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Pathogenesis of Psoriasis: The Role of Pro-Inflammatory Cytokines Produced by Keratinocytes

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1. Introduction

Psoriasis is a chronic, inflammatory skin disease affecting 2 to 3% of the white population (Gudjonsson & Elder, 2007). It is a multifactorial disease since its development depends on a complex interplay of genetic and environmental factors. As no pathogen has been consistently identified within psoriatic plaques (indeed skin infections are rare in lesions because of antimicrobial peptides) (Nomura et al., 2003), an autoimmune basis for the chronic inflammation is the dogma for this complex disorder. Psoriasis is characterized by macroscopic (clinical) and corresponding microscopic (histological) skin alterations and leads to considerable impairment of the quality of life of the affected patients. Special forms of psoriasis (e.g. arthropathic form) can be accompanied by severe extra-cutaneous changes.

2. Psoriasis pathogenesis

Psoriasis is usually identified by erythematous, raised, scaly skin lesions. These clinical features are explained by impressive growth and dilation of superficial blood vessels (elongated/hyperplastic capillaries in the papillary dermal region) and equally impressive hyperplasia of the epidermis. Epidermal growth occurs in a pattern termed “psoriasiform” hyperplasia, which describes both elongated rete pegs, thickening (acanthosis), and differentiation changes (Krueger & Bowcock, 2005). In psoriatic epidermis, keratinocytes proliferate and mature rapidly so that terminal differentiation, normally occurring in granular keratinocytes and then squamous corneocytes, is incomplete. Hence, squamous keratinocytes aberrantly retain intact nuclei (parakeratosis) and release few extracellular lipids that normally cement adhesions of corneocytes. The failure of psoriatic corneocytes to stack normally and to secrete extracellular lipids cause scaling and a break in the protective barrier whereas marked dilation of blood vessels in the dermis causes the visible redness of psoriatic skin lesions. The extensive infiltration of mononuclear immune cells in the dermis and epidermis (T cells and dendritic cells in the dermis and polymorphonuclear leucocytes such as neutrophils within small foci in the stratum corneum) is another defining feature of psoriasis histopathology and a key point of its pathogenesis. The pathogenesis of psoriasis is considered to be an immunologically mediated process that takes place upon a favourable

genetic background. According to this view, the presence of a yet unknown (auto)-antigen causes the generation of effector T-cells that infiltrate the skin and initiate the inflammatory process (Wolk et al., 2009a). Over its course, cutaneous infiltration of various immune cell populations and, subsequently, an activation of numerous immune and tissue cells in the skin take place. Secreted cytokines from activated cells then induce keratinocyte alterations such as excessive growth and aberrant differentiation forming the basis of the epidermal acanthosis, hyperkeratosis and parakeratosis which characterize psoriasis plaques. The trigger of keratinocyte response is thought to be the activation of the cellular immune system, with T cells, dendritic cells and various immune-related cytokines and chemokines implicated in pathogenesis. Rather than viewing psoriasis as a disease caused by a single cell type or a single inflammatory cytokine, it is probably best to conceptualize the disease pathogenesis as linked to many interactive responses among infiltrating leucocytes, resident skin cells, and an array of pro-inflammatory cytokines, chemokines, and chemical mediators produced in the skin (Lowe et al., 2007). Fundamentally two different cell types interact in the formation of a psoriatic lesion: keratinocytes and mononuclear leukocytes. Whereas keratinocytes might be viewed only as bystander cells in terms of immune activation, it is more likely that they are active participants in the recruitment and activation of leukocytes in psoriatic lesions. Thus, there are two sets of interactive cellular responses in the psoriatic lesion that potentially create a ying/yang relationship; the balance between the activation of innate and acquired immune cell types, and the factors produced by epidermal keratinocytes that directly affect T cells and dendritic cells, and vice versa. Psoriasis is considered a T helper 1 (Th1) condition, characterized by the production of interferon-gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α) under the influence of interleukin-12 (IL-12). However, there is increasing evidence of the importance of a novel T cell population, Th17 cells, in this inflammatory disease. Th17 cells are stimulated by IL-23 (which shares the p40 subunit with IL-12) to produce IL-17 and also IL-22, which has recently been shown to be a major driver of acanthosis in psoriasis, and so is a novel target for treatment. Effector cells of innate immunity including neutrophils, plasmacytoid dendritic cells (plasmacytoid DCs) and CD11c⁺ dendritic cells (myeloid DCs) are involved and present in psoriatic lesions creating a very intricate and complex network of interactions which is the base of the pathogenetic process of psoriasis (Nogales et al., 2010). An interplay between environmental and genetic factors sets the scene for disease-initiating events. Initial triggers such as physical trauma or bacterial products start a cascade of events that include the formation of DNA-LL-37 complexes, activation of plasmacytoid dendritic cells and secretion of interferon- α (IFN- α). IFN- α secreted by plasmacytoid dendritic cells promotes the activation of myeloid dendritic cells (Nestle et al., 2005). Activated myeloid dendritic cells migrate into draining lymph nodes and induce the differentiation of naive T cells into effector cells such as Th17 or type 17 cytotoxic T cells (Tc17) and Th1 or type 1 cytotoxic T cells (Tc1) (Nestle et al., 2010). Effector cells recirculate and slow down in skin capillaries in the presence of selectin-guided and integrin-guided receptor-ligand interactions. Immune cells expressing the chemokine receptors CCR6, CCR4, and CXCR3 emigrate into skin tissue along chemokine gradients. Dendritic cells and T cells form perivascular clusters and lymphoid-like structures around blood vessels in the presence of chemokines such as CCL19 produced by macrophages. A key checkpoint is the migration of T cells from the dermis into the epidermis; this migration is controlled through the interaction of α 1 β 1 integrin (very late antigen 1 [VLA-1]) on T cells and collagen IV at the basement membrane (Conrad et al., 2007). Unconventional T cells, including natural killer T

cells (NKT), contribute to the disease process. Key processes during disease maintenance are the presentation of putative (auto)-antigens to T cells, the release of IL-23 by dermal dendritic cells, the production of pro-inflammatory mediators such as IL-17A, IL-17F, IL-22 by Th17 and Tc17 cells and IFN- γ and TNF- α by Th1 and Tc1 cells. These mediators act on keratinocytes leading to the activation, proliferation and production of antimicrobial peptides (AMPs) (e.g., LL-37 cathelicidin and β -defensins) and chemokines (e.g., CXCL1, CXCL9 through CXCL11 and CCL20), and S100 proteins (e.g., S100A7-9) (Nestle et al., 2010). These soluble mediators feed back into the pro-inflammatory disease cycle and shape the inflammatory infiltrate (Fig.1). In fact keratinocyte products influence immune activation, and products of activated lymphocytes alter keratinocyte responses, including the induction of new adhesion molecules for T cells. However although intrinsic alterations in keratinocytes are crucial for the development of psoriatic lesions, a deregulated function of other resident skin cells, such as fibroblasts and endothelial cells, may also contribute to the pathogenesis of psoriasis. Epidermal-dermal cell interaction is a determinant for the maintenance of the psoriatic phenotype because it guarantees the local production of growth factors and cytokines stimulating keratinocyte proliferation. An important paracrine loop

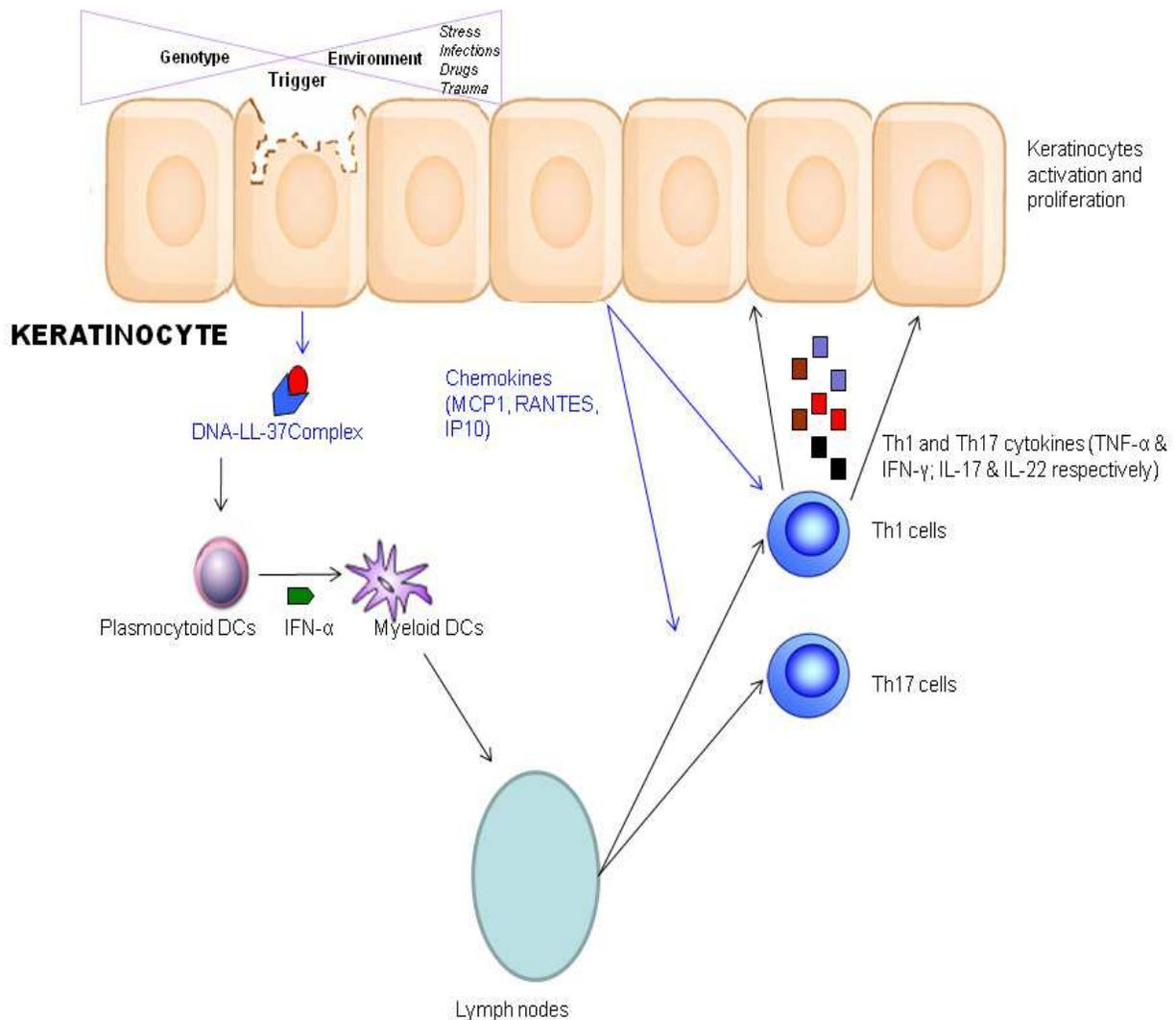


Fig. 1. Main actors of psoriasis pathogenesis.

operating between keratinocytes and fibroblasts that culminates with keratinocyte proliferation is triggered by IL-1: IL-1 α and IL-1 β neutralization and IL-1 receptor antagonist significantly reduced keratinocyte growth through the abrogation of keratinocyte growth factor (KGF) production by fibroblasts. However, IL-1 is unlikely to be the only regulator of KGF production by fibroblasts, and indeed other keratinocyte-derived factors, such as parathyroid hormone-related protein (PTHrP), induce KGF expression. In addition fibroblast growth factor (FGF) family members and granulocyte-macrophage colony stimulating factor (GM-CSF) also play a particularly important role in the fibroblast-driven regulation of keratinocyte proliferation (Albanesi et al., 2007). Moreover, the activated phenotype of lesional endothelial cells are believed to play a central role in the pathogenesis of psoriasis and are determined by the expression of a variety of membrane and soluble factors mainly responsible for T-cell recruitment in the skin like adhesion molecule 1 (ICAM-1). A key point is the endothelium expression of certain chemokines involved in the arrest of circulating T lymphocytes at inflammatory sites: upon exposure to inflammatory signals, mainly represented by TNF- α and IL-1, endothelial cells express a broad array of chemokines, including CCL20/MIP-3 α , CXCL12/SDF-1, CCL21/SLC, CCL17/TARC, CCL2/MCP-1, CXCL10/IL-8, CCL5/RANTES, CXCL1/Gro- α , and CCL4/MIP-1 β (Girolomoni et al., 2004).

In summary, feedback loops involving keratinocytes, fibroblast and endothelial cells contribute to tissue reorganization with endothelial cell activation and proliferation and deposition of extracellular matrix. The hypothesis of cytokine/chemokine network in psoriasis proposed a central role of pro-inflammatory cytokines, including TNF- α .

3. A special look at the pathogenetic functions of keratinocytes

Besides erythema, impressive hyperkeratosis manifesting as large, silvery scales, is clinically the most visible pathology and represents a hallmark of psoriasis. This typical and characteristic epidermal involvement has in the past led to discussions on whether hyperproliferation and altered differentiation of epidermal keratinocytes occur indeed only in response to skin inflammation or whether keratinocytes themselves have their share in initiation and/or propagation of psoriasis. Whereas it is widely accepted today that keratinocytes have the potential to actively participate and modulate immune reactions in the skin their role as initiators or amplifiers of the inflammatory reaction in psoriasis is still not so clear (Tschachler, 2007). Some evidence indicates that the exposure of altered auto-antigens by keratinocytes could be directly responsible for the activation and expansion of certain T-cell subpopulations in psoriatic skin (Bos et al., 2005). A keratinocyte-derived candidate auto-antigen is keratin 17. Patients with active psoriasis have an increased frequency of circulating Th1 cells reacting to peptides from keratin 17 that shares ALEEAN aminoacidic sequence with the streptococcus M-protein. Using a new approach termed SERological identification of Recombinant EXpressed antigens (SEREX), new auto-antigens were found in the serum of patients with psoriasis (Jones et al., 2004). Keratin 13, heterogeneous ribonucleoprotein-A1, and a previously uncharacterized protein, FLJ00294, were identified by SEREX as representative antigens in psoriatic patients, although auto-reactivity for these proteins was also detected in control subjects without psoriasis. Keratinocytes could be indirectly responsible for the activation of pathogenetic T cells through the exposure to viral or bacterial products. Under the influence of IL-17 and IL-22, keratinocytes, are able to produce AMPs like human beta defensin 2, and S100 proteins

(Nogralles et al., 2008). The expression of another antimicrobial peptide, LL-37 cathelicidin, can also be enhanced by IL-17 in the presence of vitamin D3 (Peric et al., 2008). These proteins may function as key inflammation inducers in psoriasis, and at the same time decrease skin infections under conditions of a dysfunctional epidermal barrier. Infections or injury to the skin can promote lesion formation in susceptible individuals and these triggers have been shown to stimulate keratinocyte production of the antimicrobial LL-37 cathelicidin that, when complexed with self-DNA, binds to TLR9 on plasmacytoid DCs. These cells produce massive amounts of IFN- α and are implicated in the initiation of psoriasis lesions (Lande et al., 2007). Accordingly, patients treated with a topical plasmacytoid DCs agonist, imiquimod, up-regulate IFN- α and experience exacerbations in psoriasis. In addition to stimulating plasmacytoid DCs, LL-37 has been shown to complex with self-RNA to trigger the activation of myeloid dendritic cells (myeloid DCs) through TLR8. This leads to production of TNF- α and IL-6, and promotes their differentiation into mature dendritic cells (Ganguly et al., 2009). Because myeloid DCs in psoriasis have been shown to produce IL-23 it is plausible that self-RNA complexes might potentially initiate the inflammatory cascade leading to expansion and activation of Th17 cells (Nogralles et al., 2010).

Recent investigations identified high levels of osteopontin (OPN) in psoriatic plaques (Buommino et al., 2009). Osteopontin is produced by both keratinocytes and activated T cells. It is a phosphorylated acidic glycoprotein of pleiotropic properties and has been recently recognized as a potential inflammatory cytokine. A model for the role of OPN in Th1/Th17 psoriatic disease was so suggested. After activation of myeloid DCs that express OPN, they migrate to skin draining lymph nodes and polarize naive T cells towards a Th1 and Th17 phenotype. In addition OPN secreted by keratinocytes attracts additional inflammatory cells. Moreover OPN inhibits keratinocyte apoptosis thereby supporting enhanced epidermal proliferation, and, through a pro-angiogenic effect on microvascular endothelial cells, OPN also promotes vessel formation subsequently supporting the influx of inflammatory cells (Buback et al., 2009).

3.1 Keratinocytes and cytokines

Cutaneous and systemic over-expression of various pro-inflammatory cytokines has been demonstrated in psoriasis. Psoriatic keratinocytes are able to produce and release IL-1 α , IL-1 β , IL-6, IL-15, IL-18 and IL-20, all of them involved in the development of different alterations which compose the complex and intricate net of psoriasis pathogenesis (Tab. 1). The cellular composition of the inflammatory infiltrate within the psoriatic plaques as well as hyperproliferation of keratinocytes and so the whole pathogenetic process of psoriasis appears to be mediated by these cytokines (Wojas-Pelc et al., 2006).

3.1.1 Keratinocytes and IL-1 α & IL-1 β

IL-1 is a pro-inflammatory cytokine stimulating, among others, IL-2 and IFN- γ production through activated T cells. IL-1 activates neutrophils, monocytes, eosinophils and basophils, triggers production of TNF- α , IL-6, IL-8 by macrophages, and in autocrine fashion, IL-1 synthesis. IL-1 promotes proliferation of bone marrow cells, B lymphocytes, neutrophils, macrophages and platelets (Dinariello, 2002). In psoriasis, keratinocytes are the main source of IL-1 α and IL-1 β in the skin stored in the form of precursor particles (Zepter et al., 1997). Monocytes/macrophages, activated endothelial cells, fibroblasts and

Langerhans cells (LCs) are additional IL-1 sources (Yoshinaga et al., 1995). Normal keratinocytes do not contain a biologically active form of interleukin 1 β -converting enzyme (ICE), and almost all IL-1 activity in the healthy epidermis results from the activity of IL-1 α . In transgenic mouse models, IL-1 α production in the basal layer of the epidermis leads to development of inflammatory lesions characterized by erythema and histology resembling psoriasis (Groves et al., 1995). Although IL-1 expression in the psoriatic epidermis appears altered, data on this finding are often conflicting. Some studies showed that IL-1 α levels in psoriatic lesions were decreased or below detection limits in comparison to non-lesional and healthy skin (Okubo & Koga, 1998), whereas others demonstrated increased levels of IL-1 β (Debets et al., 1997). Serum levels of IL-1 α and IL-1 β were low both in patients and in healthy controls. Increased levels of IL-1 α and IL-1 β were noted in supernatants of monocyte cultures obtained from patients with psoriasis (Okubo & Koga, 1998). Peripheral blood mononuclear cells (PBMCs) of inactive psoriasis patients produced lower levels of IL-1 α and IL-1 β than the cells obtained from patients with active psoriasis, although still higher than those of healthy controls. The production of IL-1 β by PBMCs from psoriatic patients positively correlated with disease severity (Mizutani et al., 1997). Higher levels of IL-1 β in blister fluid than in serum support the hypothesis that this cytokine is locally produced in psoriatic lesions. Despite fairly strong arguments for the key role of IL-1 in the activation of psoriasis, there is scarcity of data on the use of IL-1 antagonists in psoriasis treatment.

Cytokines	Role in psoriasis
IL-1	Stimulation of IL-2 and IFN- γ production through activated T cells and of TNF- α , IL-6, IL-8 by macrophages, and in autocrine fashion, of IL-1 synthesis.
IL-6	Regulation of growth and differentiation of epidermal cells and stimulation of Th17 cells differentiation.
IL-15	Anti-apoptotic effects on lymphocytes and keratinocytes; stimulation of IL-17 expression, promotion of T cell and monocyte activation, production of cytokines implicated in the pathogenesis of psoriasis, including IFN- γ and TNF- α .
IL-18	Induction of several chemokines in fibroblasts and neutrophils, increased T-cell adhesion to extracellular matrix ligands, induction of angiogenesis, induction of chemotaxis in plasmacytoid dendritic cells.
IL-20	Inhibition of normal terminal differentiation of keratinocytes, induction of anti-bacterial proteins.

Table 1. Roles of cytokines released by psoriatic keratinocytes.

3.1.2 Keratinocytes and IL-6

IL-6 is involved in the growth and differentiation of dermal and epidermal cells (Hirano, 1998), growth and differentiation of cytotoxic cells, activation of natural killer cells (NK) and maturation of hematopoietic stem cells (Pietrzak et al., 1999). Furthermore it acts as a chemotactic factor for T cells, and thus can directly stimulate T-cell migration to the epidermis. Increased levels of mRNA of IL-6 and its receptor were observed in psoriatic lesions, suction blister fluid and in keratinocytes (Krasowska et al., 1998). Previous studies have also shown a high level of IL-6 in plasma/serum of patients with psoriasis (Galadari & Sheriff, 2005; Grossman et al., 1989). Higher IL-6 levels were observed in psoriatic lesions compared to non-lesional and normal healthy skin (Chang et al., 1992; Grossman et al., 1989). Classical anti-psoriatic therapies such as phototherapy (PUVA, UVB), systemic corticosteroids and methotrexate lead to normalization of IL-6 levels (Mizutani et al., 1997). Both non-lesional and lesional psoriatic keratinocytes produce IL-6 (Grossman et al., 1989; Krasowska et al., 1998; Zalewska et al., 2006). IL-1 and TNF- α activate keratinocytes to produce IL-6. Koebner phenomenon is likely to result from the increased activity of IL-6 and its receptor in psoriasis (Grossman et al., 1989). Many studies show that IL-17F is able to induce IL-6 production both in normal human epidermal keratinocytes and in mouse skin (Fujishima et al., 2010). Moreover CD4⁺ T cells in skin from psoriasis patients express IL-17F and recent studies have demonstrated increased expression of IL-6 in IL-17F-overexpressing mice, thus further supporting a role of IL-17F in the induction of IL-6 (Hurst et al., 2002; Yang et al., 2008). IL-6 could directly contribute to the epidermal hyperplasia seen in psoriatic epithelium as well as affecting the function of dermal inflammatory cells. Moreover, it has been demonstrated that IL-6 induces Th17 cell differentiation in humans (Ishigame et al., 2009). Taken together, all these data suggest that IL-17F-induced IL-6 produced by keratinocytes promotes the development of Th17 cells as an autocrine regulator. Thus, the IL-17F/IL-6 axis may enhance inflammation of the lesional skin in psoriasis (Fujishima et al., 2010).

3.1.3 Keratinocytes and IL-15

IL-15 is a pro-inflammatory cytokine involved in chronic inflammatory processes. It is a key factor controlling the activation, proliferation and survival of NK cells (Fehniger & Caligiuri, 2001; Liu et al., 2000). IL-15 is also a strong chemotactic factor for leukocytes. This cytokine triggers angiogenesis and exerts strong anti-apoptotic effects, especially on lymphocytes, hepatocytes and keratinocytes (Berard et al., 2003; Rückert et al., 2000). Furthermore, it stimulates the expression of IL-17 by T cells (Elder, 2007). Elevated levels of IL-15 were noted in the lesional psoriatic skin (Elder, 2007; Rückert et al., 2000; Yano et al., 2003). Monocytes and macrophages represent the main source of IL-15 (Fehniger & Caligiuri, 2001; Musso et al., 1999) in lesional psoriatic skin, as well as keratinocytes (McInnes & Gracie, 2004; Yano et al., 2003). Lesional keratinocytes are strong producers of IL-15, which not only appears critical in the promotion of T cell and monocyte activation and, hence, in the maintenance of the local pro-inflammatory milieu, but also in the keratinocyte self-protection from apoptosis (Rückert et al., 2000); the pathogenic effect of this cytokine in psoriasis probably results from the stimulation of proliferation and activation of T cells and pro-inflammatory cytokines release (including TNF- α). Recent genetic studies (Elder, 2007) further supported the role of IL-15 as an important factor in psoriasis pathogenesis: IL-15 acts as a growth factor for CD8⁺ T cells, which infiltrate the epidermis during the development of psoriatic lesions, triggers

inflammatory cell recruitment, angiogenesis, and production of other cytokines implicated in the pathogenesis of psoriasis, including IFN- γ and TNF- α .

3.1.4 Keratinocytes and IL-18

IL-18 exerts its activity on the human defense system in inflammatory, infectious and autoimmune diseases (Dinarello, 2006). IL-18 over-production stimulates the recruitment of dendritic cells to the site of inflammation (Gutzmer et al., 2003). IL-18, especially together with IL-12, triggers the production of IFN- γ in many immunocompetent cells, including NK cells, T helper and cytotoxic cells. Subsequently, IFN- γ decreases Th2 response and enhances Th1 response by stimulating cytotoxic T cells (Ericson et al., 2004). Thus, IL-18 possesses the capacity to stimulate innate immunity as well as Th1-mediated responses (Nakanishi et al., 2001). IL-18 overproduction is characteristic for many diseases including psoriasis (Nakanishi et al., 2001). The role of IL-18 in psoriasis has not been fully elucidated. It is speculated that IL-18 produced by human keratinocytes enhances IFN- γ production in inflammation and thus IL-18 seems to be a promising target in Th1-type inflammatory diseases, like psoriasis (McKenzie et al., 2002; Ohta et al., 2001). Its expression in psoriasis is significantly enhanced in supra-basal keratinocytes (Flisiak et al., 2006; McKenzie et al., 2002; Ohta et al., 2001). Reverse transcription polymerase chain reaction (RT-PCR) revealed IL-18 mRNA levels to be two to eight times higher in psoriatic skin biopsies than in the non-lesional psoriatic skin and healthy controls. Overexpression of IL-18 was observed in keratinocytes of the whole epidermis in psoriatic lesions and in the basal layer of non-lesional epidermis compared to only slight IL-18 expression in the epidermis of healthy controls (McKenzie et al., 2002). McKenzie et al. reported six to eight-fold higher levels of the IL-18 receptor mRNA in the epidermis of psoriatic lesions compared to non-lesional and healthy control skin. Moreover total IL-18 protein levels were found to be 3.5 times higher in the active and progressive psoriatic epidermis compared to the normal and stable, plaque-type psoriatic epidermis. To date, there are only a few studies on IL-18 in the blood of psoriatic patients (Flisiak et al., 2006, Gangemi et al., 2003), which revealed increased plasma IL-18 levels in psoriatic patients in comparison to controls. IL-18 might act in the early phases of psoriasis via IFN- γ independent routes, such as: a) induction of several chemokines in fibroblasts and neutrophils (Leung et al., 2001; Morel et al., 2001); b) increased T-cell adhesion to extracellular matrix ligands (Ariel et al., 2002); c) induction of angiogenesis (Park et al., 2001); d) induction of chemotaxis in plasmacytoid dendritic cells (Kaser et al., 2004). Thus, IL-18 could be involved in the regulation of early inflammatory events by promoting the recruitment and adhesion of the immune system cells to the inflamed sites. However, whether IFN- γ -dependent or independent mechanisms are responsible for the IL-18 activity in early stages of psoriatic plaque development remains to be elucidated.

3.1.5 Keratinocytes and IL-20

IL-20 was demonstrated to promote hyperproliferation of keratinocytes by activating IL-20 receptor to modulate skin inflammation. It was also reported that IL-20 induced IL-6 and TNF- α in monocytes, stimulated the expression of keratinocytes growth factor (KGF), IL-6, TNF- α and reactive oxygen species (ROS) in CD8+ T cells (Wei et al., 2006). In psoriasis, the two most important effects of IL-20 are the inhibition of normal terminal differentiation of keratinocytes and the induction of anti-bacterial proteins (Wolk et al., 2009a). Keratinocyte terminal differentiation is the apoptosis-like process that generates corneocytes for the desquaming

stratum corneum from living keratinocytes of the upper (granular) epidermis layer (Candi et al., 2005). In psoriatic lesions, which contain high levels of IL-20, this process is altered. Furthermore, IL-20 simultaneously enhance the K16 expression, a keratin known to be up-regulated in psoriatic lesions and associated with keratinocyte regeneration (Wolk et al., 2006, 2009b). Apart from the inhibition of normal terminal differentiation of keratinocytes, IL-20 in addition to other mediators (Kanda & Watanabe, 2008), induce a state of enhanced antimicrobial defence of the epidermis by inducing a range of antimicrobial proteins (Sa et al., 2007; Wolk et al., 2004, 2006). In psoriatic lesions IL-20 expression was found preferentially in basal and supra-basal keratinocytes above the dermal papillae (Romer et al., 2003; Wolk et al., 2009a). Most interestingly, IL-17 and TNF- α amplified the IL-22 induced production of IL-20 in keratinocytes. In summary, the T/NK cell cytokine IL-22 induces the keratinocyte secretion of IL-20 as a second mediator that has very similar effects to its own. IL-20, therefore, may, to some extent, further amplify and/or prolong the IL-22 action on the keratinocyte differentiation that leads to the characteristic epidermal changes observed in psoriasis.

3.1.6 Keratinocytes and other cytokines

TNF- α is a key pro-inflammatory cytokine with an important pathogenetic role in psoriasis and psoriatic arthritis. The evidence includes further observations that a variety of anti-TNF- α approaches such as monoclonal antibodies and fusion proteins of soluble TNF- α receptors are effective therapies both in psoriasis and psoriatic arthritis. As for TNF- α itself, production of this cytokine is mainly attributed to immune cells (Lowes et al., 2007); however, it is noteworthy that keratinocytes are also able to elaborate TNF- α (Gottlieb et al., 2005). In psoriasis, the inflammatory response to TNF- α could be self-sustaining: activated dendritic cells are the major source of TNF- α in psoriasis lesions (Boyman et al., 2004) and at the same time TNF- α mRNA is induced in keratinocytes after TNF- α exposure (Gottlieb et al., 2005). Low level of TNF- α is present in the upper layer of the healthy epidermis, but its synthesis and release from keratinocytes are greatly augmented by injury, infection and UV irradiation. Of the two distinct cell-surface receptors for TNF- α , TNFR1 and TNFR2, keratinocytes mainly express TNFR1 (Kondo & Sauder, 1997). The binding of TNF- α to TNFR1 triggers a series of intracellular events resulting in the activation of transcription factors, including NF-KB, AP-1, CCAAT enhancer-binding protein- β , and others, which are responsible for the induction of genes important for diverse biological processes, including cell growth and death and immune, inflammatory, and stress responses (Banno et al., 2004). TNF- α activates the immune responses through inducing the production of additional signals, such as IL-1 and IL-8, transforming growth factor type- β (TGF- β) and ICAM-1. Psoriatic keratinocytes are also an important source of IL-7. Increased IL-7 levels were observed in both the psoriatic skin and serum of psoriatic patients (Bonifati et al., 1997; Pietrzak et al., 2008). However, no correlation between IL-7 levels and psoriasis area severity index (PASI) score was observed. In addition, IL-7 levels did not decrease after effective anti-psoriatic treatment, which suggests that this cytokine could not be regarded as a marker of the disease activity. IL-7 is a pleiotropic cytokine playing an essential role in the development and differentiation of T cells. IL-7 regulates survival, proliferation and cytotoxicity of maturation of T cells at the periphery. Furthermore, IL-7 together with IL-2 and IL-12, can induce the synthesis of IFN- γ , while, in turn, IFN- γ induces IL-7 secretion by keratinocytes (Ariizumi et al., 1995). In psoriasis IL-7 seems to play a key role in driving

reciprocal interactions between epithelial cells (keratinocytes) and T-lymphocytes. The concomitant T-lymphocyte activation may be dependent on IL-7, and therefore the subsequent events driving toward the clinical expression and persistence of psoriasis may be IL-7 mediated (Bonifati et al., 1997). All these findings suggest an involvement of IL-7 in psoriasis, although further studies are warranted to elucidate the exact role of this molecule in the cytokine network of psoriasis pathogenesis.

3.2 Keratinocytes and chemokines

Keratinocytes produce many different types of chemokines involved in the recruitment of immune cells in the skin. For this reason epidermal cells can play a fundamental role in collecting all the immune cells which are implicated in the beginning of the cutaneous inflammation process that characterize psoriatic disease. Specifically, keratinocytes release IL-8 (CXCL8) and related chemokines which are responsible for the intra-epidermal collection of neutrophils and so to the formation of subcorneal microabscesses, a characteristic feature of psoriasis (Nickoloff & Turka, 1994); CCL2 (MCP-1), CCL5 (RANTES), CXCL10 (IP-10), and other CXCR3 ligands are responsible to attract predominantly monocytes and Th1 cells, (Gillitzer et al., 1993; Gottlieb et al., 1998), whereas CCL20 (MIP-3 α) recruits immature Langerhans cells, dendritic cells, and CLA⁺ T cells (Dieu-Nosjan et al., 2000; Homey et al., 2000) (Tab. 2).

Chemokines	Roles
IL-8 (CXCL8)	Intra-epidermal recruitment of neutrophils
CCL-2 (MCP-1) CCL5 (RANTES) CXCL10 (IP-10)	Recruitment of monocytes and Th1 cells
CCL20 (MIP-3 α)	Recruitment of dendritic cells, CLA ⁺ T cells and immature Langherans cells

Table 2. Roles of chemokines produced by psoriatic keratinocytes.

3.3 Keratinocytes and other products

Psoriatic keratinocytes are a reservoir of inflammatory mediators. Under the influence of pro-inflammatory cytokines such as IFN- γ , TNF- α , IL-23, and IL-17, keratinocytes express a plethora of mediators, not only cytokines, thereby contributing to amplifying the inflammatory response implicated in the pathogenesis of psoriasis (Albanesi et al., 2005). Apart from pro-inflammatory cytokines as IL-1 α , IL-1 β , IL-6, IL-15, IL-18 and IL-20 psoriatic keratinocytes are able to produce other important factors involved in the development of the psoriatic process like vascular endothelial growth factor (VEGF) and CD1d (Tab. 3).

Factors	Functions
VEGF	Stimulation of angiogenesis, enhancement of vascular permeability, induction of keratinocytes hyperproliferation in an autocrine manner.
CD1d	Activation of CD161 ⁺ NK T cells and their stimulation to secrete IFN- γ .

Table 3. Roles of VEGF and CD1d in psoriasis.

3.3.1 Keratinocytes and VEGF

The typical erythema of psoriatic lesions is due to the increased, dilated, and tortuous capillaries that extend between the epidermal columns protruding into the dermis. The formation of new blood vessels starts with early psoriatic changes and disappears with disease clearance. Several angiogenic mediators like VEGF, hypoxia inducible factors, angiopoietins and pro-angiogenic cytokines, such as TNF- α , IL-8 and IL-17, are involved in psoriasis development (Heidenreich et al., 2009). Interestingly, already in uninvolved, non-lesional skin significant over-expression of several VEGF isoforms was observed in patients as compared to healthy skin of normal volunteers (Henno et al., 2009). These findings suggest that angiogenesis is also one of the key features in the pathogenesis of psoriasis and various recent studies focused on the identification and role of pro-angiogenic mediators in psoriatic skin. In general, angiogenesis is tightly regulated by a balance between pro- and anti-angiogenic mediators (Heidenreich et al., 2009). VEGF, hypoxia-inducible factor-1 α (HIF-1 α), TNF- α , IL-8 and angiopoietins are considered to be the main players responsible for the increased vessel formation in psoriasis (Creamer et al., 2002; Heidenreich et al., 2008). Interestingly, several small molecules as well as modern biologics used for systemic therapy of psoriasis have been shown to provide not only immune regulatory effects but also influence endothelial cell biology (Heidenreich et al., 2008). Thus, direct targeting of angiogenesis could help both to dissect psoriasis pathogenesis and to develop new therapeutic strategies for psoriasis treatment by blocking angiogenic pathways driving cutaneous inflammation. Strongly increased production of VEGF by keratinocytes has been found in psoriasis (Detmar et al., 1994). Furthermore, over-expression of VEGF in the epidermis of mice triggered sub-epidermal angiogenesis and increased leukocyte adhesion to these vessels (Detmar et al., 1998), and later in life, these animals develop hyperkeratotic skin lesions with a resemblance to psoriasis (Xia et al., 2003). VEGF signaling often represents a critical rate-limiting step in physiological angiogenesis (Ferrara et al., 2003). Under physiological conditions, VEGF promotes growth of endothelial cells (ECs) derived from arteries, veins and lymphatic vessels. VEGF delivery also induces lympho-angiogenesis in mice and it is known to be a survival factor for endothelial cells both in vitro and in vivo. However, VEGF is also known as a vascular permeability factor, based on its ability to induce vascular leakage. In the meantime it is well established that such permeability enhancing activity underlies significant roles of this molecule in inflammation and other pathological circumstances (Ferrara et al., 2003). Besides its potential role in causing aberrant angiogenesis and vascular leakage in the upper dermis, VEGF may also contribute to keratinocyte proliferation and epidermal barrier homeostasis (Elias et al., 2008; Heidenreich et al., 2009). In psoriatic skin, the VEGF receptors VEGFR-1 and -2 are detectable and functional in keratinocytes (Man et al., 2006). As VEGF is secreted by keratinocytes and induces VEGFR expression in the same cells, VEGF may also contribute to keratinocyte hyperproliferation in psoriasis in an autocrine manner. This could be relevant when psoriasis is triggered by external injury (Koebner phenomenon) and interestingly disruption of the epidermal barrier homeostasis induces VEGF expression (Elias et al., 2008). Further evidence for a role of VEGF in keratinocyte proliferation comes from transgenic mice deficient in epidermal VEGF: these animals have delayed permeability barrier recovery after acute perturbation, decreased density of dermal blood vessels and lack epidermal hyperplasia as well as angiogenesis in response to sustained barrier disruption (Elias et al., 2008). Thus, physiological production of VEGF contributes to normal proliferation,

differentiation and function of the epidermis (Heidenreich et al., 2009). Consequently, VEGF over-expression in psoriasis might contribute to the epidermal changes observed in this disease. Although immune cells are also able to secrete VEGF, the findings of VEGF over-expression in psoriatic epidermis together with the data reported from the transgenic animals strongly suggest that VEGF derived from epidermal keratinocytes acts as a key cytokine driving angiogenesis in psoriasis and as a central paracrine growth factor contributing to the pathology seen in psoriasis.

3.3.2 Keratinocytes and CD1d

The expression of CD1d by normal human skin and its pronounced over-expression in psoriatic skin lesions is well documented (Bonish et al., 2000) as well as the presence of NK-T cells in the epidermis of acute and chronic psoriatic plaques (Nickoloff & Wrono-Smith, 1999; Nickoloff et al., 2000). A hallmark of NK-T cells is their expression of certain C-type lectin NK cell receptors (NKR)4 such as CD94 and CD161. Classical NK-T cells may play an immunoregulatory role for recognition of both self and foreign antigens and are implicated in the pathogenesis of autoimmune and inflammatory diseases like psoriasis. An important clue to the function of NK-T cells is provided by their interaction with professional antigen presenting cells (APCs) via CD1d (Huang et al., 1999). CD1d has some similarities in structure to the major histocompatibility complex class II (MHC II) molecules. While initially CD1d was believed to bind and present peptide antigens to T cells (Castano et al., 1995), more recent studies highlight its ability to present glycolipids and GPI-linked proteins (Huang et al., 1999). NK-T cells can become activated in a CD1d-restricted fashion with subsequent proliferation and cytokine production, including IFN- γ and IL-4. Keratinocytes *in vitro* and *in vivo* synthesize and express CD1d, which is capable of triggering CD161+ NK-T cells to produce high levels of IFN- γ , but not IL-4. The stimulation by CD1d of T cells bearing NK receptors preferentially induces a cytokine switch to IFN- γ (Arase et al., 1996, 1997). Moreover, the differential induction of IFN- γ production, but not IL-4, after the NK-T cell clones recognized CD1d on keratinocytes has potentially important implications for psoriasis. Not only is there over-expression of CD1d by psoriatic epidermal keratinocytes and the presence of NK-T cells bearing CD94 and CD161, but the cytokine IFN- γ has been shown to trigger psoriatic lesions (Fierlbeck et al., 1990). Therefore a positive feedback loop could be established in skin due to the presence of NK-T cells being activated to produce IFN- γ upon contact with CD1d-positive keratinocytes, leading to further CD1d expression and subsequent NK-T cell release of more IFN- γ . The lack of a proliferative response by NK-T cells to CD1d keratinocytes is also consistent with the general number and distribution of CD94- and CD161-positive NK-T cells in psoriasis. Thus, the NK-T cells are never observed in tight clusters or in very large numbers as might be expected if they were undergoing a local proliferative response; rather, they are found as more evenly distributed single cells throughout a psoriatic plaque. In normal human skin CD1d is generally restricted to the outermost keratinocyte layers in the stratum granulosum just beneath the lipid-rich stratum corneum. In addition to epidermal keratinocytes, CD1d is detected on upper dermal dendritic cells, endothelium, eccrine ducts, acrosyringium, and the pilo-sebaceous unit, except for the dermal papillae and hair matrix cells. In psoriatic plaques CD1d expression was increased compared with that in normal and symptomless skin, beginning in the supra-basilar layer and extending to the outermost keratinocytes immediately beneath the

parakeratotic layer juxtaposed to the stratum corneum. CD161-positive T cells were frequently observed in direct contact with keratinocytes expressing CD1d in psoriatic plaques. Given this anatomical juxtaposition, it is possible for various types of glycolipids in the psoriatic scale to be directly exposed to the abundant keratinocyte cell surface CD1d. Moreover, given the large hydrophobic binding pockets in CD1d, the presence of CD1d on the outer layers of epidermis in psoriatic plaques opens up the possibility that various glycolipids present in the stratum corneum could play a role in triggering a response by NK-T cells or other T cell subsets capable of recognizing such glycolipids in the context of CD1d. During epidermal differentiation keratinocytes produce different amounts and types of various glycolipids, including glucosylceramides (Holleran et al., 1993). Alterations in these glycolipids in the stratum corneum can have a significant impact on the barrier function of skin. However, it is also clear that barrier perturbation can initiate cytokine cascades and thus influence inflammatory and mononuclear cell activation (Nickoloff & Naidu, 1994). A cycle can be envisioned in which pathogenic NK-T cells initiate barrier abnormality, which, in turn, would generate glycolipids that could be presented by keratinocyte CD1d and further activate CD161+ T cells in psoriasis (Kalish et al., 1994). Taken together, these findings support the idea that NK-T cells may play an important patho-physiological role in psoriasis. Besides the ability of keratinocytes to initiate (Barker et al., 1991), perpetuate (Nickoloff & Turka, 1994), and terminate (Gutierrez-Steil et al., 1998) immune reactions involving conventional T cell responses to nominal antigens and super-antigens, CD1d expression may also imbue the keratinocyte with the capacity to interact with NKR-bearing T cells. As a member of a non-classical, MHC independent, antigen-presenting system, CD1d expression as seen in psoriasis provides a novel opportunity for therapeutic targeting and for understanding the immunologic and genetic basis of psoriasis as well as the potential role for innate immunity in psoriasis (Nickoloff, 1999a, 1999b).

4. Conclusion

The pathogenesis of psoriasis is considered to be an immunologically mediated process that takes place upon a favourable genetic background. According to this view, the presence of a yet unknown (auto)-antigen causes the generation of effector T-cells that infiltrate the skin and initiate the inflammatory process. Over its course, cutaneous infiltration of various immune cell populations and, subsequently, an activation of numerous immune and tissue cells in the skin takes place. Two fundamentally different cell types interact in the formation of a psoriatic lesion: epidermal keratinocytes and mononuclear leukocytes. Whereas keratinocytes might be viewed only as bystander cells in terms of immune activation, it is more likely that they are active participants in the recruitment and activation of leukocytes in psoriatic lesions: the interplay between keratinocytes and immune cells can be considered the main feature of the psoriasis pathogenesis. In fact whatever the sequence of events that leads to the induction of the mentioned cytokines and mediators in epidermal keratinocytes, it is highly likely that they significantly contribute to the typical changes observed in psoriatic lesions; cytokine or growth factor secretion by epidermal keratinocytes can be sufficient to recruit immune cells into the skin and induce a hyperplastic epidermis with hyperkeratosis and reproduce features of psoriatic disease. Regulation of the inflammatory events initiated or perpetuated by keratinocytes could so represent an important strategy for the treatment of psoriasis and other chronic inflammatory skin diseases.

5. References

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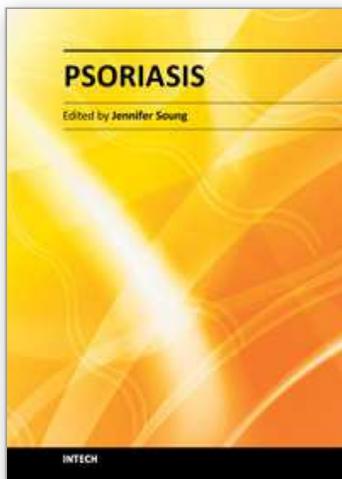
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We hope you enjoy and find the information provided in this book useful in your research or practice. We urge that you continue to keep abreast of the new developments in psoriasis and share your knowledge so that we may advance treatment and cures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

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