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The Immunogenetics of Psoriasis: A Comprehensive Review

Jamie L. Harden[1,2], **James G. Krueger**[1], and **Anne Bowcock**[3,*]

[1] The Laboratory for Investigative Dermatology, The Rockefeller University, New York, NY 10065, USA

[2] Dermira, Inc. Menlo Park, CA, 94025, USA

[3] National Heart and Lung Institute, Imperial College, London SW3 6LY, UK

Abstract

Psoriasis vulgaris is a common, chronic inflammatory skin disease with a complex etiology involving genetic risk factors and environmental triggers. Here we describe the many known genetic predispositions of psoriasis with respect to immune genes and their encoded pathways in psoriasis susceptibility. These genes span an array of functions that involve antigen presentation (*HLA-Cw6*, *ERAP1*, *ERAP2*, *MICA*), the IL-23 axis (*IL12Bp40*, *IL23Ap19*, *IL23R*, *JAK2*, *TYK2*), T-cell development and T-cells polarization (*RUNX1*, *RUNX3*, *STAT3*, *TAGAP*, *IL4*, *IL13*), innate immunity (*CARD14*, *c-REL*, *TRAF3IP2*, *DDX58*, *IFIH1*), and negative regulators of immune responses (*TNIP1*, *TNFAIP3*, *NFKBIA*, *ZC3H12C*, *IL36RN*, *SOCS1*). The contribution of some of these gene products to psoriatic disease has also been revealed in recent years through targeting of key immune components, such as the Th17/IL-23 axis which has been highly successful in disease treatment. However, many of the genetic findings involve immune genes with less clear roles in psoriasis pathogenesis. This is particularly the case for those genes involved in innate immunity and negative regulation of immune specific pathways. It is possible that risk alleles of these genes decrease the threshold for the initial activation of the innate immune response. This could then lead to the onslaught of the pathogenic adaptive immune response known to be active in psoriatic skin. However, precisely how these various genes affect immunobiology need to be determined and some are speculated upon in this review. These novel genetic findings also open opportunities to explore novel therapeutic targets and potentially the development of personalized medicine, as well as discover new biology of human skin disease.

Keywords

Psoriasis; genetics; immunology; Th17-axis; innate immunity; negative regulators

*Corresponding author: Dr. Anne Bowcock, National Heart and Lung Institute, Imperial College, London, SW3 6LY, United Kingdom; A.bowcock@imperial.ac.uk.

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1. Introduction

Psoriasis is a chronic, inflammatory skin disease, characterized by raised, red scaly plaques [1]. This disease affect affects about 2-3% of the world-wide population, although it is more prevalent in American, Canadian, and European populations [2]. Psoriasis is also associated with several comorbidities, suggesting that the underlying pathogenesis of the disease is more than “skin deep” [3].

Psoriasis arises through chronic interactions between hyper-proliferative keratinocytes and infiltrating, activated immune cells. Initially, psoriasis was considered solely to be due to dysfunction of limiting keratinocyte proliferation [4]. Infiltration of immune cells was noticed, but not considered to be key in pathogenesis, but rather just a consequence of the hyper-proliferating keratinocytes. However, the critical role of the immune system in psoriasis pathogenesis was discovered when administration of immune suppressive agents, such as cyclosporine, denileukin diftitox, and alefacept, proved successful in ameliorating disease [5-8]. Over the next several years, the cellular and molecular contributions to the overactive immune response were further elucidated. It was found that T-cells, particularly those with Th1 and Th17 polarization, are heavily present in psoriatic lesions [1, 9]. Additionally, TNFα and iNOS producing inflammatory DCs (TIP-DCs), massively infiltrate psoriatic skin, and these TIP-DCs have the ability to polarize T-cells to Th1 and Th17 fates [4, 10, 11]. Lastly, psoriatic skin is infiltrated by a myriad of other immune cells including macrophages and innate immune cells, as well as an increased amount of endothelial cells (angiogenesis); these other cell types may certainly also play a role in psoriasis pathogenesis [1].

Similar to other autoimmune diseases, the genetics of psoriasis is complex and multifactorial. There is clear evidence of an important genetic component to psoriasis. This is supported by both twin and family studies [12]. The concordance rate of monozygotic twins is approximately 70% and for dizygotic twins is about 20% [13].

Areas of chromosomes which were thought to harbor psoriasis genes were initially entitled *PSORS* (**psor**iasis-**s**usceptibility) loci. There are at least 12 different *PSORS* loci that were mainly identified through linkage analysis of multiply affected psoriasis families [1]. However, the gene or gene(s) for most *PSORS* loci that are responsible for susceptibility is not known. In recent years, our understanding of psoriasis pathogenesis has been enriched by genome-wide association studies (GWAS) where large cohorts of psoriasis cases and matched controls have been typed for single nucleotide polymorphisms (SNPs) and tested for a statistically significant excess of one SNP allele in cases versus controls. These studies have revealed over 50 regions associated with psoriasis risk and within some of these regions there is more than one independent susceptibility factor. In all of these studies, a dominant function of a significant percentage of these genes is related to the immune system. Here we summarize what is currently known about the immunogenetics of psoriasis pathogenesis.

2. Antigen presentation

The first gene that was discovered to be significantly associated with psoriasis susceptibility was HLA-Cw6, which is located at *PSORS1* at chromosomal position 6p21.3 [13, 14]. HLA-Cw6 is found in about 4-16% of healthy controls [15] and in about 20%-to over 50% of psoriasis cases, depending on the population being studied. HLA-Cw6 encodes a major histocompatibility complex I (MHCI) allele. MHCI molecules are present on almost all nucleated cells and are key molecules for immune surveillance since they present intracellular peptides (both self and non-self peptides) to the immune system. MHCI is also critical for CD8+ T-cells priming and subsequent cytolytic targeting of cells. This finding supported the important role of T-cells in the pathogenesis of psoriasis.

HLA-Cw6 is not the only antigen presentation associated molecule associated with psoriasis. A recent GWAS also revealed a role of the ERAP1 loci in and this was enriched in individuals carrying the HLA-Cw6 mutation [16, 17]. ERAP1 (endoplasmic reticulum aminopeptidase 1) plays a role in processing of peptides for loading onto MHC class I. Due to these associations, it could be postulated that psoriasis is caused by a T-cell mediated reaction to an auto-antigen, one that is most easily presented on HLA-Cw6 and via processing by particular mutations in ERAP1. Additionally, ERAP2 is also a likely candidate gene of a PSORS locus at chromosomal position 5q15 [18]. However, despite these associations of psoriasis with the MHCI allele HLA-Cw6 and MHCI processing enzymes, we still do not have a confirmed “auto-antigen”. Additionally, it has been determined through deep sequencing of the T-cell repertoire that the T-cell infiltrate is highly polyclonal, and is not dominated by a heavy clonal expansion of a particular T-cell responding to a specific epitope (JLH and JGK, unpublished results).

Although more related to the innate immune response, MICA (MHC class I polypeptide-related sequence A) is also associated with psoriasis [19]. Expression of MICA is thought to mainly be stress-induced and is a ligand for NKG2D, an activating receptor found on natural killer (NK) cells, NKT-cells, and T-cells [20]. Although the exact role of NK and NKTs cells in psoriasis have not been thoroughly explored, these innate immune cells can make several inflammatory cytokines that are known to be increased in psoriasis lesions, such as TNFα, IFNγ, and IL-22.

3. The IL12/23 axis

As a specific auto-antigen in psoriasis proved troubling to identify, attention turned to elucidation of exactly how the immune system was responding in psoriatic lesions. It was first revealed that IFNγ producing T-cells are massively increased in psoriatic lesions [21]. Dendritic cells can instruct T-cells during priming to adopt a Th1 fate through secretion of the cytokine IL-12. IL-12 is composed of two subunits, p35 and p40. It was found that p40 expression is increased in psoriasis. Therefore targeting of the IL-12/IFNγ/Th1 axis was the next logical step in disease treatment. However, treatment with anti-IFNγ proved disappointing in preliminary clinical trials [22], resulting in the need for a deeper look into psoriasis pathogenesis. It was not until several years later, with the discovery of the Th17 subset and the key Th17 polarizing cytokine IL-23, that a role for the Th17 axis in psoriasis

became apparent [23, 24]. IL-23 and IL-12 share the common p40 subunit; however IL-23 is produced by the combination of p40 with the p19 subunit [25] (Figure 1). Although expression of p35 is not increased in psoriasis, expression of both p40 and p19 are drastically increased in psoriasis lesions, and subsequently there is increased expression of biologically active IL-23 in psoriatic lesional skin.

The immunogenetic association of IL-23 with psoriasis has proven quite strong. There have been several SNPs identified in genomic regions harboring genes for both subunits of the IL-23 cytokine: *IL12Bp40* and *IL23Ap19* [26] and coding SNPs in the IL-23 receptor (*IL23R*) that are associated with psoriasis [26-28]. The most consistently associated SNP within *IL23R* encodes a R381Q amino acid substitution, where the rarer Q allele results in decreased IL-23 signaling and is therefore protective against several autoimmune diseases, including psoriasis [29].

The IL-23 receptor is a heterodimeric receptor, composed of IL-12RB1 and IL-23R. These receptor components lack intrinsic signaling activity, and signal through the interactions with downstream molecules. IL-12B1 requires Tyk2 for signaling, whereas IL-23R requires Jak2 [30, 31]. GWAS studies of psoriasis have found associations with *TYK2* [16], as well as an association of *JAK2* with both psoriasis and Crohn's disease [32]. Additionally, GWAS studies have found psoriasis associations with mutations in *STAT3* (signal transducer and activator of transcription 3), a key molecule for downstream signaling through several cytokines, one of which is IL-23 [33].

The importance of IL-23 in psoriasis pathogenesis has been further confirmed by the recent major success of targeting this cytokine in treatment of psoriasis [34-36]. Monoclonal antibody treatment targeting both the common p40 subunit and the IL-23 specific p19 subunit have demonstrated outstanding clinical efficacy. In conjunction with the heavy genetic link to the IL-23 cytokine components and the IL-23 receptor, the transcripts of all three of these products are also significantly increased in psoriatic lesional skin [1]. Thus, the genetics, the transcriptomics, and the clinical success of blocking this cytokine all point towards a key role of IL-23 in psoriasis pathogenesis. In turn, IL-23 regulates activation and expansion of Th17 T-cells that are defined by production of IL-17A and IL-17F, and as discussed below in section 4, the pathogenic activity of IL-17 in psoriasis vulgaris is now well defined.

4. T-cell polarization

As mentioned in section 1, the critical role of T-cells in psoriasis was initially discovered by observing the improvement in disease when general T-cell suppressive agents were utilized. T-cells can be subdivided into two classes: CD8+ cytotoxic T-cells and CD4+ helper T-cells, both which are found to be increased in psoriatic lesional skin. Regarding CD4+ T-helper cells, this cell type can be polarized to different fates depending on the needs of the immune response. Initially, CD4+ T-helper cell fates were considered to be one of two-options: Th1 and Th2. Th1 T-cells produce IFNγ and are important for eliciting anti-viral immune responses. Th2 cells produce IL-4 and IL-5 and are critical for anti-microbial responses. Additionally, it was thought that allergies and autoimmune/auto-inflammatory

diseases could also be characterized by the Th1 and Th2 paradigm. However in recent years, this simple dichotomy has transformed into a complex array of phenotypes which a CD4+ T-cell can acquire, including T-reg (regulatory T-cell), Th17, Th22, and Th9 T cells, to name a few. As described in section 3, psoriasis now is considered to be a disease mainly mediated by T-cells polarized to a Th17 fate, i.e. T-cells producing the cytokines, IL-17. The importance of IL-17 in psoriasis pathogenesis has been confirmed by the success of treatments targeting either the IL-17 cytokine directly (i.e. Secukinumab, Bimekizumab, and Ixelkizumab) or blocking the IL-17R (i.e. Broadalumab) [37].

Several genetic associations with psoriasis have been found in critical genes for T-cell development and polarization (Figure 2). One of these genes is *RUNX3*, which encodes a transcription factor in the Runt-domain containing family. *RUNX3* is important for CD8+ T-cell development, promotion of Th1 polarization, and possibly Th17 polarization as well [38, 39]. There are also psoriasis-associated mutations in *RUNX1*, another transcription factor in the Runt-domain containing family [18]. *RUNX1* plays an important role in normal hematopoiesis and has mainly been investigated regarding its' dysregulation in leukemia and other hematopoietic cancers [40]. RUNX1 is expressed in naïve CD4+ T-cells and is rapidly downregulated upon TCR stimulation [39]. It can also be upregulated following Th2 polarizing conditions, but contradictorily, it also suppresses expression of the master Th2 transcription factor GATA3 and the key Th2 cytokine, IL-4 [39]. RUNX1 additionally plays a role in the development and the immunosuppressive ability of T-regs [39, 41-43]. However, exactly how these psoriasis-associations at the *RUNX3 and RUNX1* loci contribute to psoriasis have not been explored. It is possible that a disruption in the balance of RUNX1 and RUNX3, through gain-of-function mutations in RUNX3 and/or reduction-of-function mutations in RUNX1, predisposes T-cells to a Th17 phenotype in psoriasis patients. However, besides modulating T-cell polarization and function, RUNX1 and RUNX3 may also modulate the activity of other immune cells, such as NK cells or DCs [39]. Furthermore, a psoriasis-associated SNP residing between the genes *SLC9A3R1* and *NAT9* results in loss of a RUNX1 binding site, supporting that either alterations in RUNX1 itself or its potential binding sites may play a role in psoriasis susceptibility [44].

As described in section 3, association with a region harboring *STAT3* has also been found in psoriasis GWAS [33]. In psoriatic lesions, STAT3 is found in a phosphorylated and activated state [45]. STAT3 is important in the signaling cascades of several cytokines, such as IL-6, IL-10, IL-22, and IL-23. Because STAT3 is required for signaling through the IL-23R, it is essential for Th17 polarization [46]. It is possible that psoriasis-associated mutations in *STAT3* decrease the threshold of IL-23 signaling required to elicit Th17 polarization. However, activation of STAT3 in psoriasis may also play a role in non-hematopoietic cells, as STAT3 signaling can directly modulate epidermal hyperplasia as well [47].

*A*nother gene with function in T-cell biology that has recently been identified as a locus receiving genome-wide significance for association with psoriasis is *TAGAP* (T-cell activation RhoGTPase activating protein). TAGAP is expressed in activated T-cells, however the exact role of this protein in T-cell biology has not been explored [48]. Several other immune mediated diseases have also noted associations of TAGAP SNPs with disease

susceptibility, including Crohns disease, celiac disease, multiple sclerosis, and rheumatoid arthritis [49-52].

Interestingly, association with a region harboring Th2 associated genes, specifically *IL4*, *IL5* and *IL13*, in a region of chromosome 5q31 that harbors genes for multiple cytokines, has also been found in psoriasis patients [53]. However, given that these cytokines do not play a role in psoriasis pathogenesis and are not detected in psoriatic skin, this association is likely to result in decreased activity of these cytokines, although this has not been shown experimentally. T-cell polarization is a delicate balance, and often a molecular "push" towards a certain T-helper phenotype will inhibit T-helper cell polarization to other fates. Several studies have demonstrated epigenetic changes in the promoter regions of key Th2 and T-regulatory phenotype genes when T-cells are pushed towards a Th1 fate, and vice-versa [54, 55]. In the case of this association at chromosome 5q31 and one possible causative SNP (rs20541; Q144R of IL13), the Q allele is protective for psoriasis, but is a risk allele for asthma [56]. Reduced functionality of the Th2-associated SNPs may more easily allow T-cells to adopt an alternate outcome, such as the Th1 polarized cells found heavily in psoriasis, or more importantly, the pathogenic Th17 cell fate.

5. Innate immunity

Although the critical role of the adaptive immune system and Th17 polarized memory T-cells in psoriasis pathogenesis is difficult to refute, recent data also suggests an important role of the innate immune system in psoriasis susceptibility. These ideas are not mutually exclusive, as initial activation of the innate immune system is required for the subsequent onslaught of the adaptive response. Although the protein products of these innate immune genes are not currently key therapeutic targets in psoriasis, they may represent a predisposition for immune activation. In other words, psoriasis associations at loci harboring these innate immune genes may decrease the threshold needed to initiate the pathogenic adaptive immune response.

Many genes in the NF-κB pathway are associated with psoriasis [57] (Figure 3). NF-κB is a key transcription factor in immune responses, and plays an important role in almost every immune cell type [58]. NF-κB is held in the cytoplasm of the cell, bound to its' inhibitor, IκB [59]. Many cellular receptors of immune signaling include innate immune pattern recognition receptors and cytokine receptors, such as TNFα. Upon initiation of NF-κB signaling, IκB is phosphorylated by IκB kinase (IKK) and subsequently targeted for proteosomal degradation. The degradation of IκB releases NF-κB for translocation to the nucleus and subsequent induction of inflammatory gene expression [59].

NF-κB is a dimeric transcription factor, which can be composed of combinations of several different subunits, p50, p52, RelA(p65), c-Rel, and Rel-B. Expression of different subunits vary depending on cell type. The NF-κB pathway is well known to be activated in psoriatic lesional skin, and is reduced upon successful treatment [57, 60]. SNPs within a region harboring a gene for one of the NF-κB components, c-Rel, are associated with psoriasis susceptibility [61]. C-Rel can also directly regulate keratinocyte growth and cell cycle progression [39, 62].

A SNP within *TRAF3IP2* (TRAF3 interacting protein 2, also known as Act1) is also associated with psoriasis [63, 64]. TRAF3IP2 interacts with TRAF6 and is important for NF-κB activation downstream of IL-17 receptor signaling [64-66]. TRAF3IP2 is also important for CCL20 production from keratinocytes in response to IL-17 [67]. A coding alteration in *TRAF3IP2* is associated with both psoriasis vulgaris and psoriatic arthritis. This likely results in increased activation of NF-κB and heightened production of inflammatory products [65].

CARD-proteins are scaffolding proteins important in activation of NF-κB [68]. CARD-proteins have specific cellular distribution, with CARD9 being predominantly in myeloid cells, CARD10 in non-hematopoietic cells, and CARD11 in hematopoietic cells [68]. *CARD14*, a less investigated member of the CARD-family, was recently described to be the causative gene at *PSORS2* [69, 70]. In this instance, rare gain-of-function, highly penetrant dominantly acting mutations lead to psoriasis with or without psoriatic arthritis. In one case a *de-novo* mutation in *CARD14* lead to generalized pustular psoriasis. A coding SNP in *CARD14* described in this earlier study (R820W) was found to be associated with psoriasis at genome-wide significance in a subsequent meta-GWAS study [33]. Although CARD14 was initially described to be expressed in placental and mucosal tissue [71], recently CARD14 was found to be expressed in keratinocytes and endothelial cells [69, 72]. Psoriasis associated mutations in *CARD14* result in increased NF-κB signaling, and production of several inflammatory cytokines and chemokines in both keratinocytes and endothelial cells [70, 72]. This suggests that *CARD14* mutations increase the ability of both keratinocytes and endothelial cells to recruit and activate immune cells. *CARD14* is one of only two genes in which a rare mutation can independently result in psoriasis; the other is *IL36RN*, which is mutated in pustular psoriasis and will be discussed in section 6 about negative regulators [1].

Interestingly, some of the more recent innate immune gene associations with psoriasis have been found in interferon and anti-viral response genes. These genes are *DDX58* (DEAD (Asp-Glu-Ala-Asp) box polypeptide 58), which encodes the protein RIG-I, and *IFIH1*, which encodes the protein MDA5. Both RIG-I and MDA5 are intracellular, innate immune sensors, critical for detection of double stranded RNAs. RIG-I specifically recognizes shorter RNAs containing 5’ triphosphate moieties and blunt-end base pairing at the 5’ end, whereas MDA5 is thought to recognize longer RNA structures [73]. Both are important for recognition of dsRNA viruses or viruses that utilize dsRNA intermediates of replication, and the subsequent elicitation of a type-I interferon response [73, 74]. RIG-I can also detect DNA viruses and bacterial RNAs [73]. Activation of RIG-I or MDA5 results in gene expression changes mainly mediated by IRF3 and NF-κB [74]. Induction of type-I interferons, as well as other innate inflammatory and anti-microbial molecules, is a common outcome of RIG-I and MDA5 activation [74], and it known that expression of type-I interferons and downstream products of type-1 interferons are increased in psoriatic lesions [75-77].

Although it is not clear how *DDX58* and *IFIH1* mutations predispose to psoriasis, there have been a few studies that have investigated these genes in relation to psoriasis. Two cytokines heavily present in psoriasis, TNFα and/or IFNγ, can increase expression of RIG-I and MDA5 expression in keratinocytes [78, 79]. Additionally, RIG-I and MDA5 have increased

expression in psoriasis lesional skin [79, 80]. Upon successful treatment of psoriatic lesions, using narrow band-ultra violet B (NB-UVB), expression of RIG-I and MDA5 are decreased [79]. A third GWAS hit was recently found in another potential innate, type-I interferon inducing gene, *RNF144* [81], supporting the role of mutations in this pathway in psoriasis susceptibility. Lastly, two rare SNPs in *MDA5*, likely leading to reduced functionality of the protein, are associated with a decreased risk of psoriasis [82].

Although classically thought to be important for sensing pathogens, these innate pattern-recognition receptors may bind self-derived molecules that have increased presence in psoriatic skin. SRSF1 (serine/arginine rich splicing factor 1) can interact with RIG-I, resulting in the ability of cytosolic DNA to elicit RIG-I mediated-production of type I interferons [83]. Some recent studies have shown that plasmacytoid DCs and myeloid DCs can respond to self-DNA and LL37 complexes, via TLR7 and TLR8, respectively [84]. In conclusion, mutations in innate pattern recognition receptors, such as RIG-I and MDA5, might have a decreased threshold for triggering by either self- or non-self stimuli, and be a key initiating step in lesion development.

6. Negative regulators

Most biological systems have mechanisms to maintain homeostasis, and the immune system is no exception. There are several immune suppressive cytokines (i.e. IL-10), cell surface signaling molecules (CTLA-4), secreted soluble receptors and natural receptor antagonists involved in suppression of immune responses. As psoriasis is a disease of an overactive immune response, it is not unexpected that mutations in genes important for maintaining homeostasis might be associated with disease susceptibility.

Several genes involved in downregulation of the NF-κB pathway have been found to have genetic associations with psoriasis. These include *TNIP1* (TNFAIP3 interacting protein 1, annexin A6), *TNFAIP3* (tumor necrosis factor, alpha-induced protein 3, also known as A20), *NFKBIA* (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha), and *ZC3H12C* (zinc finger, DHHC-type containing 23) [18, 33, 85].

TNIP1 and TNFAIP3 work together in inhibition of NF-κB signaling, via prevention of NEMO polyubiquination and subsequent degradation of the NF-κB inhibitor, IκB [86, 87]. Both *TNIP1* and *TNFAIP3* have been found as susceptibility loci for not only psoriasis [16, 17, 27, 88], but also SLE and rheumatoid arthritis [89-91]. TNIP1 inhibits NF-κB signaling through several receptors, including the TNFα receptor, the EGF receptor, and Toll-like receptors [86, 92]. TNIP1 can also inhibit PPAR signaling [93] and may protect cells from apoptosis [86]. A noncoding variant of *TNIP1* is associated with psoriasis, suggesting that reduced ability to suppress NF-κB signaling is important in elicitation of psoriasis [14]. It was also found that *TNIP1* has an altered methylation pattern in psoriasis patients, which would correlate with the observation that it is up-regulated in psoriatic skin [94]. *NFKBIA*, which encodes the protein IκBα, is an inhibitor of NF-κB signaling. It does this by sequestering of NF-κB dimers in the cytosol in the absence of inflammatory stimuli [95].

ZC3H12C is important in suppressing NF-κB signaling and pro-inflammatory gene expression in endothelial cells [96]. This finding that ZC3H12C is able to inhibit vascular

inflammation is interesting considering the cardiovascular comorbidities with psoriasis. Therefore, similar to gain-of-function psoriasis-associated mutations in CARD14, loss-of-function psoriasis-associated variants in ZC3H12C within endothelial cells may result in overactive NF-κB signaling, resulting in the heightened ability of both dermal and non-dermal endothelial cells to produce inflammatory molecules. ZC3H12C is also expressed in macrophages and although the exact role of this gene in macrophages has not been explored, it was found that a member of the same family, ZC3H12A, inhibits the ability of macrophages to produce nitric oxide species after LPS stimulation [97]. As psoriatic lesional skin contains an abundance of myeloid cells expressing iNOS, it may be possible that psoriasis-associated mutations in ZC3H12C result in heightened nitric oxide production.

As mentioned in section 5, one of the few genes with highly penetrant mutations leading to psoriasis is *IL36RN*; mutations in this gene were first found in two families with severe generalized pustular psoriasis [98, 99]. *IL36RN* encodes the IL-36Ra, an anti-inflammatory protein that is a natural antagonist for IL-1F9. These mutations in result in reduced activity of the protein, and subsequent unopposed affects of the inflammatory cytokine IL-1F9. As a consequence, NF-κB regulated cytokines are highly increased in individuals with *IL36RN* mutations.

SOCS proteins are critical in limiting STAT-mediated signaling, such as the downstream signaling activated through cytokine receptors [100]. SOCS1 (suppressor of cytokine signaling 1) is rapidly upregulated upon signaling through type I and II cytokine receptors, including IFNγ [101]. SOCS1 contains a kinase inhibitory region (KIR), which binds to JAKs and inhibits further cell signaling [102]. SOCS1 can also bind to proteins and target them for proteosomal degradation [100]. GWAS have shown that *SOCS1* is an independent predisposing locus for psoriasis in European populations [18]. SOCS1 is known to be important in suppressing a Th1/IFNγ response although how *SOCS1* alterations contribute to psoriasis is not immediately obvious, *SOCS1*−/− CD4+ T-cells have suppressed Th17 polarization [102], so the biological consequences of psoriasis mutations in *SOCS1*, including its signaling pathway in healthy and psoriatic skin need to be further investigated.

In general, the failure of inflammation to resolve in psoriasis has been much less studied than the mechanisms that actively contribute to the inflammation. These genetic examples demonstrate the importance of negative regulators in controlling inflammation in psoriasis. Mutations in these negative regulators likely result in reduced ability to control inflammation and may play as important a role as those mutations resulting in overactive immune responses.

7. Immune genes with less-well established links to psoriasis pathogenesis

As described through this review, many of the immune genes implicated by genetic associations in psoriasis have a relatively obvious rationale regarding how they might predispose to disease. However, the causative variants responsible for these variants have not been identified in the majority of cases, so confirmation of both the gene/s within an associated interval, and how the variant leads to disease, will await future studies. There are additional immune related genes in which an association to psoriasis has been made, but the

link between mutations in these genes and psoriasis susceptibility is less clear. These include *NOS2A* (nitric oxide synthase 2, inducible) and *IL28RA* (interleukin-28 receptor alpha) [88].

NOS2A is one gene that can correctly classify psoriasis versus eczema, with *NOS2A* expression being specifically only enhanced in psoriasis [103, 104]. *NOS2A* is upregulated in many cancers, including prostate and breast cancers [105-107]. NOS2 is also important in the immune response to several pathogens. However, it is unclear how *NOS2A* mutations might contribute to psoriasis susceptibility. NOS2A expression can be induced by IFNγ, a cytokine heavily present in psoriatic lesions, and the products of NOS2A can upregulate several inflammatory molecules known to be increased in psoriasis, such as S100A8, IL-6, and IL-8 [108]. NOS2 is also important for the *de novo* induction and stability of human Th17 cells in from cancer patients [109]. This last finding merits further investigation, and may be a clue to the role of *NOS2A* mutations in psoriasis predisposition.

IL28RA is a member of the class II cytokine receptor family. It can dimerize with IL-10RB, which forms the receptor for the three cytokines IL-28A, IL-28B, and IL-29. These three cytokines are also known at type III interferons (IFNλ) [110]. IFNλ, as with the other interferons, are important for the immune response to viruses and stimulates similar signaling cascades, i.e. Jak-STAT signaling [110, 111]. However, one interesting feature of IFNλ is the restriction of IFNλ-receptors (such as IL28A) to mainly cells of epithelial origin [112]. Therefore, psoriasis associated mutations in *IL28RA* may increase the responsiveness of the skin to IFNλ, and contribute to elicitation of inflammation.

Although they do not encode proteins, microRNAs may also play a role in the immunogenetics of psoriasis [113, 114]. The rs2910164 SNP of miR-146a was associated with an increased risk of psoriasis in one study [115]. This microRNA targets the EGFR (epidermal growth factor receptor) transcript. The rs2910164 SNP was found to decrease the ability of this miR-146a to suppress EGFR expression, and EGFR expression is known to be elevated in lesional skin [116]. Alternatively, it is possible that any of the SNPs mentioned above in protein-coding immune genes may destroy, alter, or even create miRNA targeting-sites for that transcript [114].

8. Conclusions

Psoriasis is a complex, multi-factorial autoimmune disease, with many complex immunogenetic contributions. Despite our increase in knowledge about disease pathogenesis and the identification of predisposing genetic risk factors in the form of SNPs, there are many unanswered questions. Most GWAS findings are in noncoding DNA, and the causative variants still need to be identified. Changes in noncoding DNA could certainly modulate splicing of the pre-mRNA transcript, but a specific understanding on the effects of these psoriasis-associated mutations on the protein and subsequent biological function still need to be addressed. Until this is achieved, it will not be easy to interpret GWAS associations and how this modulates not only the immune system, but also other cells and tissues. Additionally, many of these immunological gene associations are shared with other autoimmune diseases; specific examples were highlighted throughout the article. There are

many immunogenetic associations shared between psoriasis vulgaris and psoriatic arthritis, with most psoriasis vulgaris loci being shared with psoriatic arthritis [117].

Gaining a better understanding of how these gene associations predispose to psoriasis will likely shed light on their role in predispositions to other autoinflammatory and autoimmune diseases, as well as the psoriasis associated comorbidities. Several of the genetic predispositions, such as *CARD14* and *ZC3H12C*, were found to not only potentially alter immune cell or keratinocyte behavior, but also the biology of the vasculature. These mutations might therefore play a role in the cardiovascular comorbidities associated with psoriasis, and may also highlight a need to monitor cardiovascular health more closely in these individuals.

Enhanced understanding of the underlying biology of these immunogenetic associations with psoriasis may generally improve treatment of patients. Although we consider all of these psoriasis-associated mutations as eliciting the same disease (i.e. psoriasis vulgaris), it is interesting to speculate that in fact these are distinct diseases. In fact, we may eventually describe a person with psoriasis as having, for example, "*CARD14*-associated psoriasis". Although the disease may manifest similarly, the underlying initiators may be distinct. Those whom have psoriasis elicited by particular mutations may more likely benefit from particular treatments over others. Indeed, those with polymorphisms in TNF-related genes, such as *TNFAIP3*, are associated with a better response to anti-TNFα therapy [118, 119]. It is not unreasonable to speculate that in the future, personalized medicine and specific immunomodulatory treatment will be based upon genetic alterations in particular immune genes.

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Highlights

- Psoriasis is a chronic inflammatory, skin disease with genetic features similar to other complex inflammatory diseases.

- Many genetic associations identified through GWAS are in immune genes, highlighting the importance of immune dysregulation in psoriasis susceptibility.

- The role of the Th17/IL-23 axis in psoriasis has been well established and many genetic risk factors are found within genes in this pathway.

- Genetic-associations in both innate immunity and negative immune regulator genes points to a complex etiology of psoriasis.

- Understanding the biology of psoriasis-associated mutations may lead to improved treatment, through novel therapeutics to personalized medicine.

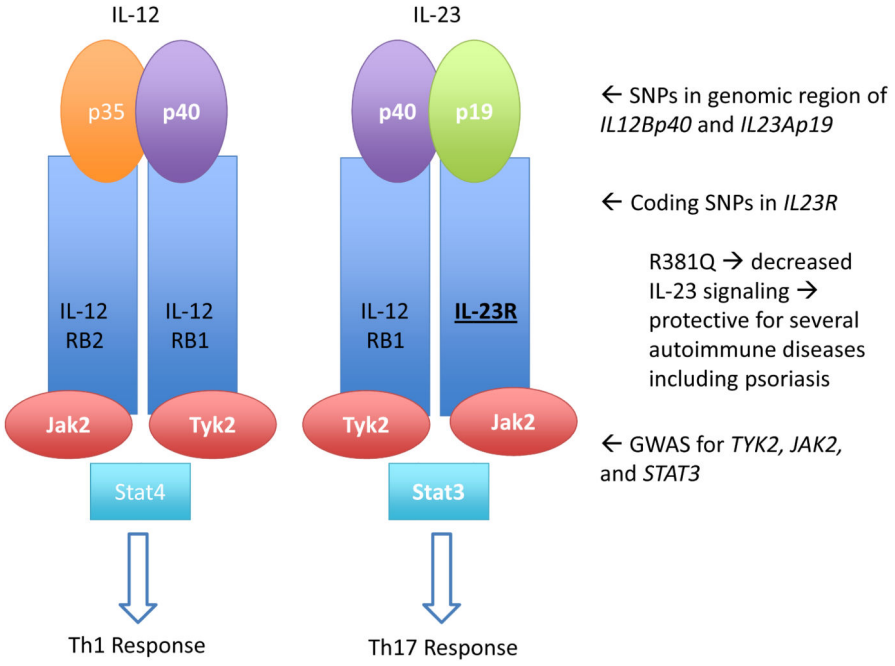

Figure 1. The IL-23 axis genes associationed with psoriasis

IL-12 and IL-23 share both a common subunit (p40), as well as a common chain in their heterodimeric receptor, IL-12RB1. Both cytokines signal though JAK-STAT signaling. However, IL-12 is composed of p35 and p40, whereas IL-23 is composed of p19 and p40. The IL-12 receptor is composed of IL-12RB1 and IL-12R2, whereas the IL-23 receptor is composed of IL-12RB1 and IL-23R. Lastly, IL-12 signaling culminates in activation of STAT4, whereas IL-23 signaling results in activation of STAT3. Components underlined and bolded represent the protein products of genes found to have associations with psoriasis; specific details are provided to the right of the diagram. Although psoriasis was initially considered to be a Th1 mediated disease (and thus would have large contributions of the IL-12 axis), it is now well understood that the disease is mainly mediated through the IL-23 driven Th17 response. In summary, many components of the IL-23 axis have genetic associations with psoriasis, including the IL-23 cytokine itself, the IL-23 receptor, and downstream signaling through the IL-23 receptor.

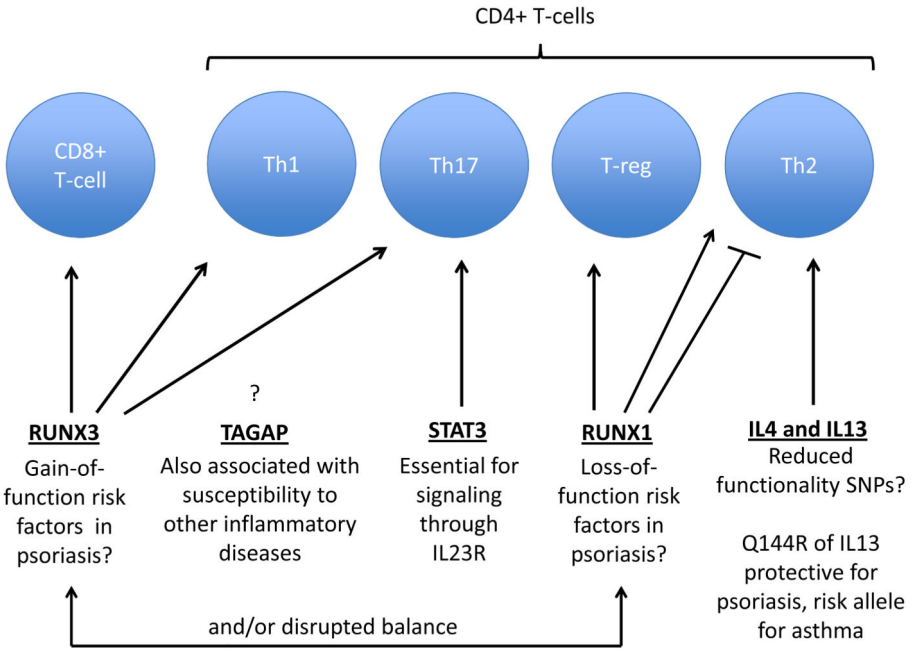

Figure 2. T-cell polarization genes associated with psoriasis

Massive T-cell infiltration is a hallmark of psoriasis and both CD8+ and CD4+ T-cells have increased prevalence in lesional skin. In response to cytokine signaling during the elicitation of inflammation, T-cells (particularly CD4+T-cells), have the plasticity to acquire unique phenotypes. Many cellular factors play important roles in this phenotype determination. Psoriasis is characterized by a predominantly Th1 and Th17 infiltrate, although the latter is considered to be the key pathogenic response. Many factors which control T-cell polarization and fate have genetic associations with psoriasis. These include both genes associated with Th1 and Th17 phenotypes (*RUNX1* and *STAT3*) and T-reg and Th2 phenotypes (*RUNX1*, *IL4*, and *IL13*). As T-cell polarization is a delicate balance of signals that determine the T-cell's fate, both gain-of-function (i.e. *RUNX1* and *STAT3*) and loss-of-function mutations (i.e. *RUNX1*, *IL4*, and *IL13)* may both contribute to disease susceptibility.

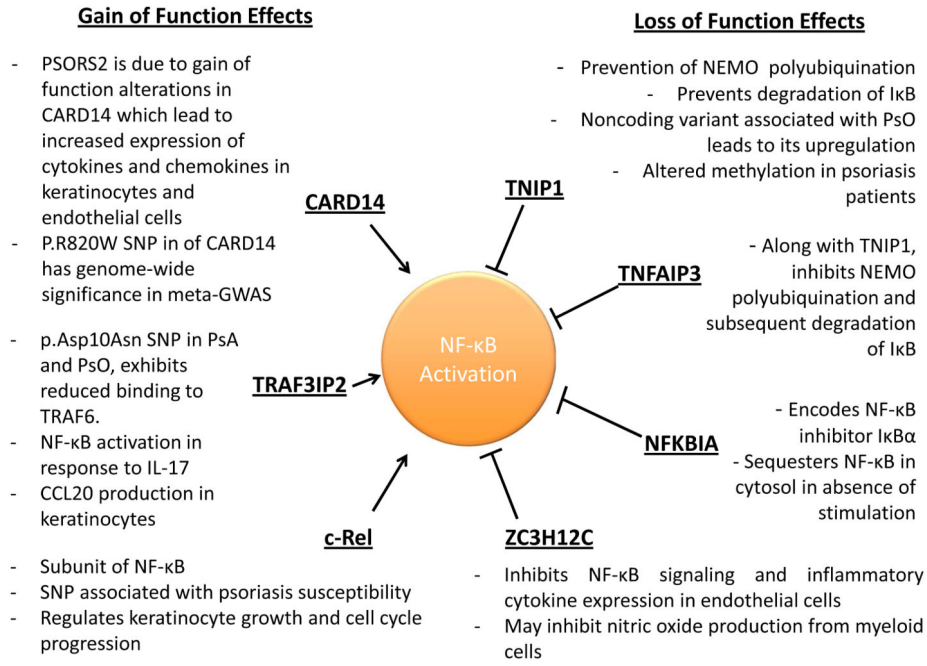

Figure 3. Multiple genes in the NF-κB pathway are associated with psoriasis

The NF-κB pathway is a critical pathway in elicitation of immune responses. Although psoriasis is considered a disease of an overactive adaptive immune response, as evidenced by the massive infiltration of T-cells and the success of treatment based upon elimination of these pathogenic T-cells, innate pathways may still play a central role in disease. Genetic associations with psoriasis have been found in both components that activate and components that repress the NF-κB pathway. It is likely that gain-of-function mutations in NF-κB activating components (left) and loss-of-function mutations in NF-κB inhibitory components (right) decreased the threshold for immune activation and the subsequent onset of psoriasis. Specific details regarding mutations and the functional consequences are provided near the corresponding gene.