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New insights in the Immunologic Basis of Psoriasis

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Abstract

Psoriasis vulgaris is a multi-factorial heritable disease characterized by severe inflammation resulting in poorly differentiated, hyperproliferative keratinocytes. Recent advances in genetic analyses have implicated components regulating the IL-23 and NFκB pathways as risk factors for psoriasis, and advanced our understanding of this complex disease. 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 biologic therapy, pave the path to tailor treatment based on an individual's genetic and immunologic profile.

Introduction

Psoriasis vulgaris is a chronic debilitating disease affecting 1–2% of the Caucasian population.[1] It is characterized by recurrent episodes of red, scaly, raised skin plaques, which develop within seemingly normal skin and triggered by a large number of factors such as drugs (i.e. beta blockers, anti-malarial drugs)[2], stress, physical injury to the skin (the Koebner response), and infection.[3]

Several defining histologic changes can be observed as lesions develop. These include (1) a thickened epidermis (acanthosis) arising from rapid keratinocyte proliferation, (2) reduced or absent granular layer (hypogranulosis) and retention of nuclei by corneocytes (parakeratosis) as a result 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.[4] (Figure 1)

Psoriasis is classified by many as an immune-mediated inflammatory disease (IMID) of the skin. Indeed, the remarkable therapeutic efficacy of a variety of immuno-modulatory agents[5–8] have reinforced the vital role of the immune system in psoriasis pathogenesis. Furthermore, a recent 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

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implicated these immunological pathways. Here, we review these recent 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 multi-factorial 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. [12]

However, the full sequencing of the human genome facilitated the identification of single nucleotide polymorphisms (SNPs) that represent subtle coding variations between individuals. These advances provided the means for "mapping" millions of SNPs throughout the human genome[10, 11] thus enabling genome-wide association scans (GWAS) to localize genetic alterations that are likely to be involved in disease pathogenesis.

Recent GWAS studies confirm previous findings that the strongest genetic association for psoriasis lies within the HLA-C region.[12] HLA-Cw6 was long ago reported to be associated with what is known as "type I psoriasis", characterized by early age of onset (<40 years), being more likely to be familial, and with a more severe clinical course.[13] Yet, 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, namely, (1) IL-23 signaling (IL23A, IL12B and IL23R), (2) modulation of Th2 immune responses (IL4, IL13), and (2) NFκB signaling.[14–16] Other associations include epidermal defense genes that are highly overexpressed in psoriasis: DEFB4[17] and late cornified envelop proteins 3B and 3C (LCE3C/3D).[18] Interestingly, some of these newly found genetic loci were found to overlap with the risk of developing other IMIDs, most notably Crohn's disease.[19]

The IL-23/Th17 pathway

IL-23 is a heterodimeric cytokine composed of p19 (encoded by IL23A), and p40 (shared with IL-12 and encoded by IL12B) sub-units, and binds to a receptor complex encoded by IL23R and IL12RB1. IL-23 is produced by dendritic cells 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 Th1 and Th2 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 Th1 and Th2 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 Staph infections are observed.[29]

Three psoriasis-associated gene signals, IL23A, IL12B and IL23R, 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 be markedly abundant in psoriasis lesions,[20,31] perhaps as a direct effect of genetic variations in regulatory regions of the above-mentioned genes.

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The over-expression 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 anti-microbials 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 anti-microbial resistance. The expression of another anti-microbial 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 also to decrease skin infections under conditions of a dysfunctional epidermal barrier.

IL-17 may also function as a potent pro-inflammatory 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 naïve T cells to the Th17 lineage, potentially activating a positive feedback loop that perpetuates Th17 inflammation.

Recently, $CD8^+$ 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 recently FDA-approved monoclonal antibody that binds to the p40 sub-unit, 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. (Figure 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 over-expressed most probably as a result of upregulated IL-23 and IL-6 levels.[42,43] As noted above, IL-22 works synergistically with IL-17 to enhance the expression of anti-microbial 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.[33,34,44] (Figure 2)

IL-22 production is commonly attributed to Th17 cells based on early studies utilizing 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 has been affirmed by other groups who have also found that majority of $IL\text{-}22^+$ cells are single producers that do not co-express IL-17 or the Th1 cytokine, IFNγ.[46]

These IL-22 producing T helper cells, Th22, co-express CCR6 and skin homing receptors CCR4 and CCR10,[47,48] thus may presumably respond to the elevated CCL20 levels in psoriatic skin. IL-6 and TNF, both upregulated in psoriasis, have been shown to enhance Th22 differentiation, while 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 vs. Th22 activation. $CD11c^+$ dermal DCs have been shown to stimulate

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Th17 cells, while epidermal langerhans cells (LCs) have been shown to stimulate Th22 responses.[49]

Th1-Th2-Th17 imbalance

Psoriasis lesions contain an excess of Th1 T cells that are activated and produce IFNγ. We have previously demonstrated that IFNγ 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. Recently, IFNγ has been shown to stimulate DCs to produce IL-1 and IL-23 that are Th17 and Th22 promoting cytokines.[39] (Figure 2)

IL-4 and IL-13 are cytokines produced by T cells committed to the Th2 lineage. These cytokines have been shown to negatively regulate pathways induced by TNF, as well as the Th1 cytokine IFNγ, 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 Th1 cells.[53] IL-4 and IL-13 have been shown to inhibit development of Th17 cells from naïve T cells.[54,55] As Th2 T cells, and consequently IL-4 and IL-13 expression, are decreased in psoriasis lesions, this suppression of Th1 and Th17 T cell activity is likely absent. Thus, genetic signals from the IL4/IL13 locus that promote an imbalance in effector T cell subsets might be a determinant for psoriasis. (Figure 3)

Dysregulated NFκB signaling

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

One of these regulators is the ubiquitin-editing protein A20, encoded by TNFAIP3.[56] Mice that are deficient in A20 expire from massive inflammation and tissue damage caused by sustained NFκB 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 could be relevant for psoriasis pathogenesis as TNF is over-expressed, in part from TNF and iNOS-expressing dendritic cells (TIP-DCs) that are abundant psoriatic dermis.[59] In addition to TNF and other innate defense molecules, IL-17 has recently been shown to activate the classical NFκB pathway.[60] (Figure 4)

TNIP1 is another negative regulator that binds to A20 to inhibit NFκB activation.[56] (Figure 4) Counter-intuitively, TNIP1 was found to be upregulated 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 inhibits 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?

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Infections or injury to the skin can promote lesion formation in susceptible individuals. These triggers have recently been shown to stimulate keratinocyte production of the anti-microbial cathelicidin (LL-37)[63] that, when complexed with self-DNA, binds to TLR9 on plasmacytoid DCs (pDCs).[64] These pDCs produce massive amounts of IFNα and are implicated in the initiation of psoriasis lesions.[65] (Figure 5) Accordingly, patients treated with a topical pDC agonist, imiquimod, upregulate IFNα 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 myeloid DCs (mDC) through TLR8.[67] This stimulates mDC production of TNFα and IL-6, and promotes their differentiation into mature DCs.[67] (Figure 5) Interestingly, the self-RNA complexes were found to co-localize with the clusters of DC-LAMP$^+$ mDCs in psoriasis dermis[67] previously described by Lowes et al in 2007.[59] As myeloid dendritic cells in psoriasis have been shown to produce IL-23[20], it is plausible that self-RNA complexes might potentially initiate the inflammatory cascade. (Figure 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 IL4/IL13 locus may cause downregulated Th2 responses and promote unregulated Th17/Th1 activity. Finally, decreased efficiency of negative NFκB regulators, TNFAIP3 and TNIP1, might sustain inflammation initiated by TNF, IL-1, TLR ligation, and IL-17, in susceptible individuals.

Recent 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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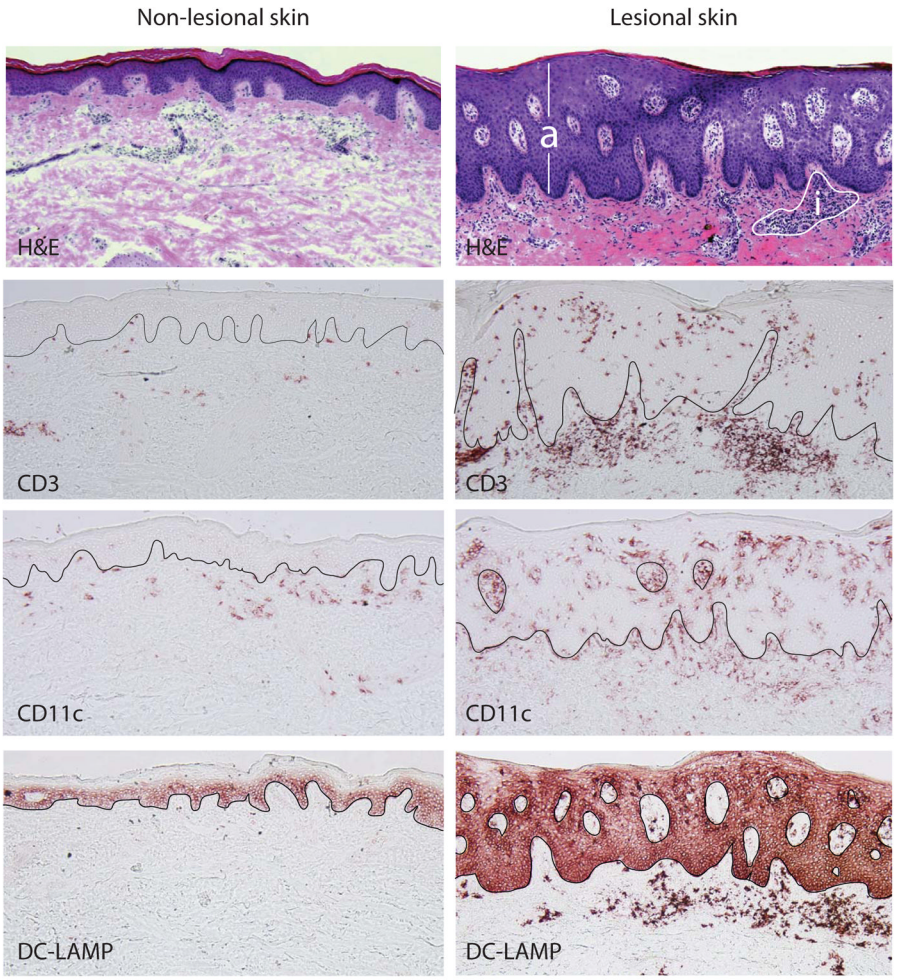

Figure 1.

Comparative histologic pictures of non-lesional and lesional psoriatic skin demonstrate marked acanthosis (a) and dermal inflammation (i) in psoriasis lesions compared to non-lesional skin (H&E 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).

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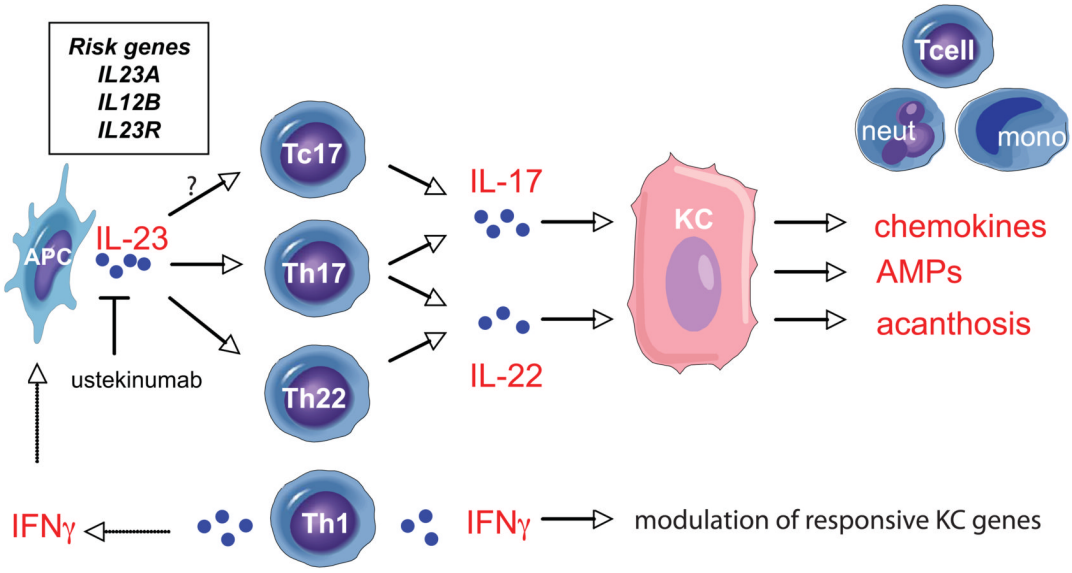

Figure 2. Model of immune interactions in the psoriatic lesion

Antigen-presenting cells (APC) produce IL-23 and stimulate Th17 and Th22 cells, and possibly Tc17 cells, to release IL-17 and IL-22. Keratinocytes (KC), in response to IL-17, upregulate pro-inflammatory chemokines that attract T cells, neutrophils (neut) and mononuclear cells (mono) into the lesion. IL-22 promotes epidermal acanthosis, while both cytokines trigger anti-microbial protein (AMP) production. IFNγ, from Th1 cells, modulates numerous KC responsive genes, and stimulates APCs to release IL-23. Ustekinumab, an FDA-approved monoclonal antibody, blocks the p40 sub-unit of IL-23. Recently identified genes associated with psoriasis (box) include IL23A, IL12B and IL23R.

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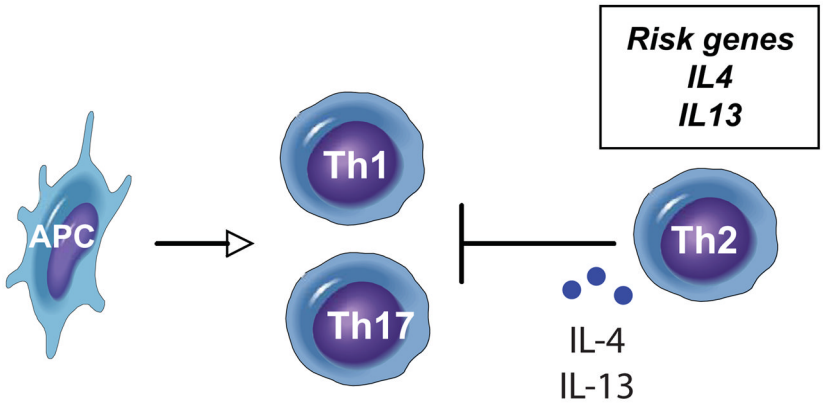

Figure 3. Model of Th1-Th2-Th17 interactions

Effector T cells subsets stimulated by antigen-presenting cells (APC) in psoriasis include Th1 and Th17 cells. Th2 cells and associated cytokines, IL-4 and IL-13, that can suppress Th1 and Th17 activity, are decreased in psoriasis. Genes that confer risk of having psoriasis include IL4 and IL13 (box).

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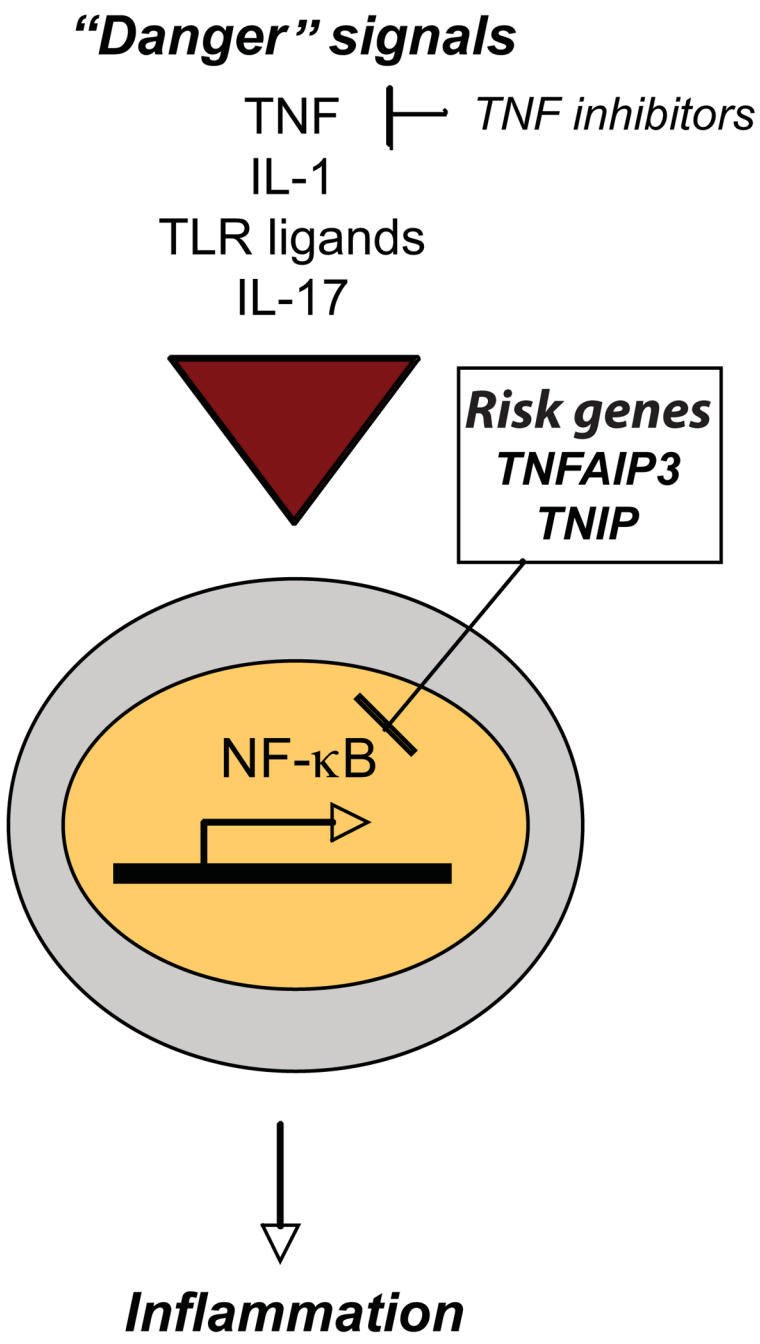

Figure 4. NFκB pathway in psoriasis

Multiple "danger" signals, including TNF, IL-1, toll-like receptor (TLR) ligands and IL-17, may stimulate the transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), to translocate into the nucleus and promote the transcription of inflammatory genes. Gene polymorphisms that promote unregulated NFkB activity may contribute to psoriasis susceptibility. Genome-wide associated studies (GWAS) have identified polymorphisms in TNFAIP3 and TNIP1, both negative regulators of the NFκB pathway (box).

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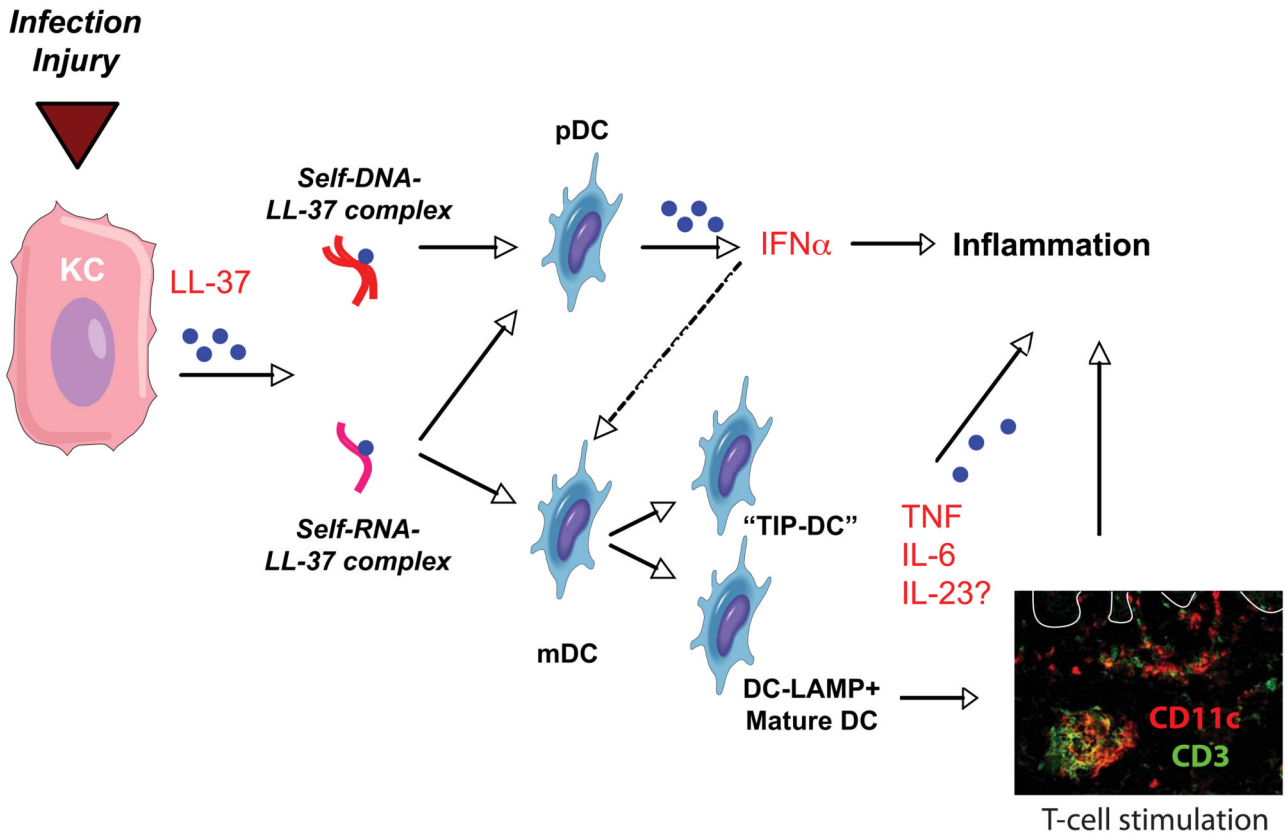

Figure 5. Potential initiators of the inflammatory cascade in psoriasis

Infection and injury stimulate keratinocytes (KC) to release the anti-microbial, cathelicidin (LL-37). LL-37 forms complexes with self-DNA from damaged cells, and stimulates plasmacytoid dendritic cells (pDC) to release IFNα that activates myeloid dendritic cells (mDC). 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-LL37 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.