Review Article

Dermatology

Dermatology 2019;235:91–100
DOI: 10.1159/000495291

Received: August 15, 2018
Accepted after revision: November 12, 2018
Published online: December 19, 2018

Psoriasis: Keratinocytes or Immune Cells – Which Is the Trigger?

Farida Benhadou[a, b] Dillon Mintoff[c] Véronique del Marmol[a]

[a]Dermatology Department, Erasme Hospital, Université Libre de Bruxelles – ULB, Brussels, Belgium;
[b]Laboratory of Stem Cells and Cancer, Unversité Libre de Bruxelles – ULB, Brussels, Belgium;
[c]Dermatology Department, Sir Paul Boffa Hospital, Floriana, Malta

Downloaded from http://karger.com/drm/article-pdf/235/2/91/2663712/000495291.pdf by guest on 19 April 2024

Keywords
Psoriasis · Keratinocytes · Immune cells

Abstract
Background: Psoriasis is a common, chronic inflammatory skin disorder, which can significantly impact quality of life. Despite major breakthroughs in our understanding of the pathogenesis of psoriasis, the chronological order of the underlying mechanisms leading to the development of psoriatic plaques remains to be completely understood. ***Summary:*** Although psoriasis is classically perceived as a T-cell disease, it is now well recognized that T lymphocytes do not function in exclusivity. This theory is supported by evidence from transgenic murine models that develop marked psoriasiform disease. In addition, immune cells and cytokines regulate both early and late events involved in the pathogenesis of psoriasis. ***Key Messages:*** Psoriasis is a complex disease – a dynamic interplay between immune cells, keratinocytes, and various other skin-resident cells, such as endothelial and immune cells. The contribution of each cell type is crucial in the initiation and maintenance phases of psoriatic alterations.
© 2018 S. Karger AG, Basel

Introduction

Psoriasis is one of the commonest and most researched immune-mediated chronic skin disorders, affecting approximately 3% of the population worldwide [1]. Beyond its dermatological manifestations, psoriasis can have significant impact on a patient's quality of life [2]. Chronic plaque psoriasis, referred to as psoriasis vulgaris, is characterized by well-demarcated, erythematous, scaly plaques, which can involve any part of the skin but most commonly the extensor surfaces (such as the elbows and knees) and the scalp.

In 1985, Heng et al. [3] attempted to describe the microscopic sequence of events associated with psoriasis by studying the different stages of psoriatic plaques induced by tape-stripping. At the time, the research concluded that the proliferation of the epidermis was maintained and clearly identified.

It is now well established that psoriasis is the product of interactions between environmental factors and a complex genetic background [1]. Psoriatic plaques are characterized by (1) an abnormal proliferation and differentiation of keratinocytes leading to epidermal hyperplasia, (2) dermal infiltration of the dermis by various immune cells, and (3) increased dermal capillary density, with enhanced

KARGER
© 2018 S. Karger AG, Basel
E-Mail karger@karger.com
www.karger.com/drm

Farida Benhadou
Dermatology Department, Erasme Hospital
Université Libre de Bruxelles – ULB
Route de Lennik 808, BE 1070 Brussels (Belgium)
E-Mail farida.benhadou@erasme.ulb.ac.be

permeability in wide-caliber vessels [4]. Despite the major breakthroughs made in understating the pathophysiology of psoriasis, the sequence of how these pathognomonic changes arise is not completely understood.

Psoriasis is mainly studied as an autoimmune condition [5]; nevertheless, other potential triggers of psoriasis have been evaluated. The skin epidermis has been identified as a key player in the early pathogenic steps of psoriasis by contributing to the activation of the immune response as well as the recruitment of inflammatory and endothelial cells [6]. Moreover, the elucidation of the major influence exerted by the psoriasis susceptibility gene has allowed for a fine tuning of the understanding of the pathophysiology of psoriasis [7–9].

This extensive review aims to discuss the contributions of immune cells and keratinocytes to the pathogenesis of psoriasis and to highlight the specificity of each category.

Results

We conducted a review of the literature investigating the role of keratinocytes and immune cells in the pathogenesis of psoriasis. The primary review of the scientific literature was conducted in PubMed, Science Direct, and Google Scholar. Mesh terms used were "psoriasis," "pathophysiology," "pathogenesis," "keratinocyte," "PSORS," "genetics," "immunity" and "HLA." The Boolean operators used were AND and OR. No exclusion criteria were defined. The pertinence of each article was evaluated with an attentive and critical view regarding the type and content of the article, the date of publication, and the impact factor of the publishing journal.

Psoriasis: An Immune-Driven Disease

Loci within the Major Histocompatibility Complex Confer the Risk of Psoriasis

In view of its association with multiple diseases, ranging from autoimmune to malignant diseases [10], the major histocompatibility complex (MHC) located on the short arm of chromosome 6 is one of the most studied areas of the human genome. Among all the MHC loci, the best characterized is undoubtedly the classic human leukocyte antigen (HLA). It has long been established that the HLA is associated with psoriasis [11]. The MHC is recognized as a major susceptibility locus for psoriasis; indeed, class I molecules on antigen-presenting cells are involved in activating T cells that are crucial in psoriasis pathophysiology [12].

Within the MHC class 1 region, psoriasis susceptibility locus 1 (*PSORS1*) is the most significant genetic determinant of psoriasis [13]. This locus accounts for 50% of the genetic variance in psoriasis [14]. Patients with early-onset psoriasis exhibit HLA-Cw6 allele variability in the HLA-C locus, compared to patients with sporadic, late-onset psoriasis [7, 15]. The presence of HLA-Cw6 has been shown to affect different aspects of psoriasis, including genetic susceptibility, clinical manifestation, comorbidity, and treatment efficacy [16]. HLA may prime the immune response and in addition HLA-C is a subunit of MHC I, which allows antigen presentation to CD8+ T cells and regulates their activation, proliferation, and cytotoxicity (according to the Cluster 17 Collaboration, 2005). However, given the complex nature of psoriasis pathogenesis more studies are needed to elucidate the functional role of HLA-Cw6 in psoriasis.

Characterization of the Main Skin-Infiltrating Immune Cells in Psoriasis

The predominant cell type in human skin is the keratinocyte. Skin turnover involves a series of programmed changes that transform basal keratinocytes into anucleate corneocytes. This transformation occurs over the span of approximately 50 days in healthy skin but takes only 5 days in lesional psoriatic skin – a testament to the increased cell turnover in this disease [17]. Various other cells with immunoregulatory properties lie interspersed among keratinocytes [18].

Plasmacytoid Dendritic Cells

Although the pathophysiology of psoriasis remains to be fully elucidated, the roles of various cells in the development of psoriasis have been described [18]. A crucial cell in the initiation phase of psoriasis is the plasmacytoid dendritic cell (PDC). Viral and bacterial particles can stimulate PDCs by activating toll-like receptor (TLR)7 and TLR9, the secretion of type 1 IFN-α [19] bringing about the inflammatory response associated with psoriasis through the activation of myeloid dendritic cells (MDCs) [20].

Understanding the role of TLRs is pivotal in unraveling the pathophysiology of psoriasis. TLRs are fundamental to the ability of dendritic cells to recognize antimicrobial particles and influence the adaptive immune system [21]. TLR7 and TLR9 are highly homologous [22], but the recognition of unmethylated CpG DNA expressed by bacteria is attributed to TLR9 [23], and the recognition of imidazoquinoline-like viral RNA particles is attributed to TLR7 [22].

Downloaded from http://karger.com/drm/article-pdf/235/2/91/2663712/000495291.pdf by guest on 19 April 2024

The mechanism by which PDCs initiate a psoriasiform reaction can be partly explained by observational studies conducted with imiquimod [24, 25] – a synthetic imidazoquinoline recognized by TLR7 [22]. Application of imiquimod to nonlesional skin of susceptible patients [25] induces PDCs to release type I IFN-α [24, 25] and interferon regulatory factor 7 (IRF7) [26]. This response is similar to that observed when PDCs recognize bacterial and viral peptides [24, 25].

The antimicrobial peptide, LL37, is identified as a key activator of PDCs in vivo. It has been suggested that the release of LL37 by activated keratinocytes and the subsequent binding of the molecule to self-DNA in susceptible individuals might cause conformational changes to the bound DNA molecule, transforming this otherwise innocuous molecule into an aggregated, dense structure that is recognized by early ribosomal TLR9, which results in IFN-α production, but not PDC maturation [27, 28]. Consequently, LL37-activated PDCs migrate into the epidermis, where they recognize keratinocyte-expressed autoantigens, which might then perpetuate the pathogenic mechanism. This hypothesis suggests that dysregulated LL37 might be the link between keratinocytes and PDCs in the pathophysiology of psoriasis [28]. LL37 is also associated with the activation of both CD4+ and CD8+ LL37-specific psoriatic T cells through its interaction with HLA-DR and class-I alleles [27].

Myeloid Dendritic Cells

In addition to PDC activation, MDCs are activated by other triggering factors, such as the skin microbiome, drugs, and trauma. These factors can stimulate keratinocytes to release CCL20, leading to PDC-independent MDC activation and T-helper 17 (Th17) cell recruitment [29]. Once activated, MDCs orchestrate the inflammatory phases of psoriasis. Psoriatic skin is dominated by two subtypes of MDC, namely CD11c+BDCA-1+ (which is also found in normal skin) and pathogenic CD11c+BDCA-1–. Both MDC subtypes secrete interleukin (IL)-12, a chemokine involved in T-cell proliferation and the polarization of Th1 cells [30]. BDCA-1 MDCs, referred to as "inflammatory MDCs," are responsible for the IL-23-mediated stimulation of Th17 cells, which subsequently release IL-17, IL-22, and INF-γ [30]. Inflammatory MDCs also co-express cytokines, including tumor necrosis factor α (TNF-α), enzyme inducible nitric oxide synthetase (iNOS), and IL-12, which are all well-known mediators of inflammation. TNF-α (also produced by keratinocytes) not only activates MDCs and Langerhans cells but also stimulates the transformation of macrophages to dendritic cells [31].

Myeloid Dendritic Cells: The IL-12/IL-23 and IL-17 Axis. The IL-12/IL-23 pathway has been highlighted in the pathophysiology of psoriasis [32]. IL-12 is a heterodimer, composed of IL-12p35 and IL-12p40 subunits. These subunits can stimulate Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2), upregulating the signal transducer of transcription (STAT) transcription factors, particularly STAT4 [32]. IL-12 skews the differentiation of naïve CD4 cells to IFN-γ-secreting Th1 [33].

Similar to IL-12, IL-23 is a heterodimer, composed of IL-12p40 (IL-12B) and IL-23p19 (IL-12A) subunits. IL-23 is highly expressed in psoriatic skin [34]. IL-23 is also involved in the induction of JAK2 and TYK2, resulting in the preferential upregulation of STAT3 [33]. Sources of IL-23 include monocytes (also under the influence of CCL20 [29]) in the dermis, and keratinocytes and Langerhans cells in the epidermis. Binding of IL-23 to the IL-23 receptor expressed by Th17 cells triggers intracellular downstream signaling that results in the production of IL-17A (the most potent IL-17 activator [35]) and IL-17F [36] (less potent than IL-17A, despite being 50% homologous [35]). On the other hand, IL-12 receptor activation leads to Th1 maturation and IFN-γ secretion [33].

This pathological cycle is completed by the IL-17A- and IL-17F-mediated activation of epidermal keratinocytes, which subsequently release a barrage of inflammatory mediators, including (but not limited to) IL-8 and chemokine CXC ligands (CXCL) 2, 3, 9, 10, 11, and 20. This culminates in the attraction of more T cells into the dermis and epidermis [37]. IL-23 also drives IL-17 synthesis in dermal γδT cells, which further expands the Th17 pool [38]. The influence of IL-17 extends beyond T cells. The chemokine has pleiotropic effects on keratinocytes and fibroblasts, which subsequently upregulate mediators of inflammation, such as IL-6, IL-1β, TNF-α, granulocyte-macrophage colony stimulating factor, matrix metalloproteinases, and antimicrobial peptides. This upregulation results in the recruitment of neutrophils, lymphocytes, and myeloid cells to the area [37].

Biologics targeting the IL-12/IL-23/IL-17 axis are therapeutic modalities for the treatment of psoriasis [5]. Ustekinumab is a human MAB targeting IL-12p40, a subunit shared by both IL-12 and IL-23 [39]. Tildrakizumab is a humanized IgG1/κ MAB, which has high affinity for IL-23p19, but no affinity for IL-12 or IL-23p40 [40]. Secukinumab is a first-in-class IgG1κ, fully human MAB targeting IL-17A [41]. Ixekizumab is a humanized IgG4 MAB that neutralizes IL-17A [42]. Brodalumab is a fully human, IgG2 anti-Il-17RA MAB, which binds IL-17RA with high affinity; this activity impedes the interaction

Downloaded from http://karger.com/drm/article-pdf/235/2/91/2663712/000495291.pdf by guest on 19 April 2024

between the receptor and IL-17A/E/F, which thereby disrupts the IL-17 pathway [43] (Appendix).

Myeloid Dendritic Cells: The TNF-α Axis. The role of TNF-α in psoriasis cannot be underestimated. TNF recognizes two receptors: TNFR1 which is universally expressed, and TNFR2, which is expressed in lymphocytes, endothelial cells, and neurons. TNFR1 and TNFR2 bind both TNF-α and lymphotoxin-α [44]. TNF-α induces the expression of endothelial adhesion molecules ECAM and ICAM on dermal endothelial cells. The latter subsequently release CCL20, thereby stimulating MDCs. The TNF-α-driven CCL20 release is mediated by keratinocytes and dermal fibroblasts [45]. Upregulation of these proinflammatory cytokines by TNF-α is facilitated through the activation of Nf-κB [46] – a transcription factor that is constitutively activated in psoriatic epidermis [47]. Elevated levels of Nf-κB facilitate keratinocyte hyperproliferation by inhibiting the cell cycle regulator protein, phosphatase 6, via the upregulation of the microRNA miR-31 [47]. Three TNF-α inhibitors are approved for the treatment of psoriasis: infliximab, adalimumab, and etanercept. Infliximab and adalimumab are bivalent IgG1 MABs, which bind the Fc portions.

T Lymphocytes

The success of cyclosporine A for treating psoriasis [48, 49] highlights the crucial role played by T cells in the pathophysiology of psoriasis [50]. The rapid immunosuppressive action of cyclosporine is related to the suppression of T lymphocytes and the subsequent drop in IL-2 levels [48]. These observations led to the notion that psoriasis was a T-cell-mediated disease [51]. However, the concept of psoriasis as a strictly Th1/Th2 disease has been recently challenged by the discovery of other T cells such as CD4+ Th17 cells (which produce IL-17 [65], IL-23 [52], IL-22 [53], IFN-γ, and TNF-α) and Th22 cells which produce IL-22 exclusively. Elevated plasma IL-22 levels have been associated with a worse disease severity [53]. Th22 cells may work in concert with other IL-22-producing cells in the epithelium, such as NK22 cells [53], and normalization of IL-22, IL-17, and INF-γ mRNA levels [54].

Other T cells involved in the pathophysiology of psoriasis include the dermal γδ [55], dendritic epidermal [56], and Vγ9Vδ2 [38] cells. Dermal γδ T cells constitutively express IL-23 receptors, making them susceptible to the actions of cytokines and the subsequent release of IL-17. Cutaneous antigen-positive and CCR-6-positive Vγ9Vδ2 T cells were shown to gravitate towards stressed skin, activating keratinocytes by the release of IL-17A and subsequently, TNF-α and INF-γ. Successful treatment of active psoriatic plaques results in the elevation of circulating Vγ9Vδ2 T cells to normal levels, suggesting that the Vγ9Vδ2 T cells were redistributed from skin lesions to the peripheral circulation [38]. At the opposite end of the spectrum, in patients with chronic plaque psoriasis, CD-25^{high}, CTLA-4^{+}, and Fox3^{high} (CD4^{+}CD25^{high}) cells, known as regulatory T cells, are deficient in their capacity as T-cell response suppressors [57].

On another note, T-cell-mediated molecular mimicry has been suggested as a potential explanation for the close relationship between the skin microbiome [58] and psoriasis. The streptococcal M surface antigens are known to be highly homologous to human keratins, particularly type 1 keratin [59]. This homology can result in cross-reactivity with subsequent T-cell-mediated responses [60].

Psoriasis: A Keratinocyte-Driven Disease

Intrinsic alterations in epidermal keratinocytes might also contribute to various aspects of psoriasis pathogenesis in an autocrine or paracrine manner. This potential contribution has further challenged the concept of psoriasis as a disease mediated exclusively by T-cell activation [18, 61]. This theory is supported by murine models in which transgenic mice lacking B and T lymphocytes were transplanted with either healthy or nonlesional skin, but only developed a psoriasiform reaction in the former subset of mice upon the injection of immunocytes [62].

The Immunomodulatory Functions of Keratinocytes

The epidermal barrier is the first line of defense against skin injury and invading pathogens. Keratinocytes are a major source of inhibitory cytokines. These cytokines allow the skin to remain inflammatory quiescent, in the absence of triggers that would otherwise activate local dendritic cells [63]. However, an imbalance between anti- and proinflammatory signals may lead to the development of chronic inflammatory skin diseases, such as psoriasis and atopic dermatitis [61]. Through the cell surface receptors, keratinocytes are also able to regulate the immune response. As mentioned previously, psoriatic skin is infiltrated by various immune cells [18]. Moreover, upon activation, keratinocytes can indirectly attract immune cells into the skin through the release of potent chemokines. The role of CXCL8 has been highlighted, as it is believed to be responsible for the accumulation of intraepidermal neutrophils [64]. Other cytokines, such as CCL2, CCL5, CXCL10, and CXCR3 ligands, predominantly attract monocytes and Th1 cells [65]. In contrast,

Downloaded from http://karger.com/drm/article-pdf/235/2/91/2663712/000495291.pdf by guest on 19 April 2024

CCL20 and IL-18 recruit Langerhans cells, dendritic cells, and CLA+ T cells [66, 67].

Another important role of keratinocytes is their ability to function as antigen-presenting cells initiating or enhancing the activity of immune cells by expressing HLA antigens [68]. As mentioned previously, HLA-Cw 0602 is the disease allele in the *PSORS1* locus [69]. It is known that keratinocytes can express class I and II HLA antigens upon stimulation [70, 71], but the function of this ability in the pathogenesis of psoriasis remains to be understood.

Cell surface receptors enable keratinocytes to play an important role as key regulators of both the innate immunity as well as in adaptive immunity. These receptors interact with conserved microbial structures, referred to as pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide and CpG DNA. The TLR family is the most important group of cell surface receptors expressed, mainly by immune cells and keratinocytes, under pathological conditions [72, 73]. TLR expression in psoriatic epidermis has been studied, but the results have not provided a coherent picture. In one study, TLR2 expression was enhanced in the upper epidermis in psoriasis, but expression was stronger in the lower layers of normal and nonlesional skin [74]. Another study showed that TLR5 expression was reduced in basal keratinocytes of lesional psoriatic skin when compared to normal skin [75]. Yet another study showed that TLR1 was highly expressed in the psoriatic epidermis [76]. Beyond the essential role of TLRs in both innate immune responses and adaptive immune systems, the functional roles of TLR expression in keratinocytes remain to be investigated.

Intrinsic alterations in epidermal keratinocytes may be involved in regulating major inflammatory pathways. This notion was illustrated in a transgenic mouse model, which carried an epidermal keratinocyte-specific deletion of IκB, a negative regulator of the NF-κB transduction pathway, which is involved in the synthesis of important proinflammatory cytokines. Those mice developed a severe inflammatory skin disease shortly after birth [77].

The idea of the epidermis as the primary site for orchestrating epidermal and distant inflammation associated with skin inflammatory disease was also substantiated in studies with transgenic mice models. By studying transgenic mice with the deletion of tristetraprolin (TTP/Zfp36; a keratinocyte-specific gene), Andrianne et al. [78] illustrate how TTP acts as an RNA-binding protein that downregulates the expression of genes that encode proinflammatory cytokines in the skin epidermis. Such mice developed a psoriasiform phenotype associated with a strong inflammatory reaction. Furthermore, this inflammatory reaction did not occur when TTP was specifically deleted in immune cells, such as dendritic cells or leucocytes. In another transgenic murine model, mice depleted of the IL-1 antagonist receptor (IL1rn) (an endogenous inhibitor of the proinflammatory cytokine, IL-1) developed severe psoriasis-like disease that histologically mimicked human psoriatic skin. Moreover, the researchers demonstrate that this psoriasis-like disease developed in a TNF-α dependent manner [79]. Interestingly, this psoriasis-like disease also occurred in *IL-1rn*–/– SCID mice [80]. Consequently, such data suggested that T lymphocytes are not essential for the development of psoriasis.

Keratinocyte Autoantigen Loop in Psoriasis

The recently described "psoriasis autoantigens" LL37 [27] (cathelicidin – an antimicrobial peptide) and a disintegrin-like and metalloprotease domain containing thrombospondin type 1 motif-like 5 (ADAMTSL5) might shed new insights into the pathophysiological mechanism of psoriasis. Autoantigens can be described as chemokines released by native cells which initiate or sustain a pathological state against self.

ADAMTSL5, previously thought to be related exclusively to melanocytes, was found to be highly expressed by keratinocytes and playing a role in the activation of IL-17-realeasing psoriatic cells [81] as well as microfibril modulation [82]. LL37 and ADAMTSL5 are both potential antigens found at significantly higher concentrations in lesional skin, but they are also expressed by immune cells that are classically associated with psoriasis, namely, dendritic cells and macrophages [83]. These autoantigens also appear to be under the influence of well-established psoriatic treatment, with the concentration of ADAMTSL5 and LL37 downregulated by etanercept, ixekizumab, and brodalumab [83].

Self-DNA can also be considered as a psoriasis autoantigen by virtue of its potential to activate PDCs after undergoing electrostatic LL37-induced conformational changes which subsequently allow the molecule to interact with the cells' TLR9 receptors [28]. LL37 is also able to form complexes with self-RNA, which then interact with TLR7 and TLR8, activating both PDCs and classical myeloid dendritic cells, respectively [84]. Interestingly, complexes of LL37 and self-DNA and self-RNA released at sites of trauma may partly explain the isomorphic phenomenon in psoriasis [85].

The Proangiogenic Role of Keratinocytes

Keratinocytes are a reservoir of growth factors for endothelial cells such as vascular endothelial growth factor

Downloaded from http://karger.com/drm/article-pdf/235/2/91/2663712/000495291.pdf by guest on 19 April 2024

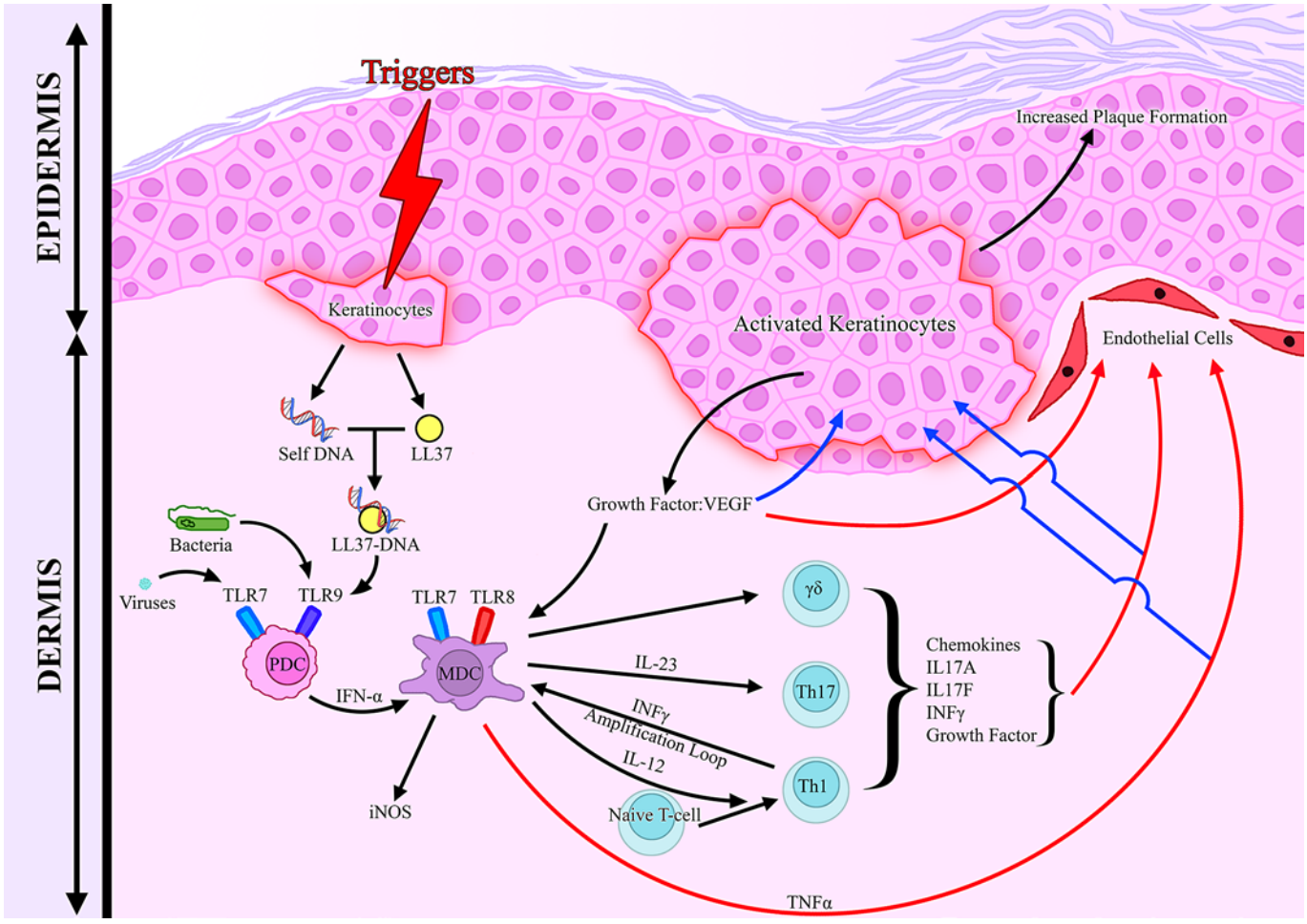

Fig. 1. Summary of the main pathogenesis steps leading to psoriasis plaque formation.

(VEGF), hypoxia-inducible factors, angiopoietins, and proangiogenic cytokines, such as TNF-α, IL-8, and IL-17 [86].

Proangiogenic VEGF is the main factor overexpressed in psoriatic skin. VEGF can be released by activated keratinocytes and immune cells [87], contributing to an increase in the density of psoriatic dermal capillaries, in addition to enhanced permeability and dilatation [88]. Dilated capillaries support a pathologically hyperproliferative epidermis and regulate immune cell trafficking by expressing intercellular adhesion molecules (ICAM-1). In addition to its proangiogenic effects, VEGF can act in an autocrine manner and stimulate the proliferation of tumor cells in skin malignancies [89, 90]. A potential autocrine effect of VEGF on keratinocytes remains to be investigated.

Altered Proliferation and Differentiation in Psoriatic Keratinocytes

Epidermal homeostasis is maintained by a tightly regulated balance of renewal and differentiation processes [91]. This homeostatic balance is disturbed in chronic inflammatory diseases, such as psoriasis, leading to abnormal differentiation associated with a shortened cellular turnover time [92].

PSORS4 is a psoriasis susceptibility gene in the chromosome 1q21 region. The 1q21 region harbors the epidermal differentiation complex (EDC) [93], which contains major genes involved in epidermal differentiation. EDC genes are divided into 3 main families that encode (a) the cornified envelope precursor proteins (loricrin, involucrin, small proline-rich proteins, and the family of late cornified envelope proteins), (b) the keratin filament-

Downloaded from http://karger.com/drm/article-pdf/235/2/91/2663712/000495291.pdf by guest on 19 April 2024

associated proteins (filaggrin, trichohyalin, repetin, hornerin, and cornulin), and (c) the S100 calcium-binding proteins [94]. Altered epidermal differentiation is an important hallmark of psoriatic skin; therefore, the EDC genes have been considered psoriasis gene candidates.

Psoriatic skin has exhibited overexpression of the calcium-binding proteins, S100A7, S100A8, and S100A9 [95]. S100 proteins are key regulators of intra- and extracellular biological pathways that regulate cell proliferation, differentiation, death, and immune responses. S100A8/S100A9 proteins, referred to as the calprotectin complex, were shown to be overexpressed in a transgenic murine model of psoriasis, which lacked epidermal expression of cJun and JunB [96, 97]. cJun and JunB belong to the transcriptional factor activator protein 1 (AP-1) family, which includes dimers principally composed of the critical epidermal homeostatic factors, Jun and Fos [98]. Interestingly, *JunB* is located in the *PSORS6* locus [96]. As previously mentioned, the psoriasis phenotype was observed in *Rag-2* mice, which have epidermal deletions of cJun and JunB. This observation suggested that dysregulated AP-1 activity might be causally involved in the initiation of disease development, before inflammation takes place [96].

During the psoriasis process, keratinocyte growth is promoted through the activation of an autocrine loop. This loop involves various growth factors, such as insulin-like growth factor, keratinocyte growth factor, transforming growth factor α (TGF-α), amphiregulin, and members of the inhibitory TGF-β family [99, 100].

Conclusions

Psoriasis remains one of the most researched chronic inflammatory skin diseases [101, 102]. Early murine models of psoriasis and response of disease to immunosuppressive therapies supported the idea of psoriasis as a T-cell disease.

Despite the undisputed fact that activated T cells are crucial to the development and persistence of psoriatic lesions, the disease pathophysiology cannot be explained by the role of T lymphocytes exclusively. Other resident skin cells, including (but not limited to) keratinocytes and dendritic cells, contribute to the development of psoriatic plaques. This cellular contribution is combined with a strong, complex genetic influence.

In this review, we have highlighted, and attempted to associate, the major scientific breakthroughs that have revealed clues to the pathophysiology of psoriasis. We aimed to provide order to the various pathophysiological mechanisms that contribute to the development of psoriatic plaques (Fig. 1). The exact sequence of events that lead to the initiation of the psoriasis cascade remains unknown, but the identification of early triggers and the role played by keratinocytes may provide novel, promising therapeutic targets for the prevention and control of psoriasis.

Key Message

Keratinocytes and immune cells play key roles in the pathogenesis of psoriasis.

Acknowledgments

We would like to thank Dr. Muscat Gordon (Department of Medicine, Mater Dei Hospital, Msida), who helped with the design of Figure 1.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

F.B. designed the structure of the manuscript. F.B. and D.M. wrote the manuscript. V.M. supervised the redaction of the manuscript.

Appendix

IL-12/23 and IL-17 are therapeutic targets of psoriasis.

Monoclonal antibody target	Therapeutic agents
IL-12p40	Ustekinumab
IL-23p40	Briakinumab
IL-23p19	Tildrakizumab
	Guselkumab
IL-17A	Secukinumab
	Ixekizumab
IL-17RA	Brodalumab

Downloaded from http://karger.com/drm/article-pdf/235/2/91/2663712/000495291.pdf by guest on 19 April 2024

References

1 Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis. 2005 Mar;64 Suppl 2:ii18–23.
2 Bhosle MJ, Kulkarni A, Feldman SR, Balkrishnan R. Quality of life in patients with psoriasis. Health Qual Life Outcomes. 2006 Jun; 4(1):35.
3 Heng MC, Kloss SG, Kuehn CS, Chase DG. The sequence of events in psoriatic plaque formation after tape-stripping. Br J Dermatol. 1985 May;112(5):517–32.
4 McKee PH, Calonje E, Granter SR: Pathology of the skin: with clinical correlations. 3rd ed. 2011 September 15.
5 Krueger G, Ellis CN. Psoriasis—recent advances in understanding its pathogenesis and treatment. J Am Acad Dermatol. 2005 Jul; 53(1 Suppl 1):S94–100.
6 Reich K, Papp KA, Matheson RT, Tu JH, Bissonnette R, Bourcier M, et al. Evidence that a neutrophil-keratinocyte crosstalk is an early target of IL-17A inhibition in psoriasis. Exp Dermatol. 2015 Jul;24(7):529–35.
7 Elder JT, Nair RP, Henseler T, Jenisch S, Stuart P, Chia N, et al. The genetics of psoriasis 2001: the odyssey continues. Arch Dermatol. 2001 Nov;137(11):1447–54.
8 Chandran V. Genetics of psoriasis and psoriatic arthritis. Indian J Dermatol. 2010 Apr-Jun;55(2):151–6.
9 Bowcock AM. The genetics of psoriasis and autoimmunity. Annu Rev Genomics Hum Genet. 2005;6(1):93–122.
10 Petersdorf EW. The major histocompatibility complex: a model for understanding graft-versus-host disease. Blood. 2013 Sep;122(11): 1863–72.
11 Russell TJ, Schultes LM, Kuban DJ. Histocompatibility (HL-A) antigens associated with psoriasis. N Engl J Med. 1972 Oct; 287(15):738–40.
12 Capon F, Barker JN. The quest for psoriasis susceptibility genes in the postgenome-wide association studies era: charting the road ahead. Br J Dermatol. 2012 Jun;166(6):1173–5.
13 Jenisch S, Henseler T, Nair RP, Guo SW, Westphal E, Stuart P, et al. Linkage analysis of human leukocyte antigen (HLA) markers in familial psoriasis: strong disequilibrium effects provide evidence for a major determinant in the HLA-B/-C region. Am J Hum Genet. 1998 Jul;63(1):191–9.
14 Clop A, Bertoni A, Spain SL, Simpson MA, Pullabhatla V, Tonda R, et al. An in-depth characterization of the major psoriasis susceptibility locus identifies candidate susceptibility alleles within an HLA-C enhancer element. PLoS One. 2013 Aug;8(8):e71690.
15 Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. J Am Acad Dermatol. 1985 Sep;13(3):450–6.
16 Gulliver WP, Macdonald D, Gladney N, Alaghehbandan R, Rahman P, Adam Baker K. Long-term prognosis and comorbidities associated with psoriasis in the Newfoundland and Labrador founder population. J Cutan Med Surg. 2011 Jan-Feb;15(1):37–47.
17 Li J, Li X, Hou R, Liu R, Zhao X, Dong F, et al. Psoriatic T cells reduce epidermal turnover time and affect cell proliferation contributed from differential gene expression. J Dermatol. 2015 Sep;42(9):874–80.
18 Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. Annu Rev Immunol. 2014;32(1):227–55.
19 Liu YJ. IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. Annu Rev Immunol. 2005; 23(1):275–306.
20 Nestle FO, Conrad C, Tun-Kyi A, Homey B, Gombert M, Boyman O, et al. Plasmacytoid predendritic cells initiate psoriasis through interferon-alpha production. J Exp Med. 2005 Jul;202(1):135–43.
21 Iwasaki A, Medzhitov R. Toll-like receptor control of the adaptive immune responses. Nat Immunol. 2004 Oct;5(10):987–95.
22 Takeda K, Kaisho T, Akira S. Toll-like receptors. Annu Rev Immunol. 2003;21(1):335–76.
23 Hemmi H, Kaisho T, Takeda K, Akira S. The roles of Toll-like receptor 9, MyD88, and DNA-dependent protein kinase catalytic subunit in the effects of two distinct CpG DNAs on dendritic cell subsets. J Immunol. 2003 Mar;170(6):3059–64.
24 Gilliet M, Conrad C, Geiges M, Cozzio A, Thürlimann W, Burg G, et al. Psoriasis triggered by toll-like receptor 7 agonist imiquimod in the presence of dermal plasmacytoid dendritic cell precursors. Arch Dermatol. 2004 Dec;140(12):1490–5.
25 Vinter H, Iversen L, Steiniche T, Kragballe K, Johansen C. Aldara®-induced skin inflammation: studies of patients with psoriasis. Br J Dermatol. 2015 Feb;172(2):345–53.
26 Honda K, Ohba Y, Yanai H, Negishi H, Mizutani T, Takaoka A, et al. Spatiotemporal regulation of MyD88-IRF-7 signalling for robust type-I interferon induction. Nature. 2005 Apr;434(7036):1035–40.
27 Lande R, Botti E, Jandus C, Dojcinovic D, Fanelli G, Conrad C, et al. The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. Nat Commun. 2014 Dec;5(1):5621.
28 Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. Nature. 2007 Oct; 449(7162):564–9.
29 Kennedy-Crispin M, Billick E, Mitsui H, Gulati N, Fujita H, Gilleaudeau P, et al. Human keratinocytes' response to injury upregulates CCL20 and other genes linking innate and adaptive immunity. J Invest Dermatol. 2012 Jan;132(1):105–13.
30 Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, Abello MV, Novitskaya I, Pierson KC, et al. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. J Invest Dermatol. 2009 Jan;129(1):79–88.
31 Lowes MA, Chamian F, Abello MV, Fuentes-Duculan J, Lin SL, Nussbaum R, et al. Increase in TNF-alpha and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). Proc Natl Acad Sci USA. 2005 Dec;102(52): 19057–62.
32 Toichi E, Torres G, McCormick TS, Chang T, Mascelli MA, Kauffman CL, et al. An anti-IL-12p40 antibody down-regulates type 1 cytokines, chemokines, and IL-12/IL-23 in psoriasis. J Immunol. 2006 Oct;177(7):4917–26.
33 Teng MW, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM, et al. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med. 2015 Jul;21(7):719–29.
34 Piskin G, Sylva-Steenland RM, Bos JD, Teunissen MB. In vitro and in situ expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. J Immunol. 2006 Feb;176(3):1908–15.
35 Malakouti M, Brown GE, Wang E, Koo J, Levin EC. The role of IL-17 in psoriasis. J Dermatolog Treat. 2015 Feb;26(1):41–4.
36 Kikly K, Liu L, Na S, Sedgwick JD. The IL-23/Th(17) axis: therapeutic targets for autoimmune inflammation. Curr Opin Immunol. 2006 Dec;18(6):670–5.
37 Lowes MA, Russell CB, Martin DA, Towne JE, Krueger JG. The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. Trends Immunol. 2013 Apr;34(4): 174–81.
38 Cai Y, Shen X, Ding C, Qi C, Li K, Li X, et al. Pivotal role of dermal IL-17-producing γδ T cells in skin inflammation. Immunity. 2011 Oct;35(4):596–610.
39 Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al.; PHOENIX 2 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008 May;371(9625):1675–84.
40 Papp K, Thaçi D, Reich K, Riedl E, Langley RG, Krueger JG, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. Br J Dermatol. 2015 Oct;173(4):930–9.
41 Garnock-Jones KP. Secukinumab: a review in moderate to severe plaque psoriasis. Am J Clin Dermatol. 2015 Aug;16(4):323–30.

Downloaded from http://karger.com/drm/article-pdf/235/2/91/2663712/000495291.pdf by guest on 19 April 2024

42 Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012 Mar;366(13):1190–9.
43 Bauer E, Lucier J, Furst DE. Brodalumab -an IL-17RA monoclonal antibody for psoriasis and psoriatic arthritis. Expert Opin Biol Ther. 2015 Jun;15(6):883–93.
44 Eissner G, Kolch W, Scheurich P. Ligands working as receptors: reverse signaling by members of the TNF superfamily enhance the plasticity of the immune system. Cytokine Growth Factor Rev. 2004 Oct;15(5):353–66.
45 Fantuzzi F, Del Giglio M, Gisondi P, Girolomoni G. Targeting tumor necrosis factor alpha in psoriasis and psoriatic arthritis. Expert Opin Ther Targets. 2008 Sep;12(9):1085–96.
46 Moorchung N, Kulaar JS, Chatterjee M, Vasudevan B, Tripathi T, Dutta V. Role of NF-κB in the pathogenesis of psoriasis elucidated by its staining in skin biopsy specimens. Int J Dermatol. 2014 May;53(5):570–4.
47 Yan S, Xu Z, Lou F, Zhang L, Ke F, Bai J, et al. NF-κB-induced microRNA-31 promotes epidermal hyperplasia by repressing protein phosphatase 6 in psoriasis. Nat Commun. 2015 Jul;6(1):7652.
48 Rebora A. Cyclosporine A in psoriasis. Clin Dermatol. 1991 Oct-Dec;9(4):515–22.
49 Mueller W, Herrmann B. Cyclosporin A for psoriasis. N Engl J Med. 1979 Sep;301(10):555.
50 Valdimarsson H, Bake BS, Jónsdótdr I, Fry L. Psoriasis: a disease of abnormal Keratinocyte proliferation induced by T lymphocytes. Immunol Today. 1986 Sep;7(9):256–9.
51 Voorhees JJ. Pathophysiology of psoriasis. Annu Rev Med. 1977;28(1):467–73.
52 Volpe E, Servant N, Zollinger R, Bogiatzi SI, Hupé P, Barillot E, et al. A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T(H)-17 responses. Nat Immunol. 2008 Jun;9(6):650–7.
53 Duhen T, Geiger R, Jarrossay D, Lanzavecchia A, Sallusto F. Production of interleukin 22 but not interleukin 17 by a subset of human skin-homing memory T cells. Nat Immunol. 2009 Aug;10(8):857–63.
54 Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol. 2008 May;128(5):1207–11.
55 Sumaria N, Roediger B, Ng LG, Qin J, Pinto R, Cavanagh LL, et al. Cutaneous immunosurveillance by self-renewing dermal gammadelta T cells. J Exp Med. 2011 Mar;208(3):505–18.
56 Heath WR, Carbone FR. Dendritic cell subsets in primary and secondary T cell responses at body surfaces. Nat Immunol. 2009 Dec;10(12):1237–44.
57 Sugiyama H, Gyulai R, Toichi E, Garaczi E, Shimada S, Stevens SR, et al. Dysfunctional blood and target tissue CD4+CD25high regulatory T cells in psoriasis: mechanism underlying unrestrained pathogenic effector T cell proliferation. J Immunol. 2005 Jan;174(1):164–73.
58 Benhadou F, Mintoff D, Schnebert B, Thio HB. Psoriasis and Microbiota: A Systematic Review. Diseases. 2018 Jun;6(2):6.
59 McFadden J, Valdimarsson H, Fry L. Cross-reactivity between streptococcal M surface antigen and human skin. Br J Dermatol. 1991 Nov;125(5):443–7.
60 Valdimarsson H, Baker BS, Jónsdóttir I, Powles A, Fry L. Psoriasis: a T-cell-mediated autoimmune disease induced by streptococcal superantigens? Immunol Today. 1995 Mar;16(3):145–9.
61 Albanesi C, De Pità O, Girolomoni G. Resident skin cells in psoriasis: a special look at the pathogenetic functions of keratinocytes. Clin Dermatol. 2007 Nov-Dec;25(6):581–8.
62 Wrone-Smith T, Nickoloff BJ. Dermal injection of immunocytes induces psoriasis. J Clin Invest. 1996 Oct;98(8):1878–87.
63 Salmon JK, Armstrong CA, Ansel JC. The skin as an immune organ. West J Med. 1994 Feb;160(2):146–52.
64 Nickoloff BJ, Turka LA. Immunological functions of non-professional antigen-presenting cells: new insights from studies of T-cell interactions with keratinocytes. Immunol Today. 1994 Oct;15(10):464–9.
65 Gillitzer R, Wolff K, Tong D, Müller C, Yoshimura T, Hartmann AA, et al. MCP-1 mRNA expression in basal keratinocytes of psoriatic lesions. J Invest Dermatol. 1993 Aug;101(2):127–31.
66 Homey B, Wang W, Soto H, Buchanan ME, Wiesenborn A, Catron D, et al. Cutting edge: the orphan chemokine receptor G protein-coupled receptor-2 (GPR-2, CCR10) binds the skin-associated chemokine CCL27 (CTACK/ALP/ILC). J Immunol. 2000 Apr;164(7):3465–70.
67 Homey B, Dieu-Nosjean MC, Wiesenborn A, Massacrier C, Pin JJ, Oldham E, et al. Up-regulation of macrophage inflammatory protein-3 alpha/CCL20 and CC chemokine receptor 6 in psoriasis. J Immunol. 2000 Jun;164(12):6621–32.
68 Sugita K, Kabashima K, Atarashi K, Shimauchi T, Kobayashi M, Tokura Y. Innate immunity mediated by epidermal keratinocytes promotes acquired immunity involving Langerhans cells and T cells in the skin. Clin Exp Immunol. 2007 Jan;147(1):176–83.
69 Nair RP, Stuart PE, Nistor I, Hiremagalore R, Chia NV, Jenisch S, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet. 2006 May;78(5):827–51.
70 Gottlieb AB, Lifshitz B, Fu SM, Staiano-Coico L, Wang CY, Carter DM. Expression of HLA-DR molecules by keratinocytes, and presence of Langerhans cells in the dermal infiltrate of active psoriatic plaques. J Exp Med. 1986 Oct;164(4):1013–28.
71 Hoos A, D'Incan C, Gissmann L, Altmann A, Momburg F, Nindl I, et al. Human papillomavirus type 16 (HPV 16) E7 and major histocompatibility complex (MHC) class I and II expression in human keratinocytes in culture. Arch Virol. 1996;141(3-4):449–58.
72 Mempel M, Voelcker V, Köllisch G, Plank C, Rad R, Gerhard M, et al. Toll-like receptor expression in human keratinocytes: nuclear factor kappaB controlled gene activation by Staphylococcus aureus is toll-like receptor 2 but not toll-like receptor 4 or platelet activating factor receptor dependent. J Invest Dermatol. 2003 Dec;121(6):1389–96.
73 McInturff JE, Modlin RL, Kim J. The role of toll-like receptors in the pathogenesis and treatment of dermatological disease. J Invest Dermatol. 2005 Jul;125(1):1–8.
74 Baker BS, Ovigne JM, Powles AV, Corcoran S, Fry L. Normal keratinocytes express Toll-like receptors (TLRs) 1, 2 and 5: modulation of TLR expression in chronic plaque psoriasis. Br J Dermatol. 2003 Apr;148(4):670–9.
75 Miller LS, Sørensen OE, Liu PT, Jalian HR, Eshtiaghpour D, Behmanesh BE, et al. TGF-alpha regulates TLR expression and function on epidermal keratinocytes. J Immunol. 2005 May;174(10):6137–43.
76 Curry JL, Qin JZ, Bonish B, Carrick R, Bacon P, Panella J, et al. Innate immune-related receptors in normal and psoriatic skin. Arch Pathol Lab Med. 2003 Feb;127(2):178–86.
77 Pasparakis M, Courtois G, Hafner M, Schmidt-Supprian M, Nenci A, Toksoy A, et al. TNF-mediated inflammatory skin disease in mice with epidermis-specific deletion of IKK2. Nature. 2002 Jun;417(6891):861–6.
78 Andrianne M, Assabban A, La C, Mogilenko D, Salle DS, Fleury S, et al. Tristetraprolin expression by keratinocytes controls local and systemic inflammation. JCI Insight. 2017 Jun;2(11):2.
79 Groves RW, Rauschmayr T, Nakamura K, Sarkar S, Williams IR, Kupper TS. Inflammatory and hyperproliferative skin disease in mice that express elevated levels of the IL-1 receptor (type I) on epidermal keratinocytes. Evidence that IL-1-inducible secondary cytokines produced by keratinocytes in vivo can cause skin disease. J Clin Invest. 1996 Jul;98(2):336–44.
80 Nakajima A, Matsuki T, Komine M, Asahina A, Horai R, Nakae S, et al. TNF, but not IL-6 and IL-17, is crucial for the development of T cell-independent psoriasis-like dermatitis in Il1rn-/- mice. J Immunol. 2010 Aug;185(3):1887–93.

Downloaded from http://karger.com/drm/article-pdf/235/2/91/2663712/000495291.pdf by guest on 19 April 2024

81 Bonifacio KM, Kunjravia N, Krueger JG, Fuentes-Duculan J. Cutaneous Expression of A Disintegrin-like and Metalloprotease domain containing Thrombospondin Type 1 motif-like 5 (ADAMTSL5) in Psoriasis goes beyond Melanocytes. J Pigment Disord. 2016 Oct;3(3):3.
82 Tsutsui K, Manabe R, Yamada T, Nakano I, Oguri Y, Keene DR, et al. ADAMTSL-6 is a novel extracellular matrix protein that binds to fibrillin-1 and promotes fibrillin-1 fibril formation. J Biol Chem. 2010 Feb;285(7):4870–82.
83 Fuentes-Duculan J, Bonifacio KM, Hawkes JE, Kunjravia N, Cueto I, Li X, et al. Autoantigens ADAMTSL5 and LL37 are significantly upregulated in active Psoriasis and localized with keratinocytes, dendritic cells and other leukocytes. Exp Dermatol. 2017 Nov;26(11):1075–82.
84 Ganguly D, Chamilos G, Lande R, Gregorio J, Meller S, Facchinetti V, et al. Self-RNA-antimicrobial peptide complexes activate human dendritic cells through TLR7 and TLR8. J Exp Med. 2009 Aug;206(9):1983–94.
85 Conrad C, Meller S, Gilliet M. Plasmacytoid dendritic cells in the skin: to sense or not to sense nucleic acids. Semin Immunol. 2009 Jun;21(3):101–9.
86 Heidenreich R, Röcken M, Ghoreschi K. Angiogenesis drives psoriasis pathogenesis. Int J Exp Pathol. 2009 Jun;90(3):232–48.
87 Canavese M, Altruda F, Ruzicka T, Schauber J. Vascular endothelial growth factor (VEGF) in the pathogenesis of psoriasis—a possible target for novel therapies? J Dermatol Sci. 2010 Jun;58(3):171–6.
88 Canavese M, Altruda F, Silengo L, Castiglioni V, Scanziani E, Radaelli E. Clinical, pathological and immunological features of psoriatic-like lesions affecting keratin 14-vascular endothelial growth factor transgenic mice. Histol Histopathol. 2011 Mar;26(3):285–96.
89 Beck B, Driessens G, Goossens S, Youssef KK, Kuchnio A, Caauwe A, et al. A vascular niche and a VEGF-Nrp1 loop regulate the initiation and stemness of skin tumours. Nature. 2011 Oct;478(7369):399–403.
90 Lichtenberger BM, Tan PK, Niederleithner H, Ferrara N, Petzelbauer P, Sibilia M. Autocrine VEGF signaling synergizes with EGFR in tumor cells to promote epithelial cancer development. Cell. 2010 Jan;140(2):268–79.
91 Sotiropoulou PA, Blanpain C. Development and homeostasis of the skin epidermis. Cold Spring Harb Perspect Biol. 2012 Jul;4(7):a008383.
92 Weinstein GD, Van Scott EJ. Autoradiographic analysis of turnover times of normal and psoriatic epidermis. J Invest Dermatol. 1965 Oct;45(4):257–62.
93 Capon F, Semprini S, Chimenti S, Fabrizi G, Zambruno G, Murgia S, et al. Fine mapping of the PSORS4 psoriasis susceptibility region on chromosome 1q21. J Invest Dermatol. 2001 May;116(5):728–30.
94 Eckert RL, Broome AM, Ruse M, Robinson N, Ryan D, Lee K. S100 proteins in the epidermis. J Invest Dermatol. 2004 Jul;123(1):23–33.
95 Saintigny G, Schmidt R, Shroot B, Juhlin L, Reichert U, Michel S. Differential expression of calgranulin A and B in various epithelial cell lines and reconstructed epidermis. J Invest Dermatol. 1992 Nov;99(5):639–44.
96 Zenz R, Eferl R, Kenner L, Florin L, Hummerich L, Mehic D, et al. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. Nature. 2005 Sep;437(7057):369–75.
97 Schonthaler HB, Huggenberger R, Wculek SK, Detmar M, Wagner EF. Systemic anti-VEGF treatment strongly reduces skin inflammation in a mouse model of psoriasis. Proc Natl Acad Sci USA. 2009 Dec;106(50):21264–9.
98 Zenz R, Wagner EF. Jun signalling in the epidermis: from developmental defects to psoriasis and skin tumors. Int J Biochem Cell Biol. 2006;38(7):1043–9.
99 Glick AB, Kulkarni AB, Tennenbaum T, Hennings H, Flanders KC, O'Reilly M, et al. Loss of expression of transforming growth factor beta in skin and skin tumors is associated with hyperproliferation and a high risk for malignant conversion. Proc Natl Acad Sci USA. 1993 Jul;90(13):6076–80.
100 Piepkorn M, Pittelkow MR, Cook PW. Autocrine regulation of keratinocytes: the emerging role of heparin-binding, epidermal growth factor-related growth factors. J Invest Dermatol. 1998 Nov;111(5):715–21.
101 Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. J Am Acad Dermatol. 2002 Jan;46(1):1–23.
102 Boehncke WH, Schön MP. Animal models of psoriasis. Clin Dermatol. 2007 Nov-Dec;25(6):596–605.

Downloaded from http://karger.com/drm/article-pdf/235/2/91/2663712/000495291.pdf by guest on 19 April 2024