henry WL Jr, Mastrofrancesco B *et al.* (2005) Modulation of macrophage phenotype by soluble product(s) released from neutrophils. *J Immunol* 174:2265-72
- Diegelmann RF, Evans MC (2004) Wound healing: an overview of acute, fibrotic and delayed healing. *Front Biosci* 9:283-9
- Dimitrakopoulos I, Lazaridis N, Scordalaki A (1998) Dermal psoriasis involving an oral split-skin graft. Case report. *Aust Dent J* 43:321-3
- Djemadjji-Oudjil N, Goerdts S, Kodelja V, Schmutz M, Orfanos CE (1996) Immunohistochemical identification of type II alternatively activated dendritic macrophages (RM 3/1+3, MS-1+/-, 25F9-) in psoriatic dermis. *Arch Dermatol Res* 288:757-64
- Doi H, Shibata MA, Kiyokane K, Otsuki Y (2003) Downregulation of TGFbeta isoforms and their receptors contributes to keratinocyte hyperproliferation in psoriasis vulgaris. *J Dermatol Sci* 33:7-16
- Dovi JV, He LK, DiPietro LA (2003) Accelerated wound closure in neutrophil-depleted mice. *J Leukoc Biol* 73:448-55

- Dunsche A, Acil Y, Dommisch H, Siebert R, Schroder JM, Jepsen S (2002) The novel human beta-defensin-3 is widely expressed in oral tissues. *Eur J Oral Sci* 110:121-4
- Elias AN, Barr RJ, Nanda VS (2004) p16 expression in psoriatic lesions following therapy with propylthiouracil, an antithyroid thioureylene. *Int J Dermatol* 43:889-92
- Elias PM, Wood LC, Feingold KR (1999) Epidermal pathogenesis of inflammatory dermatoses. *Am J Contact Dermatol* 10:119-26
- Eyre RW, Krueger GG (1982) Response to injury of skin involved and uninvolved with psoriasis, and its relation to disease activity: Koebner and 'reverse' Koebner reactions. *Br J Dermatol* 106:153-9
- Fadok VA, Bratton DL, Konowal A, Freed PW, Westcott JY, Henson PM (1998) Macrophages that have ingested apoptotic cells *in vitro* inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE2, and PAF. *J Clin Invest* 101:890-8
- Florin L, Hummerich L, Dittrich BT, Kokocinski F, Wrobel G, Gack S et al. (2004) Identification of novel AP-1 target genes in fibroblasts regulated during cutaneous wound healing. *Oncogene* 23:7005-17
- Freedberg IM, Tomic-Canic M, Komine M, Blumenberg M (2001) Keratins and the keratinocyte activation cycle. *J Invest Dermatol* 116:633-40
- Gilliet M, Conrad C, Geiges M, Cozzio A, Thurlimann W, Burg G et al. (2004) Psoriasis triggered by toll-like receptor 7 agonist imiquimod in the presence of dermal plasmacytoid dendritic cell precursors. *Arch Dermatol* 140:1490-5
- Gillitzer R, Goebeler M (2001) Chemokines in cutaneous wound healing. *J Leukoc Biol* 69:513-21
- Goerd S, Orfanos CE (1999) Other functions, other genes: alternative activation of antigen-presenting cells. *Immunity* 10:137-42
- Goldstein DR (2004) Toll-like receptors and other links between innate and acquired alloimmunity. *Curr Opin Immunol* 16:538-44
- Gordon KB, Bonish BK, Gierut A, Hoffman R, Nickoloff BJ (2005) Indoleamine 2,3 dioxygenase expression by dermal CD68+ mononuclear cells is increased in psoriatic plaques after treatment with anti-TNF mAb, adalimumab. *J Invest Dermatol* 124:253
- Gottlieb AB, Chamian F, Masud S, Cardinale I, Abello MV, Lowes MA et al. (2005) TNF inhibition rapidly down-regulates multiple proinflammatory pathways in psoriasis plaques. *J Immunol* 175:2721-9
- Grange F, Djilali-Bouzina F, Weiss AM, Polette A, Guillaume JC (2002) Corticosteroid-resistant pyoderma gangrenosum associated with Crohn's disease: rapid cure with infliximab. *Dermatology* 205:278-80
- Gratchev A, Kzhyshkowska J, Utikal J, Goerd S (2005) Interleukin-4 and dexamethasone counterregulate extracellular matrix remodelling and phagocytosis in type-2 macrophages. *Scand J Immunol* 61:10-7
- Graycar JL, Miller DA, Arrick BA, Lyons RM, Moses HL, Derynck R (1989) Human transforming growth factor-beta 3: recombinant expression, purification, and biological activities in comparison with transforming growth factors-beta 1 and -beta 2. *Mol Endocrinol* 3:1977-86
- Haase I, Hobbs RM, Romero MR, Broad S, Watt FM (2001) A role for mitogen-activated protein kinase activation by integrins in the pathogenesis of psoriasis. *J Clin Invest* 108:527-36
- Harder J, Bartels J, Christophers E, Schroder JM (1997) A peptide antibiotic from human skin. *Nature* 387:861
- Heng MC, Kloss SG, Kuehn CS, Chase DG (1985) The sequence of events in psoriatic plaque formation after tape-stripping. *Br J Dermatol* 112:517-32
- Hubbard VG, Friedmann AC, Goldsmith P (2005) Systemic pyoderma gangrenosum responding to infliximab and adalimumab. *Br J Dermatol* 152:1059-61
- Huh WK, Oono T, Shirafuji Y, Akiyama H, Arata J, Sakaguchi M et al. (2002) Dynamic alteration of human beta-defensin 2 localization from cytoplasm to intercellular space in psoriatic skin. *J Mol Med* 80:678-84
- Hunt TK (1980) *Wound healing and wound infection: theory and surgical practice*. New York: Appelton-Century-Crafts
- Hunt TK, Knighton DR, Thakral KK, Goodson WH III, Andrews WS (1984) Studies on inflammation and wound healing: angiogenesis and collagen synthesis stimulated *in vivo* by resident and activated wound macrophages. *Surgery* 96:48-54
- Hutson JM, Niall M, Evans D, Fowler R (1979) Effect of salivary glands on wound contraction in mice. *Nature* 279:793-5
- Igarashi A, Nashiro K, Kikuchi K, Sato S, Ihn H, Fujimoto M et al. (1996) Connective tissue growth factor gene expression in tissue sections from localized scleroderma, keloid, and other fibrotic skin disorders. *J Invest Dermatol* 106:729-33
- Kane CJ, Knapp AM, Mansbridge JN, Hanawalt PC (1990) Transforming growth factor-beta 1 localization in normal and psoriatic epidermal keratinocytes *in situ*. *J Cell Physiol* 144:144-50
- Kauffman CL, Aria N, Toichi E, McCormick TS, Cooper KD, Gottlieb AB et al. (2004) A phase I study evaluating the safety, pharmacokinetics, and clinical response of a human IL-12 p40 antibody in subjects with plaque psoriasis. *J Invest Dermatol* 123:1037-44
- Latijhousers MA, Bergers M, Van Bergen BH, Spruijt KI, Andriessen MP, Schalkwijk J (1996) Tenascin expression during wound healing in human skin. *J Pathol* 178:30-5
- Li AG, Lu S, Han G, Kulesz-Martin M, Wang X (2005) Current view of the role of transforming growth factor beta 1 in skin carcinogenesis. *J Invest Dermatol Symp Proc* 10:110-7
- Li AG, Wang D, Feng XH, Wang XJ (2004) Latent TGFbeta1 overexpression in keratinocytes results in a severe psoriasis-like skin disorder. *EMBO J* 23:1770-81
- Lowes MA, Chamian F, Abello MV, Fuentes-Duculan J, Lin SL, Nussbaum R et al. (2005) Increase in TNF- α and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). *Proc Natl Acad Sci USA* 102:19057-62
- Mansbridge JN, Knapp AM (1987) Changes in keratinocyte maturation during wound healing. *J Invest Dermatol* 89:253-63
- Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M (2004) The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol* 25:677-86
- Martin P, Parkhurst SM (2004) Parallels between tissue repair and embryo morphogenesis. *Development* 131:3021-34
- Marucha PT, Kiecolt-Glaser JK, Favagehi M (1998) Mucosal wound healing is impaired by examination stress. *Psychosom Med* 60:362-5
- Mathews M, Jia HP, Guthmiller JM, Losh G, Graham S, Johnson GK et al. (1999) Production of beta-defensin antimicrobial peptides by the oral mucosa and salivary glands. *Infect Immun* 67:2740-5
- Matsuura H, Myokai F, Arata J, Noji S, Taniguchi S (1994) Expression of type II transforming growth factor-beta receptor mRNA in human skin, as revealed by *in situ* hybridization. *J Dermatol Sci* 8:25-32
- McCormick LL, Zhang Y, Tootell E, Gilliam AC (1999) Anti-TGF-beta treatment prevents skin and lung fibrosis in murine sclerodermatous graft-versus-host disease: a model for human scleroderma. *J Immunol* 163:5693-9
- McKay IA, Leigh IM (1995) Altered keratinocyte growth and differentiation in psoriasis. *Clin Dermatol* 13:105-14
- Mehic D, Bakiri L, Ghannadan M, Wagner EF, Tschachler E (2005) Fos and jun proteins are specifically expressed during differentiation of human keratinocytes. *J Invest Dermatol* 124:212-20
- Millan FA, Denhez F, Kondaiah P, Akhurst RJ (1991) Embryonic gene expression patterns of TGF beta 1, beta 2 and beta 3 suggest different developmental functions *in vivo*. *Development* 111:131-43
- Miyazono K, Kusanagi K, Inoue H (2001) Divergence and convergence of TGF-beta/BMP signaling. *J Cell Physiol* 187:265-76
- Morhenn VB (1988) Keratinocyte proliferation in wound healing and skin diseases. *Immunol Today* 9:104-7
- Mori R, Kondo T, Ohshima T, Ishida Y, Mukaida N (2002) Accelerated wound healing in tumor necrosis factor receptor p55-deficient mice with reduced leukocyte infiltration. *FASEB J* 16:963-74
- Munn DH, Shafiqzadeh E, Attwood JT, Bondarev I, Pashine A, Mellor AL (1999) Inhibition of T cell proliferation by macrophage tryptophan catabolism. *J Exp Med* 189:1363-72

- Munn DH, Zhou M, Attwood JT, Bondarev I, Conway SJ, Marshall B *et al.* (1998) Prevention of allogeneic fetal rejection by tryptophan catabolism. *Science* 281:1191-3
- Murai N, Nagai K, Fujisawa H, Hatanaka K, Kawamura M, Harada Y (2003) Concurrent evolution and resolution in an acute inflammatory model of rat carrageenin-induced pleurisy. *J Leukoc Biol* 73:456-63
- Murase JE, Chan KK, Garite TJ, Cooper DM, Weinstein GD (2005) Hormonal effect on psoriasis in pregnancy and post partum. *Arch Dermatol* 141:601-6
- Nestle FO, Conrad C, Tun-Kyi A, Homey B, Gombert M, Boyman O *et al.* (2005) Plasmacytoid dendritic cells initiate psoriasis through interferon-alpha production. *J Exp Med* 202:135-43
- Nestle FO, Gilliet M (2005) Defining upstream elements of psoriasis pathogenesis: an emerging role for interferon alpha. *J Invest Dermatol* 125:xiv-xv
- Nickoloff BJ (2006) Keratinocytes regain momentum as instigators of cutaneous inflammation. *Trends Mol Med* 12:102-6
- Nickoloff BJ (1999) Skin innate immune system in psoriasis: friend or foe? *J Clin Invest* 104:1161-4
- Nickoloff BJ (2000) Characterization of lymphocyte-dependent angiogenesis using a SCID mouse: human skin model of psoriasis. *J Invest Dermatol Symp Proc* 5:67-73
- Nickoloff BJ (2001) Creation of psoriatic plaques: the ultimate tumor suppressor pathway. A new model for an ancient T-cell-mediated skin disease. Viewpoint. *J Cutan Pathol* 28:57-64
- Nickoloff BJ (2004) The skin cancer paradox of psoriasis: a matter of life and death decisions in the epidermis. *Arch Dermatol* 140:873-5
- Nickoloff BJ, Karabin GD, Barker JN, Griffiths CE, Sarma V, Mitra RS *et al.* (1991) Cellular localization of interleukin-8 and its inducer, tumor necrosis factor-alpha in psoriasis. *Am J Pathol* 138:129-40
- Nickoloff BJ, Naidu Y (1994) Perturbation of epidermal barrier function correlates with initiation of cytokine cascade in human skin. *J Am Acad Dermatol* 30:535-46
- Nickoloff BJ, Nestle FO (2004) Recent insights into the immunopathogenesis of psoriasis provide new therapeutic opportunities. *J Clin Invest* 113:1664-75
- Nickoloff BJ, Qin JZ, Chaturvedi V, Bacon P, Panella J, Denning MF (2002) Life and death signaling pathways contributing to skin cancer. *J Invest Dermatol Symp Proc* 7:27-35
- Nickoloff BJ, Ben Neriah Y, Pikarsky E (2005) Inflammation and cancer: is the link as simple as we think? *J Invest Dermatol* 124:x-xiv
- Pasparakis M, Courtois G, Hafner M, Schmidt-Supprian M, Nenci A, Toksoy A *et al.* (2002) TNF-mediated inflammatory skin disease in mice with epidermis-specific deletion of IKK2. *Nature* 417:861-6
- Paukkonen K, Naukkarinen A, Horsmanheimo M (1992) The development of manifest psoriatic lesions is linked with the invasion of CD8+T cells and CD11c+macrophages into the epidermis. *Arch Dermatol Res* 284:375-9
- Richardson LJ, Kratochvil FJ, Zieper MB (2000) Unusual palatal presentation of oral psoriasis. *J Can Dent Assoc* 66:80-2
- Sadowski T, Dietrich S, Muller M, Havlickova B, Schunck M, Proksch E *et al.* (2003) Matrix metalloproteinase-19 expression in normal and diseased skin: dysregulation by epidermal proliferation. *J Invest Dermatol* 121:989-96
- Sano S, Chan KS, Carbajal S, Clifford J, Peavey M, Kiguchi K *et al.* (2005) Stat3 links activated keratinocytes and immunocytes required for development of psoriasis in a novel transgenic mouse model. *Nat Med* 11:43-9
- Sano S, Itami S, Takeda K, Tarutani M, Yamaguchi Y, Miura H *et al.* (1999) Keratinocyte-specific ablation of Stat3 exhibits impaired skin remodeling, but does not affect skin morphogenesis. *EMBO J* 18:4657-68
- Schon MP (2005) Advances in psoriasis treatment. *Lancet* 366:1333-5
- Schon MP, Boehncke WH (2005) Psoriasis. *N Engl J Med* 352:1899-1912
- Serbina NV, Salazar-Mather TP, Biron CA, Kuziel WA, Pamer EG (2003) TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. *Immunity* 19:59-70
- Shah M, Foreman DM, Ferguson MW (1992) Control of scarring in adult wounds by neutralising antibody to transforming growth factor beta. *Lancet* 339:213-4
- Shah M, Foreman DM, Ferguson MW (1995) Neutralisation of TGF-beta 1 and TGF-beta 2 or exogenous addition of TGF-beta 3 to cutaneous rat wounds reduces scarring. *J Cell Sci* 108(Part 3): 985-1002
- Shimizu T (2005) Role of macrophage migration inhibitory factor (MIF) in the skin. *J Dermatol Sci* 37:65-73
- Singer AJ, Clark RA (1999) Cutaneous wound healing. *N Engl J Med* 341:738-46
- Sorensen OE, Cowland JB, Theilgaard-Monch K, Liu L, Ganz T, Borregaard N (2003) Wound healing and expression of antimicrobial peptides/polypeptides in human keratinocytes, a consequence of common growth factors. *J Immunol* 170:5583-9
- Szell M, Bata-Csorgo Z, Koreck A, Pivarcsi A, Polyanka H, Szeg C *et al.* (2004) Proliferating keratinocytes are putative sources of the psoriasis susceptibility-related EDA+ (extra domain A of fibronectin) oncofetal fibronectin. *J Invest Dermatol* 123:537-46
- Szpaderska AM, DiPietro LA (2005) Inflammation in surgical wound healing: friend or foe? *Surgery* 137:571-3
- Szpaderska AM, Zuckerman JD, DiPietro LA (2003) Differential injury responses in oral mucosal and cutaneous wounds. *J Dent Res* 82:621-6
- Tam MA, Wick MJ (2004) Dendritic cells and immunity to *Listeria*: TipDCs are a new recruit. *Trends Immunol* 25:335-9
- Tan MH, Gordon M, Leibold O, George J, Leibold MG (2001) Improvement of Pyoderma gangrenosum and psoriasis associated with Crohn disease with anti-tumor necrosis factor alpha monoclonal antibody. *Arch Dermatol* 137:930-3
- Thelu J, Rossio P, Favier B (2002) Notch signalling is linked to epidermal cell differentiation level in basal cell carcinoma, psoriasis and wound healing. *BMC Dermatol* 2:7
- Ting KM, Rothaupt D, McCormick TS, Hammerberg C, Chen G, Gilliam AC *et al.* (2000) Overexpression of the oncofetal Fn variant containing the EDA splice-in segment in the dermal-epidermal junction of psoriatic uninvolved skin. *J Invest Dermatol* 114:706-11
- Triantafyllidis JK, Cheracakis P, Sklavaina M, Apostolopoulou K (2002) Favorable response to infliximab treatment in a patient with active Crohn disease and pyoderma gangrenosum. *Scand J Gastroenterol* 37:863-5
- Uyemura K, Yamamura M, Fivenson DF, Modlin RL, Nickoloff BJ (1993) The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response. *J Invest Dermatol* 101:701-5
- van den Oord JJ, Wolf-Peters C (1994) Epithelium-lining macrophages in psoriasis. *Br J Dermatol* 130:589-94
- Weiss G, Shemer A, Trau H (2002) The Koebner phenomenon: review of the literature. *J Eur Acad Dermatol Venereol* 16:241-8
- Werner S, Beer HD, Mauch C, Luscher B, Werner S (2001) The Mad1 transcription factor is a novel target of activin and TGF-beta action in keratinocytes: possible role of Mad1 in wound repair and psoriasis. *Oncogene* 20:7494-504
- Wollenberg A, Mommaas M, Opiel T, Schottdorf EM, Gunther S, Moderer M (2002a) Expression and function of the mannose receptor CD206 on epidermal dendritic cells in inflammatory skin diseases. *J Invest Dermatol* 118:327-34
- Wollenberg A, Wagner M, Gunther S, Towarowski A, Tuma E, Moderer M *et al.* (2002b) Plasmacytoid dendritic cells: a new cutaneous dendritic cell subset with distinct role in inflammatory skin diseases. *J Invest Dermatol* 119:1096-102
- Xiao BG, Liu X, Link H (2004) Antigen-specific T cell functions are suppressed over the estrogen-dendritic cell-indoleamine 2,3-dioxygenase axis. *Steroids* 69:653-9
- Yang D, Chertov O, Bykovskaia SN, Chen Q, Buffo MJ, Shogan J *et al.* (1999) Beta-defensins: linking innate and adaptive immunity through dendritic and T cell CCR6. *Science* 286:525-8

- Yates S, Rayner TE (2002) Transcription factor activation in response to cutaneous injury: role of AP-1 in reepithelialization. *Wound Repair Regen* 10:5-15
- Zelles T, Purushotham KR, Macauley SP, Oxford GE, Humphreys-Beher MG (1995) Saliva and growth factors: the fountain of youth resides in us all. *J Dent Res* 74:1826-32
- Zenz R, Eferl R, Kenner L, Florin L, Hummerich L, Mehic D *et al.* (2005) Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. *Nature* 437:369-75
- Zhang X, Kohli M, Zhou Q, Graves DT, Amar S (2004) Short- and long-term effects of IL-1 and TNF antagonists on periodontal wound healing. *J Immunol* 173:3514-23