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New Insights in the Immunologic Basis of Psoriasis

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Psoriasis vulgaris is a multifactorial heritable disease characterized by severe inflammation resulting in poorly differentiated, hyperproliferative keratinocytes. Recent advances in genetic analyses have implicated components regulating the interleukin (IL)-23 and nuclear factor-κB pathways as risk factors for psoriasis. These inflammatory pathways exhibit increased activity in skin lesions, and promote secretion of various cytokines, such as IL-17 and IL-22. Unrestrained, the activated inflammatory cytokine network in psoriasis may trigger a vicious cycle of inflammation and cellular proliferation that ultimately results in lesion formation. These advances in genetic analyses, together with the progress made in targeted biological therapy, pave the path to tailor treatment on the basis of an individual's genetic and immunologic profile.
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Psoriasis vulgaris is a chronic debilitating disease affecting 1% to 2% of the white population.[1] It is characterized by recurrent episodes of red, scaly, raised skin plaques that develop within seemingly normal skin and is triggered by a large number of factors, such as drugs (ie, beta-blockers, antimalarial drugs),[2] stress, physical injury to the skin (the Koebner response), and infection.[3]

Several defining histologic changes can be observed as lesions develop, including (1) a thickened epidermis (acanthosis) arising from rapid keratinocyte proliferation; (2) reduced or absent granular layer (hypogranulosis) and retention of nuclei by corneocytes (parakeratosis) because of aberrant differentiation of keratinocytes; (3) marked dilation of blood vessels in the papillary dermis causing visible erythema; and (4) a dense inflammatory infiltrate composed of clusters of $CD4^+$ T helper cells and antigen-presenting dendritic cells (DCs) in the dermis and $CD8^+$ T cells and neutrophils in the epidermis (Fig. 1).[4]

Psoriasis is classified by many as an immune-mediated inflammatory disease of the skin. Indeed, the remarkable therapeutic efficacy of a variety of immunomodulatory agents[5–8] has reinforced the vital role of the immune system in psoriasis pathogenesis. Furthermore, an explosion of knowledge surrounding emerging T-cell, and DC, subsets, have shed more light on specific immune pathways that may be central to lesion formation. The success of targeted therapeutics, as well as advances in genomic analyses, have further implicated these immunologic pathways. Here, we review these findings and consolidate them into our current understanding of this complex disease.

Clues from Genetic Analyses

Psoriasis is a complex genetic disorder, which means that it is a multifactorial heritable disease that is influenced by multiple genes and environmental factors.[3,9] Several psoriasis-associated chromosomal regions (PSORS 1-10) have been identified by conventional family-associated on genetic linkage approach, with PSORS 1, tightly linked to HLA-Cw6, as the most frequent detected allele.[10,11]

However, the full sequencing of the human genome facilitated the identification of single nucleotide polymorphisms, which represent subtle coding variations between individuals. These advances provided the means for "mapping" millions of single nucleotide polymorphisms throughout the human genome,[12] thus enabling genome-wide association scans (GWAS) to localize genetic alterations that are likely to be involved in disease pathogenesis.

The authors of a GWAS study[13] confirm previous findings that the strongest genetic association for psoriasis lies within the HLA-C region. HLA-Cw6 was reported to be associated with what is known as "type I psoriasis," characterized by early age of onset (<40 years), by being more likely to be familial, and by a more severe clinical course.[13] However, the precise role of HLA-C in psoriasis is still unclear.

Interestingly, significant associations have also been found in gene regions involving specific inflammatory pathways,

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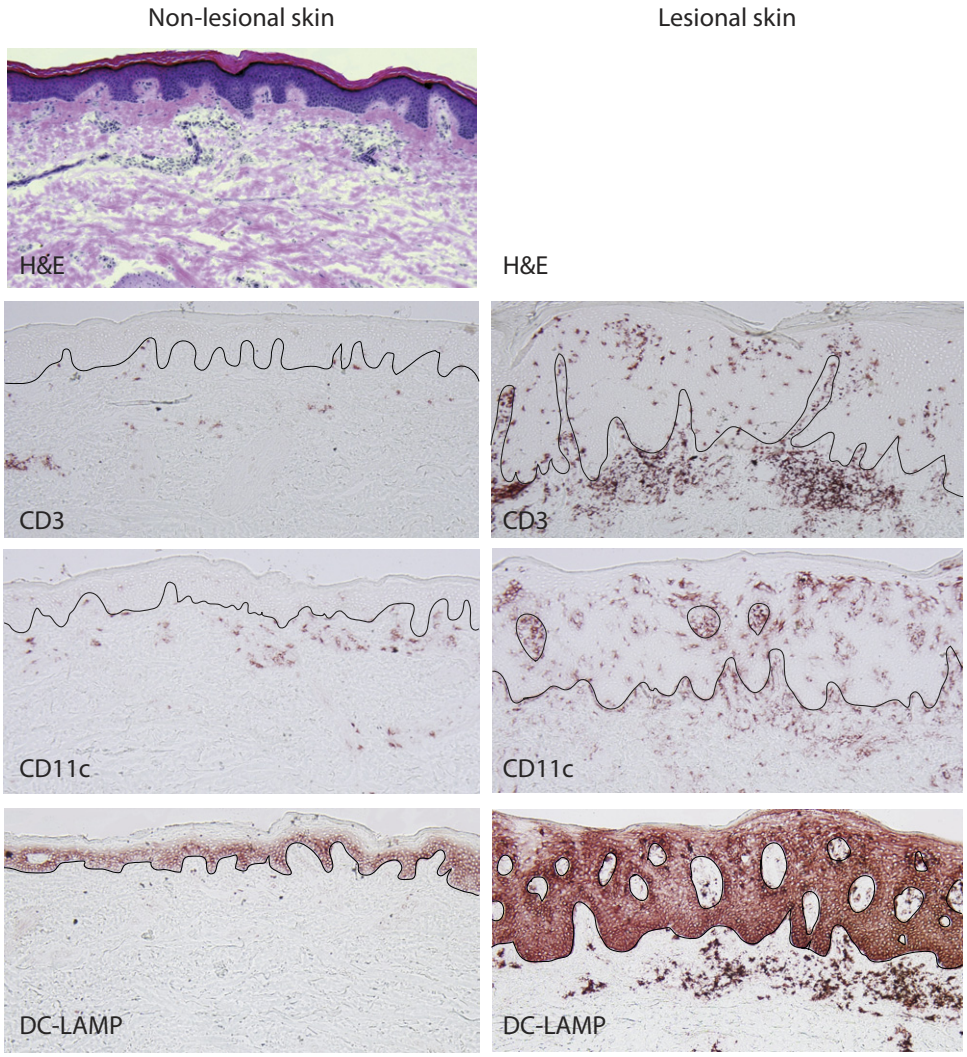

Figure 1 Comparative histologic pictures of nonlesional and lesional psoriatic skin demonstrate marked acanthosis (A) and dermal inflammation (i) in psoriasis lesions compared with nonlesional skin (hematoxylin and eosin stain). Inflammatory infiltrates in the psoriatic lesion consist of numerous T cells (CD3) as well as dendritic cells (CD11c), many of which are mature (DC-LAMP).

namely, (1) interleukin (IL)-23 signaling (IL-23A, IL-12B, and IL-23R); (2) modulation of T_h2 immune responses (IL-4, IL-13); and (2) nuclear factor (NF)-κB signaling.[14–16] Other associations include epidermal defense genes that are highly overexpressed in psoriasis: DEFB4[17] and late cornified envelop proteins 3 B and 3 C (LCE3C/3D).[18] Interestingly, some of these newly found genetic loci were found to overlap with the risk of developing other immune-mediated inflammatory diseases, most notably Crohn's disease.[19]

The IL-23/Th17 Pathway

IL-23 is a heterodimeric cytokine composed of p19 (encoded by IL-23A) and p40 (shared with IL-12 and encoded by IL-12B) subunits and binds to a receptor complex encoded by IL-23R and IL-12RB1. IL-23 is produced by DCs and macrophages[20] and is required for the growth, survival, and effector functions of Th17 cells.[21]

Th17 cells are $CD4^+$ effector T helper cells that are developmentally and functionally distinct from the classic T_h1 and T_h2 lineages.[22] Defined by the ability to produce IL-17, Th17 cells have also been shown to secrete other cytokines, including IL-22.[23] Similar to T_h1 and T_h2 cells, Th17 cells are thought to have evolved to provide adaptive immunity against pathogens. Organisms that can trigger a Th17 response include gram-positive bacteria *Propionibacterium acnes*; gram-negative bacteria *Citrobacter rodentium*, *Klebsiella penumoniae* and *bacteroides*; Borrelia; *Mycobacterium tuberculosis*; and fungi *Candida albicans*.[24–28] If Th17 cell differentiation is impaired, as in hyper IgE syndrome, recurrent *C. albicans* and *Staphylococcus aureus* infections are observed.[29]

Three psoriasis-associated gene signals, IL-23A, IL-12B, and IL-23R, involve components of the IL-23/IL-23R ligand-receptor complex prompting speculation that inappropriate immune responses in psoriasis might center on aberrations in IL-23 signaling.[30] Indeed, IL-23 and Th17 cells were found to

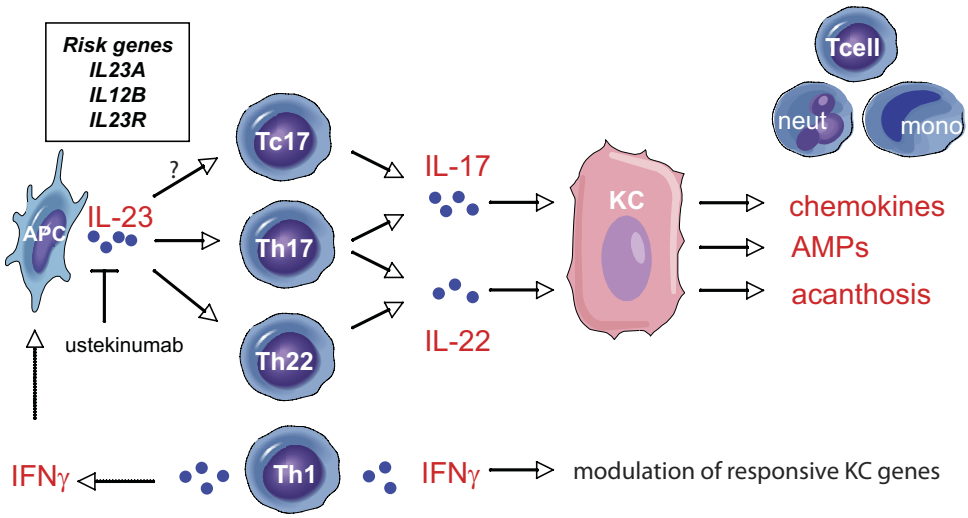

Figure 2 Model of immune interactions in the psoriatic lesion. Antigen-presenting cells (APCs) produce IL-23 and stimulate Th17 and Th22 cells, and possibly Tc17 cells, to release IL-17 and IL-22. Keratinocytes (KCs), in response to IL-17, up-regulate proinflammatory chemokines that attract T cells, neutrophils (neut.) and mononuclear cells (mono) into the lesion. IL-22 promotes epidermal acanthosis, whereas both cytokines trigger anti-microbial protein (AMP) production. IFN-γ, from T_h1 cells, modulates numerous KC-responsive genes, and stimulates APCs to release IL-23. Ustekinumab, an FDA-approved monoclonal antibody approved by the Food and Drug Administration, blocks the p40 subunit of IL-23. Identified genes associated with psoriasis (box) include *IL23A, IL12B,* and *IL23R.*

be markedly abundant in psoriasis lesions,[20,31] perhaps as a direct effect of genetic variations in regulatory regions of the above-mentioned genes.

The overexpression of the IL-23/Th17 pathway in psoriasis can explain the overproduction of psoriasin (S100A7) and other innate-defense molecules that typify psoriasis.[32] Th17-associated cytokines, IL-17 and IL-22, have been shown to induce keratinocyte expression of antimicrobials β-defensin 2, β-defensin 3, lipocalin, and S100 proteins.[33,34] Alternatively, genetic polymorphisms in DEFB4 that encodes β-defensin 2 may also contribute to antimicrobial resistance. The expression of another antimicrobial peptide, cathelicidin, can also be enhanced by IL-17 in the presence of vitamin D3.[35] These proteins may function as key inflammation inducers, as discussed later, and to decrease skin infections under conditions of a dysfunctional epidermal barrier.

IL-17 may also function as a potent proinflammatory cytokine that stimulates keratinocytes to produce neutrophil-attracting CXC chemokines (such as CXCL1, CXCL5, and CXCL8/IL-8), as well as CCL20 that draws $CCR6^+$ cells into sites of inflammation.[34,36] $CCR6^+$ cells relevant to the inflammation in psoriasis include myeloid dendritic cells (mDCs) as well as Th17 cells.[34,37] Finally, IL-17 can induce fibroblasts to produce IL-6,[38] a cytokine that commits naive T cells to the Th17 lineage, potentially activating a positive feedback loop that perpetuates Th17 inflammation.

$CD8^+$ T cells (Tc17) that produce IL-17 have been identified within the psoriatic epidermis.[39] These cells may have an important role in promoting psoriatic epidermal response as their contributions obviate the need for cytokines to diffuse from the dermis.[30] It is still unclear whether human Tc17 cells are influenced by the same conditions as Th17 cells, although murine models suggest that they might also be driven by IL-23.[40] Ustekinumab, a Food and Drug Administration-approved monoclonal antibody that binds to the p40 subunit, has been shown to be highly effective for the treatment of psoriasis,[41] thus further supporting the fundamental role of the IL-23/Th17 pathway in the pathogenesis of psoriasis (Fig. 2).

IL-22 Function and Regulation

IL-23 also stimulates the production of IL-22, an IL-10 family member cytokine that acts mainly on epithelial cells lining the digestive, respiratory, and integumentary systems. IL-22 promotes epithelial resistance to injury after microbial infections of the lungs and gut, and may be involved in homeostasis and first-line defense against pathogens.[23]

In psoriasis, IL-22 is remarkably overexpressed most probably because of up-regulated IL-23 and IL-6 levels.[42,43] As noted previously, IL-22 works synergistically with IL-17 to enhance the expression of antimicrobial peptides that are elevated in psoriasis.[33] More significantly, it mediates epidermal acanthosis and abnormal differentiation of keratinocytes that are key pathologic findings in psoriasis (Fig. 2).[33,34,44]

IL-22 production is commonly attributed to Th17 cells on the basis of early studies in which the authors used murine models.[33,43] Accordingly, we found that ~40% of IL-22-producing T helper cells in psoriasis are Th17 cells.[45] However, we have also consistently observed very little overlap between T cells expressing IL-17 and those expressing IL-22 in normal or psoriatic skin.[34,45] This finding has been affirmed by other groups who have also found that majority of $IL\text{-}22^+$ cells are single producers that do not coexpress IL-17 or the T_h1 cytokine, IFN-γ.[46]

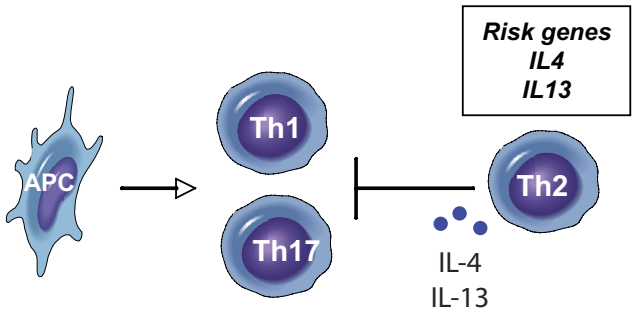

Figure 3 Model of T_h1-T_h2-Th17 interactions. Effector T cells subsets stimulated by APCs in psoriasis include T_h1 and Th17 cells. T_h2 cells and associated cytokines IL-4 and IL-13, which can suppress T_h1 and Th17 activity, are decreased in psoriasis. Genes that confer risk of having psoriasis include *IL4* and *IL13*. (box).

These IL-22-producing T helper cells, Th22, coexpress CCR6 and skin-homing receptors CCR4 and CCR10;[47,48] thus, they may presumably respond to the elevated CCL20 levels in psoriatic skin. IL-6 and tumor necrosis factor (TNF), both up-regulated in psoriasis, have been shown to enhance Th22 differentiation, whereas the addition of IL-1β to this mix may promote differentiation of Th17 cells that produce both IL-17 and IL-22.[48] Potentially, different DC subsets in psoriasis lesions might regulate Th17 versus Th22 activation. $CD11c^+$ dermal DCs have been shown to stimulate Th17 cells, whereas epidermal Langerhans cells have been shown to stimulate Th22 responses.[49]

T_h1-T_h2-Th17 Imbalance

Psoriasis lesions contain an excess of T_h1 T cells that are activated and produce interferon (IFN)-γ. We have previously demonstrated that IFN-γ induces numerous inflammatory molecules in keratinocytes and contributes to inflammation in psoriasis.[34] Much of this biology is described in past reports,[50] so it will not be furthered discussed here. IFN-γ has been shown to stimulate DCs to produce IL-1 and IL-23 that are Th17- and Th22-promoting cytokines (Fig. 2).[39]

IL-4 and IL-13 are cytokines produced by T cells committed to the T_h2 lineage. These cytokines have been shown to negatively regulate pathways induced by TNF, as well as the T_h1 cytokine IFN-γ, in keratinocytes via the activation of STAT6, SOCS1, and SOCS3.[51] Significant clinical improvement was observed with IL-4 treatment for psoriasis,[52] that might be attributed to the reduced expression of IL-12 and subsequently T_h1 cells.[53] IL-4 and IL-13 have been shown to inhibit development of Th17 cells from naive T cells.[54,55] As T_h2 T cells, and consequently IL-4 and IL-13 expression, are decreased in psoriasis lesions, this suppression of T_h1 and Th17 T cell activity is likely absent. Thus, genetic signals from the IL-4/IL-13 locus that promote an imbalance in effector T cell subsets might be a determinant for psoriasis (Fig. 3).

Dysregulated NF-κB Signaling

NF-κB is a major transcription factor that plays a crucial role in immunology. In resting cells, NF-κB is kept inactive by inhibitor of kappa B (IκB) proteins. Innate "danger" signals, ie, TNF, IL-1, and toll-like receptor (TLR) signaling, trigger a cascade that phosphorylates, ubiquitinates, and ultimately degrades IκB, releasing NF-κB, which translocates inside the nucleus to promote the transcription of responsive inflammatory genes.[56] When unrestrained, chronic NF-κB activation is associated with multiple autoimmune diseases.[57] It is, thus, important to have negative feedback mechanisms in place to regulate the NF-κB pathway.

One of these regulators is the ubiquitin-editing protein A20, encoded by TNFAIP3.[56] Mice that are deficient in A20 die from massive inflammation and tissue damage caused by sustained NF-κB activation and enhanced cytokine production.[58] This indicates that A20 is crucial for the termination of innate immune responses and that genetic variations in TNFAIP3 may result in sustained inflammation. This finding could be relevant for psoriasis pathogenesis because TNF is overexpressed in part from TNF and iNOS-expressing DCs (TIP-DCs) that are abundant psoriatic dermis.[59] In addition to TNF and other innate defense molecules, IL-17 has been shown to activate the classical NF-κB pathway (Fig. 4).[60]

TNIP1 is another negative regulator that binds to A20 to inhibit NF-κB activation (Fig. 4).[56] Counterintuitively, TNIP1 was found to be up-regulated in the skin of psoriasis patients versus controls.[15] This might imply that defective protein may be produced by gene variations in TNIP1. An alternative explanation could be that excessive TNIP1 inhib-

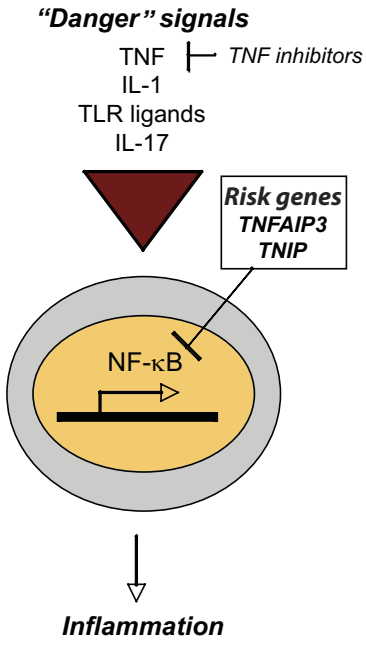

Figure 4 NF-κB pathway in psoriasis. Multiple "danger" signals, including TNF, IL-1, toll-like receptor (TLR) ligands, and IL-17, may stimulate the transcription factor, NF-κB, to translocate into the nucleus and promote the transcription of inflammatory genes. Gene polymorphisms that promote unregulated NF-κB activity may contribute to psoriasis susceptibility. GWAS have identified polymorphisms in *TNFAIP3* and *TNIP1*, both negative regulators of the NF-κB pathway (box).

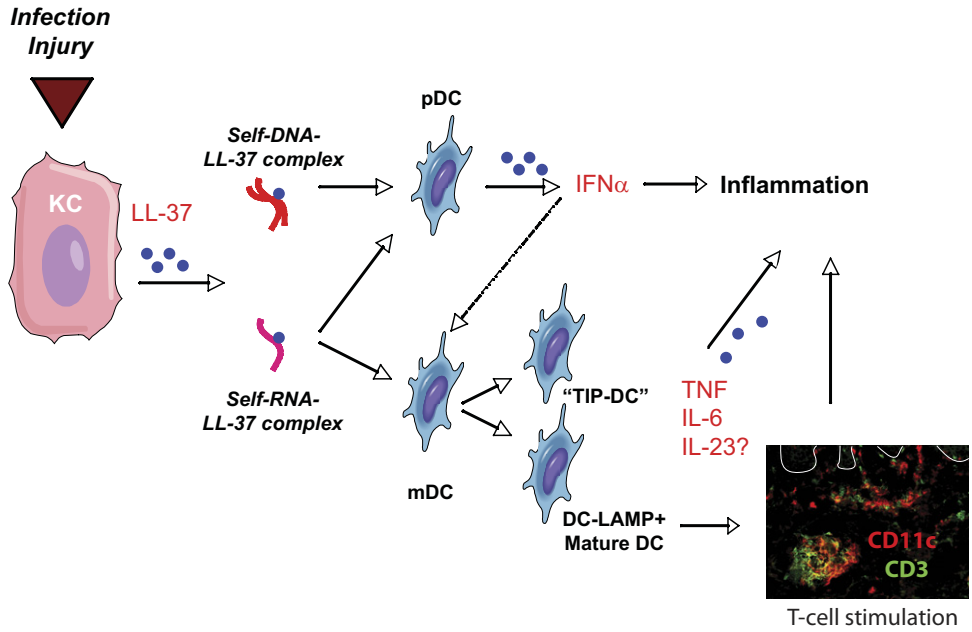

Figure 5 Potential initiators of the inflammatory cascade in psoriasis. Infection and injury stimulate keratinocytes (KC) to release the antimicrobial, cathelicidin (LL-37). LL-37 forms complexes with self-DNA from damaged cells, and stimulates plasmacytoid dendritic cells (pDCs) to release IFN-α that activates myeloid dendritic cells (mDCs). Simultaneously, LL-37 might form complexes with self-RNA to stimulate pDCs, as well as mDCs, triggering the release of inflammatory cytokines TNF, IL-6 and, possibly, IL-23. Activation of mDCs by self-RNA-LL 37 complexes promotes maturation of dendritic cells (DC-LAMP$^+$ mature DCs) that enhances antigen-presenting capabilities to T cells. Double-label immunofluorescence demonstrates proximity of dendritic cells (CD11c, red) and T cells (CD3, green) in psoriatic dermis. White line delineates dermo-epidermal junction.

its RARα[61] potentially disrupting the Th17/Treg balance in psoriasis.[62]

Consolidating the Immunologic Pathways

We now have compelling scientific evidence that points to dysregulated immunologic circuits as the core of psoriasis inflammation. But what triggers the inflammatory cascade? Infections or injury to the skin can promote lesion formation in susceptible individuals. These triggers have been shown to stimulate keratinocyte production of the antimicrobial cathelicidin (LL-37)[63] that, when complexed with self-DNA, binds to TLR9 on plasmacytoid DCs (pDCs).[64] These pDCs produce massive amounts of IFN-α and are implicated in the initiation of psoriasis lesions (Fig. 5).[65] Accordingly, patients treated with a topical pDC agonist, imiquimod, up-regulate IFN-α and experience exacerbations in psoriasis.[66]

In addition to stimulating pDCs, LL-37 has been shown to complex with self-RNA to trigger the activation of mDCs through TLR8.[67] This stimulates mDC production of TNF-α and IL-6, and promotes their differentiation into mature DCs (Fig. 5).[67] Interestingly, the self-RNA complexes were found to colocalize with the clusters of DC-LAMP$^+$ mDCs in psoriasis dermis[67] previously described by Lowes et al in 2007.[59] Because mDCs in psoriasis have been shown to produce IL-23,[20] it is plausible that self-RNA complexes might potentially initiate the inflammatory cascade (Fig. 5).

Upon initiation of the inflammatory cascade, dysregulations in the IL-23 pathway may lead to expansion and activation of Th17 and Th22 T cells. Effects of their cytokine products, as well as TNF and INF-γ, on keratinocytes, induce complex inflammatory circuits that stimulate keratinocyte proliferation, vascular proliferation, and further leukocyte accumulation and activation in psoriasis lesions. In addition, genetic variations in the IL-4/IL-13 locus may cause down-regulated T_h2 responses and promote unregulated Th17/T_h1 activity. Finally, decreased efficiency of negative NF-κB regulators TNFAIP3 and TNIP1 might sustain inflammation initiated by TNF, IL-1, TLR ligation, and IL-17 in susceptible individuals.

Advances in genetics and immunology have demonstrated the immune pathways relevant to psoriasis pathogenesis. The simultaneous expansion of our pharmacologic armamentarium for psoriasis have made it conceivable that we may eventually be able to stratify patients based on genetic risk factors and immunologic profiles, and tailor their individual treatment accordingly.

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