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Innate Immunity and antimicrobial defense systems in psoriasis

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Abstract

Psoriasis is a chronic inflammatory disorder that is mediated by elements of the innate and adaptive immune systems. Its characteristic features in the skin consist of inflammatory changes in both dermis and epidermis, with abnormal keratinocyte differentiation and proliferation. Despite the elucidation of many aspects of psoriasis pathogenesis, some puzzling questions remain to be answered. A major question currently debated is if psoriasis is a primary abnormality of the epidermal keratinocyte or a reflection of dysregulated bone-marrow derived immunocytes. In this review we will focus on understanding the role of the innate immune system in psoriasis and how this provides a rational solution to address the origin of this multifactorial disease. Innate immunity is non-specific and genetically-based. It protects the body against the constant risk of pathogens through the use of rapidly mobilized defenses that are able to recognize and kill a wide variety of threats (bacteria, fungi, viruses, etc.). The key mechanisms of innate immune responses are the existence of receptors to recognize pathogens, and the production of factors that kill pathogens, such as antimicrobial peptides and proteins. Any combination of excessive sensitivity of the innate detection system, or dysregulation of the response system, can manifest both an epidermal phenotype and abnormal T-cell function. Thus, the multidimensional action of the innate immune system, its triggers, and its recently understood role in T-cell function, argue for an important role for innate mechanisms of recognition and response in the pathogenesis of psoriasis.

Introduction

Over 2–3% of the world-wide population suffers from psoriasis, a chronic inflammatory skin disease characterized by the formation of typical scaly plaques.[1] Over the last decades, many researchers have tried to uncover the responsible elements of psoriasis pathogenesis. However, given difficulties in identifying a clear genetic locus associated with the disease, today psoriasis is considered a combination of genetic, immunologic and environmental factors. Psoriasis is recognized by a disturbed proliferation and differentiation of keratinocytes (hyperproliferation, orthokeratosis) accompanied by vascular alterations and epidermal infiltration of activated Th1 type lymphocytes and antigen-presenting cells together with a local Th1-type cytokine immune response.[2,3] As a consequence of this diversity in etiology, the understanding of a multifactorial pathogenesis of psoriasis has evolved into a remarkable number of therapeutic concepts. These facts prompt further questions: Is the aberrant keratinocyte differentiation a primary defect or is it the consequence of an influx of pathogenic immunocytes?

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Psoriatic plaques occur throughout the body and appear as scaly hypertrophic lesions of characteristic morphology. Because of the aberrant epidermal differentiation program in such lesions, psoriatic plaques lack a normal granular cell layer or intact stratum corneum.[4] The cause of increased keratinocyte proliferation and disturbed cell maturation and thereby an impaired barrier defect), has been suggested as i) the consequence of high levels of cAMP, ii) a disturbed arachidonic acid metabolism, ii) high activity of proteases and decrease in anti-protease activity, iii) overexpression of growth factors iv) disturbed metabolism and efficiency of calcium and vitamin D.[5–13] These theories may in part explain why glucocorticosteroids, vitamin D analogs, retinoids, and phototherapy are useful drugs in psoriasis treatment. However, many different types of skin barrier defects have been produced in transgenic mice but they do not develop a psoriatic plaque. For example in keratin-10 knockout mice hyperkeratosis is observed, IFN-β transgenic mice display profound barrier defects, but other typical signs of psoriasis, such as a loss of a granular layer or an angiogenic tissue reaction, are not present.[14,15] On the other hand in double knockout mice for epidermal JunB/c-Jun kinase, showing a convincing psoriatic phenotype, S100A8 and S100A9 were both highly upregulated in pre-diseased skin.[16] S100A8 and S100A9 are both antimicrobial proteins with chemotactic activity and a well known role in keratinocyte maturation and proliferation processes.[17] These results were furthermore substantiated *in vitro*, showing that the S100A8 and S100A9 upregulation was increased by *cre* deletion of both Jun kinases in primary keratinocytes.[16] Moreover, Zenz et al., excluded an exclusive role of T-cells in his mouse model, using also Rag2-deficient JunB/c-Jun double mutant mice that developed psoriasis-typical epidermal thickening, altered keratinocyte maturation, vascular dilatation and epidermal micro-abscesses in the absence of Band T-cells. Overall, these observations argue for the origin of psoriasis in the epidermis.

Much work also supports a role for the immunocyte, especially the T-cell, in the pathogenesis of psoriasis. The identification of T-cells in psoriatic lesions and the characterization of T-cell derived cytokines on inflammation and keratinocyte growth and differentiation became a new target of investigation and initiated a systematic search for therapies targeted to interfere with these activated T-cells, such as immunosuppressive drugs (phototherapy, cyclosporin, methotrexate). The psoriatic plaque is characterized by the presence of Th1 cytokines including TNF-β, IFN-β, IL-2.[18] In addition to these T-cell derived cytokines, numerous antigen presenting cells (APCs) infiltrate psoriatic skin and produce inflammatory cytokines and chemokines. TNF-β has been identified as a promising target molecule and psoriasis patients treated with TNF-β inhibiting agents (Infliximab, Etarnercept) showed impressive decreases of their disease severity. The occurrence of rare but severe side effectsremains a problem for these treatment approaches. Many more soluble immune mediators including chemokines and their receptors have been recently identified in psoriatic plaques. CCL20, CCL22, CCL5 and CCL19 are only a few chemokines that deserve attention and may be new target molecules in psoriasis treatment.[8,19]

Reconciliation of the findings of the two approaches outlined above (the primary keratinocyte disorder and the immunocyte disorder) can be explained by the functions of the innate immune system.

It was previously recognized that despite a compromised “structural shield” in psoriasis, the fully-developed psoriatic plaque provides a rather impressive chemical protective shield for the skin. This may be one explanation why psoriasis patients are rather resistant to invasion by infectious organisms.[20,21] This observation led to the hypothesis that a local “chemical shield” provides psoriatic skin with resistance against microbial infections in contrast to patients with other inflammatory skin diseases, such as atopic dermatitis. Indeed, the compensatory response by immune cells together with the overexpression of innate immunity response genes in psoriasis are discussed as the molecular basis for this phenomenon of microbial resistance.

[22,23] Interestingly, many antimicrobial peptides and proteins (AMPs), endogenous natural antibiotics, were identified in psoriatic-scale extracts such as cathelicidin [24,25], S100-proteins [26], human beta-defensins (hBD) [22], RNase 7 [26], and lysozyme [26] and many more (Table 1). In contrast, deficiency in expression of AMPs in skin lesions of patients with atopic dermatitis have been reported to account for the high occurrence of Gram-positive skin infections in those patients.[25] Taking these observations into account, another question should be addressed when looking at psoriasis pathogenesis, namely whether the overexpression of AMPs is responsible for the psoriasis phenotype. Focussing on the broad range properties of many cutaneous antimicrobial peptides and proteins, such as proteinase inhibitors, chemokines, and neuropeptides, one could assume that these AMPs may contribute to psoriasis pathogenesis by recruiting immune cells to the epidermis, mediating a proinflammatory immune response and initiating proliferation of blood vessels and keratinocytes.[27,28]

These observations challenge to review the role innate immunity and the role of antimicrobial peptides and proteins in psoriasis.

General principle of innate host defense

The immune system is designed to protect the host from infection and other insults. There are two major approaches that the immune system uses to protect the host: the innate and the adaptive system, which both contribute to the pathophysiology of psoriasis. In this review, the innate immune response system of psoriasis will be highlighted.

Innate immunity is non-specific and genetically-based. It protects the body against the constant risk of pathogens, through the use of rapidly mobilized defenses that are able to recognize and kill a wide variety of threats (bacteria, fungi, viruses, etc.). The key mechanisms of innate immune responses are 1) the existence of receptors to recognize pathogens [29,30] and 2) to employ mechanisms that kill pathogens, such as antimicrobial peptides and proteins. The major cellular elements of innate immunity in the skin are granulocytes, dendritic cells (DCs), macrophages and keratinocytes. The innate immune system triggers a sequence of factors that results in the production of cytokines, chemokines, endogenous antimicrobial substances, the activation of immune cells and transcription factors, and in the end initiates the killing of the pathogenic microbe and activation of adaptive immunity.

The innate immune system senses invading microbes through their pathogen associated molecular patterns (PAMPs) via pathogen recognition receptors (PRRs), such as Toll like receptors (TLRs). TLRs are structurally related to the Drosophila Toll receptor and are expressed in human keratinocytes.[31,32] As effectors of innate immunity, antimicrobial peptides (AMPs) play a predominant role providing the first line of defense in the skin against invading microbes.[33] The production of antimicrobial peptides are the phylogenetically oldest innate immune responses.[29,34] AMPs directly kill a broad spectrum of microbes including Gram-positive and Gram-negative bacteria, fungi and certain viruses. They have been identified in resident cells, such as keratinocytes, as well as in infiltrating cells and, are more than simple antibiotics. Their additional function as proteinase inhibitors, chemokines, neuropeptides and much more might be overlooked even more important to skin biology.

Toll-like receptors (TLRs)

The innate immune response is the initial nonspecific response to a microbial attack. As one member of pattern recognition receptors, Toll-like-receptors (TLRs) are used by cells of the innate immune system to recognize molecular structures, so called pathogen associated molecular patterns (PAMPs). PAMPs are conserved by microbes and are essential for the survival or pathogenecity of microorganisms.[29] Typical examples of PAMPs include

lipopolysaccharide (LPS) from Gram-negative bacteria, lipoteichoic acids and peptidoglycan of Gram-positive bacteria and mannans of yeasts/fungi.

TLRs are the mammalian homologues of the *Drosophila* Toll family that control the dorso-ventral patterning in the developing embryo and the antimicrobial response in the adult fly.[35] Structurally, TLR family members are characterized by the presence of a leucine-rich extracellular domain and a highly conserved intracellular Toll/Interleukin (IL)-1 receptor (TIR) domain.[36] While the extracellular part is responsible for specific ligand-recognition, the intracellular part mediates the signal transduction.

TLR2 is a heterodimer that associates with TLR1 or TLR6 and CD14 to recognize lipopeptides from bacteria, peptidoglycan (PGN) and lipoteicheic acid (LTA), TLR3 recognizes double-stranded RNA (dsRNA) produced during virus replication, while TLR4/CD14 is activated by lipopolysaccharide (LPS) derived from Gram-negative bacteria. Flagellin is recognized by TLR5, viral single stranded RNA (ssRNA) by TLR 7 and TLR8. TLR9 recognizes unmethylated CpG DNA primarily found in bacteria. TLR11 recognizes uropathogenic *E. coli*.[37,38] Moreover, further ligands for many TLRs have been found, including endogenous proteins like heat-shock-proteins, and small fragments of hyaluronan.[39,40] The common downstream signalling pathway of activated TLRs leads to activation of nuclear factor (NF)-βB via myeloid differentiation protein (MyD88)- IRAK-TRAF6- signal cascade ultimately triggering the transcription of chemokines, proinflammatory cytokines, antimicrobial substances, and upregulation of cell surface molecules involved in the initiation of adaptive immune responses to pathogens and antimicrobial peptides and proteins.[29] TLR3 in contrast activates NF-βB without the MyD88 pathway and TLR4 is only partially dependent on MyD88 for signalling.

Few authors have conceived that TLRs may be important in psoriasis pathogenesis. Earlier, an association between psoriasis and streptococcal infections was discovered.[41,42] not aware of the presence of TLRs as potential receptors for PAMPs. Later, it was proposed that microorganisms on the skin are directly implicated in psoriasis pathogenesis and aggravation [43–45] and it was suggested that certain microorganisms induce and/or exacerbate disease process through the activation of TLRs in the skin.[46] It was found that TLR1, TLR2, and TLR5 are constitutively expressed in healthy epidermal keratinoyctes, while TLR3 and TLR4 are almost absent. TLR1 and TLR2 are expressed throughout the epidermis with higher expression in the basal keratinocytes and TLR5 is exclusively expressed in the basal cell layer. In contrast, in lesional psoriatic skin strong TLR1 staining is observed in keratinocytes of the upper epidermis. TLR2 is highly expressed on keratinoyctes of the upper epidermis, but not in the basal layer, while TLR5 is downregulated in basal keratinocytes of psoriatic patients. TLR3 and TLR4 are weakly expressed in healthy and psoriatic skin. Other authors however, reported that TLRs are not differently expressed in psoriatic compared to atopic skin.[47]

The role of TLRs in the pathogenesis of psoriasis is not fully understood. Too many questions remain to be clarified concerning TLR induced immune response. Until today, many studies have been performed on TLR expression, some with conflicting results.[48,49] In conclusion, detection of TLR gene expression is not consistent with its activation and its biological function. For example, IL-8 but not TLR2, is transcriptionally upregulated upon stimulation with *Candida albicans*. However, pre-treatment of NHEK with TLR2 and TLR4 antibodies abrogated *Candida albicans* killing activity of NHEK.[50]

Topical application of Imiquimod, a TLR7 agonist, triggered aggravation of a psoriatic plaque.[51] Its antiviral and antitumoral effects is considered the consequence of type 1 IFN-β/β induction.[52] This observation offers new sights into the pathophysiology of psoriasis, since a defined TLR activation has not been observed as a trigger for psoriasis.

Antimicrobial peptides and proteins in the skin

AMPs are mostly small cationic molecules binding to and interacting with the negatively charged membranes of microbes and are thereby able to kill. The exact mechanisms by which antimicrobial peptides kill microbes are still not fully understood. It is proposed that AMPs may form pores in the membrane of microbes which leads to lysis of the pathogenic threat.[53] AMPs that are made in the skin provide a soluble barrier that forms an impediment to infection. In case of infection, inflammation or injury, many antimicrobial peptides in the skin are upregulated due to increased synthesis by keratinocytes and deposition from degranulation of recruited neutrophils. Interestingly, AMPs are abundantly expressed in psoriatic skin [22,25,54,55], while they are present in only very low concentrations in skin from atopic dermatitis patients.[21,25] Clinically, expression levels of these natural antibiotics correlate with the susceptibility to skin infections, because atopic dermatitis patients suffer from frequent occurring skin infections, while psoriatic patients do not. These observations indicate that 1) AMP expression may depend on cytokine profiles present in the micromilieu of inflamed skin, 2) that AMP dysregulation may cause disease. Psoriasis and atopic dermatitis (AD) are the two most common chronic inflammatory skin diseases found in Caucasian population. However, their mechanisms for skin inflammation are quite different. While psoriasis is known to be associated with a Th1 type cytokine pattern and involves predominantly T-cells and neutrophils, AD is believed to exhibit a Th2-type directed cytokine pattern contributing to the high IgE levels and eosinophilia characteristics in this condition. On the other hand, recent studies hint that AMPs function also as chemokines, proteinase inhibitors, or neuropeptides rather than simple antibiotics.[56] AMPs are involved in wounding, wound healing and vascularization [57,58], can induce a proinflammatory cytokine response [27] and are involved in skin differentiation processes, since antimicrobial peptides and proteins expression in epidermal keratinocytes are inducible by high calcium concentrations, retinoid acid, and 1,25 (OH)-vitamin D_3.[59–62] Thereby it is possible that an imbalance or dysregulation of AMPs itself will lead to the formation of psoriatic lesions by recruiting inflammatory cells to certain areas of the skin, accumulate a proinflammatory cytokine response and trigger angiogenesis and keratinocyte proliferation. In line with this hypothesis is the fact that AMPs show a certain distribution on human healthy skin, that reflects the predicted areas of psoriasis development.[63] Moreover, the frequent discussed Koebner phenomenen (formation of a psoriatic plaque after trauma of unaffected skin) could be explained by the presence of AMPs in human skin: injury, the trigger for the Koebner phenomenen, is known to induce upregulation of AMPs in the skin and could thereby trigger the formation of a psoriatic plaques in a genetic predisposed individual. Many different AMPs have been described so far, of which some will be presented in the following.

Human β-defensins

Defensins contain six cysteine residues that form characteristic disulfide bridges. Disulfide bridge alignment and molecular structure separate this major antimicrobial peptide family into β-, β-, and β-defensins. β-Defensins are expressed by human neutrophils, which are also referred to as human neutrophil peptides 1 through 4. Human defensins (hD) 5 and 6 are abundantly expressed in Paneth cells of small intestinal crypts and in cells of the female urogenital tract.[64] Human β-defensins contain three disulfide bridges. The four best known human β-defensins (hBD), hBD-1 to -4 have been identified in various cell types including epithelia and peripheral blood cells.[65,66] HBD-1 is constitutively expressed in epithelia, whereas hBD-2 is highly upregulated in inflamed skin including psoriasis. HBD-3, which like HBD-2 was purified from psoriatic skin, is inducible in a variety of tissues.[66] β-Defensins have a broad-spectrum antimicrobial activity and additional immune-related functions.

HBD-1 and hBD-2 have antimicrobial activity directed against Gram-negative bacteria but are less effective against Gram-positive bacteria, hBD-3 is active against preferentially Gram-positive bacteria. Only hBD-2 and hBD-3 are both strongly expressed in psoriatic skin.[21,22] Several studies on the regulation of expression of β-defensins have been published. HBD-2 and hBD-3 expression have been reported to be inducible by TNF-β and IFN-β and can be inhibited by Th2 cytokines, such as IL-4 and IL-13 in normal human epidermal keratinocytes.[21,22] Other authors describe that IL-1 was the strongest inducer of hBD-2, while IFN-β does not induce hBD-2 but is the strongest inducer of hBD-3.[67] However, the typical Th1 cytokine pattern of psoriasis and low levels of Th2 cytokines may account for the high expression of hBD in psoriatic skin and low expression levels in AD.

Previous studies showed that hBD-2 was also inducible by bacteria, such as *Fusobacterium nucleatum* [68] and *Pseudomonas aeruginosa*.[69] Hence, the mechanisms of hBD-2 induction by bacteria are not clear. Most likely, it is mediated via PAMPs which are known activators of eligible PRRs.

Furthermore hBD-2 expression is induced by high calcium concentrations and 1,25(OH)-vitamin D_3. [59,61]

Human Cathelicidin

Cathelicidins form a distinct class of proteins present in the innate immunity of mammals. Similar to defensins, they act as precursor molecules that can release an antimicrobial peptide after cleveage. Their precursors contain a highly conserved N-terminal “cathelin” domain flanked by a signal peptide domain on its N-terminus and by an antimicrobial peptide region on its C-terminus. In man, one cathelicidin gene, named CAMP has been identified as a coding region for the 18kD pre-pro-protein hCAP18, which includes the C-terminal human antimicrobial peptide LL-37. Cathelicidin LL-37 is expressed by various types of cells, tissues and body fluids such as epidermal keratinocytes and intestinal cells [60], T cells and monocytes [70], wound fluids [71], bronchoalveolar lavage fluids [72], and vernix caseaosa of newborns.[73] Furthermore LL-37 expression is increased in psoriasis [74] and other inflammatory skin disorders such as lupus erythematodes and contact dermatitis [24], but is downregulated in atopic dermatitis.[74] Vitamin D has been recently found a potent inducer of LL-37 in cultured human keratinocytes, but not in other human epidermal cells such as colonocytes.[59,60] Stimulation of human myeloid cells with vitamin D also upregulated LL-37.[75] Regulation of human LL-37 occurs via a consensus vitamin D responsive element in the LL-37 promoter. Interestingly, induction of cathelicidin is absent in murine cells probably due to the absence of a vitamin D responsive element in the murine cathelicidin promoter.[75] This observation may be important for the role of LL-37 in psoriasis since vitamin D has many biological effects, including calcium regulation, stimulation of cellular differentiation, inhibition of proliferation, antioxidative, antitumorigenic, and immune modulatory functions.[75,76] Interestingly, other mediators of epidermal keratinocyte differentiation, such as high calcium and retinoid acid are not able to upregulate LL-37 in NHEK, in contrast to hBD-2.[60] Vitamin D metabolism in psoriatic patients has been a matter of dispute, because one group of investigators observed no difference in levels of circulating $1,25(OH)_2D_3$ between psoriatic and normal patients, whereas another group found reduced concentrations in psoriatic patients associated with higher disease severity.[13] These findings suggest the existence of an inverse relationship between severity of psoriasis and serum vitamin D. However, the importance of vitamin D in the pathogenesis of psoriasis needs to be further elucidated.

Cathelicidin LL-37 mounts antimicrobial activity against a wide range of microbes (Group A *streptococci*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecium*, *Escherichia coli*, different types of *Salmonella*, and *Candida albicans*) and in higher dosage

antimicrobial activity was observed also against sphirochaete.[77] The antimicrobial activitiy of cathelicidin *in vivo* has been proven in a mouse model. Mice deficient in the cathelicidin protein CRAMP, the murine equivalent to human LL-37, were more susceptible to severe infection caused by group A Streptococcus than their wildtype littermates.[78]

S100 proteins

S100 proteins comprise a family of low molecular weight (9–13 kDa) proteins that are characterized by the presence of calcium-binding EF-hands. Fourteen out of 21 S100 genes are located within the epidermal differentiation complex on chromosome 1.q21 and 13 S100 proteins are expressed in normal and/or diseased epidermis. Certain S100 proteins are overexpressed in skin cancer, metastasis, psoriasis, arthritis, wound healing, inflammation and cellular stress.[79,80]

For S100A7, S100A8 (calgranulin A), S100A9 (calgranulin B), and S100A12 a role in innate immunity has been demonstrated so far.[63,81,82] For S100A15, which is highly homologous to S100A7 (93% identity), a role in innate immunity is proposed as well.[83] Interestingly, all of the recent mentioned S100 proteins are highly overexpressed in psoriatic skin [26,84–87] or are elevated in serum from psoriatic patients.[17]

S100A7 mounts antimicrobial activity directed preferentially against *Escherichia coli*.[63] S100A8 is regulated by LPS derived from Gram negative bacteria and interleukin (IL)-1β. Calprotectin consisting of a heterodimer of 2 individual peptide chains -migration inhibitory factor-related protein (MRP)-8 (S100A8, calgranulin A) and MRP-14 (S100A9, calgranulin B)- has been proposed to play a role in antifungal innate host defense of epithelia.[82,88,89] Increased calprotectin expression is also observed in herpes simplex virus-and Epstein-Barr virus-infected oral keratinocytes [88] and antimicrobial activity of calprotection was found against *Borrelia burgdorferi*.[90] S100A12, also called human calgranulin C, has been implicated as an important component of the host responses that limits the parasite burden during filarial nematode infections.[81] Furthermore, in keratinocytes S100A7 [62] as well as S100A15 have been shown to be strongly upregulated upon stimulation with high calcium and proinflammatory cytokines.[91] Beside of their antimicrobial properties many S100 proteins are involved in the regulation of epidermal maturation and are highly upregulated in psoriatic skin.[17,91]

Conclusion

Skin innate immune defense is greatly enhanced by an antimicrobial peptide barrier that is activated when physical barriers fail to prevent a microbial attack. Under physiological conditions, low levels of antimicrobial peptides are present in the skin. In certain disease states, such as psoriasis, AMP levels are increased. AMPs which are expressed by resident keratinocytes and immunocytes, may link the two main hypotheses about psoriasis pathogenesis as either a primary keratinocyte disorder or an immunocyte-mediated chronic skin inflammatory disorder. AMPs are more than simple antibiotics, they can trigger chemotaxis, angiogenesis, and keratinocyte proliferation, which are all important features in psoriasis pathogenesis.

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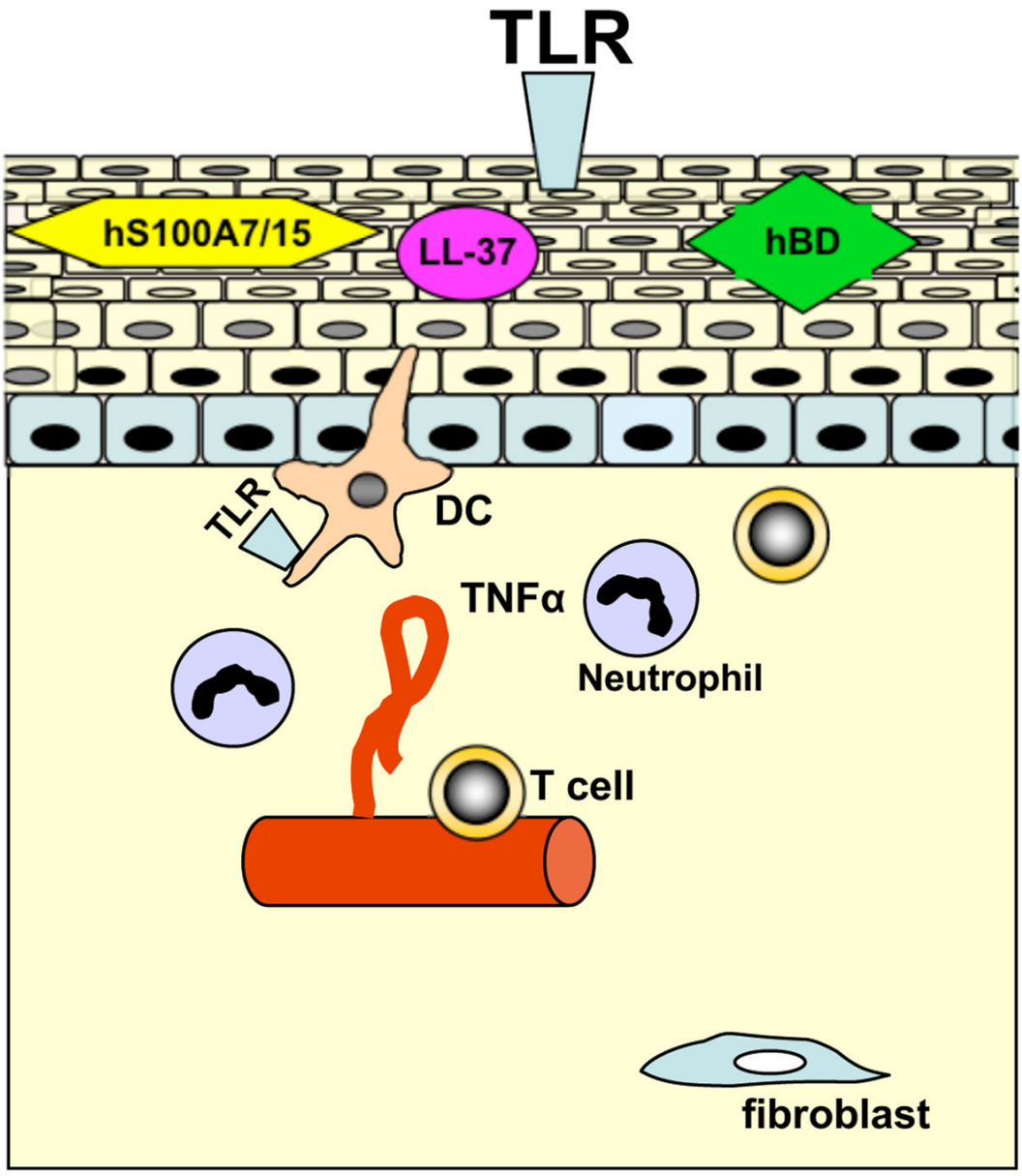

Figure 1.

Schematic summary of important innate immunity events in the pathophysiology of psoriasis. The fully developed psoriatic plaque comprises structural and molecular changes in the dermis and epidermis, that results in resistance against infections, apoptosis, and differentiation. Either triggered by an exogenous event disrupting barrier function (with or without bacterial infection) or by endogenous-derived infitration of activated immunocytes, the formation of a psoriatic lesion occurs. Toll-like receptors (TLR) may recognize pathogens and thereby orchestrate a vitious circle of innate immune response genes, including antimicrobial peptides and proteins (AMPs). Such AMPs including cathelicidin (LL-37) human beta defensins (hBD), human S100A7 (psoriasin) and human S100A15 (hS100A7/15) have not only antimicrobial activity, but also act as chemokines and can alter adaptive immune cell function, including thus of dendritic cells (DC) and T-cells. Thereby, AMPs that are expressed by resident keratinocytes as well as by immunocytes, may link the two main hypotheses of psoriasis pathogenesis

discussed as a primary keratinocyte disorder or as an immunocyte-derived chronic inflammation disorder.

Table 1

Summary of antimicrobial peptides and proteins that are overexpressed in psoriatic skin, their inducers, and their expression patterns.

AMPs overexpressed in psoriasis	Inducers of AMP expression	Expression in cells, tissues, skin diseases	Reference
hBD-2	TNF-α, IFN-γ, IL-1, *Fusobacterium nucleatum*, *Pseudomonas aeruginosa*, calcium, vitamin D	Epidermal keratinocytes, psoriasis	21; 22; 59; 61; 68; 69
hBD-3	INF-α, IFN-γ	epidermal keratinocytes	
Cathelicidin/LL-37	Vitamin D	epidermal keratinocytes, T-cells, monocytes, neutrophils, psoriasis, wound fluids, LE, contact dermatitis	59; 60; 70; 71; 72; 73
S100A7 (psoriasin)	Calcium, vitamin D, retinoid acid, *Escherichia coli*, *Staphylococus aureus* TNF-α, IFN-γ, IL-1β,	epidermal keratinocytes, breast cancer, oral sqamous cell carcinoma	26; 62; 63; 79; 80; 82; 83; 84; 85; 86; 87; 88, 89, 90; 91
S100A8 (calgranulin A)	UVA	Epidermal keratinocytes, wound healing, neutrophils, monocytes, sqamous cell carcinoma	
S100A9 (calgranulin B)		Epidermal keratinocytes, wound healing, neutrophils, monocytes, sqamous cell carcinoma	
S100A12 (calgranulin C)	IL-6	Epidermal keratinocytes, neutrophils, lymphocytes, monocytes	
S100A15	*Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, TNF-α IFN-γ, IL-1β, calcium, TPA	Epidermal keratinocytes	
RNase 7	*Pseudomonas aeruginisa*, *Staph aureus*, *E. coli*, *Streptococcus pyogenes*, TNF-α, IFN-γ, IL-β	Epidermal keratinocytes, respiratory tract, genitourinary tract, gut	26; 92
Lysozyme		Leukocytes, monocytes, macrophages, epidermal keratinocytes	92; 93

Abbreviations used: IFN (interferon), TNF (tumor necrosis factor), IL (interleukin), UVA (ultraviolett A), LE (lupus erythematodes), TPA (12-0-tetradecanoylphorbol-13-acetat)