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Genome-wide Association Scan Yields New Insights into the Immunopathogenesis of Psoriasis

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Abstract

Psoriasis is a common, immunologically-mediated, inflammatory and hyperproliferative disease of the skin and joints, with a multifactorial genetic basis. We previously mapped *PSORS1*, the major psoriasis susceptibility gene in the major histocompatibility complex, to within or very near *HLA-Cw6*. In an effort to identify non-MHC psoriasis genes, we carried out a collaborative genome-wide association study. After initial follow-up genotyping of 21 SNPs from 18 loci showing strong evidence of association in the initial scan, we confirmed evidence of association at seven loci. Three of these loci confirm previous reports of association (*HLA-C*, *IL12B*, *IL23R*) and four identify novel signals located near plausible candidate genes (*IL23A, IL4/IL13, TNFAIP3*, and *TNIP1*). In other work, we have also shown that interferon-γ (IFN-γ) treatment induces IL-23 mRNA and protein in antigen-presenting cells (APC), leading to the proliferation of CD4+ and CD8+ memory T-cells expressing IL-17. While functional variants remain to be identified, we speculate that genetic variants at the *IL4/IL13* locus contribute to the Th1 bias that is characteristic of psoriasis, that Th1-derived IFN-γ supports expansion of IL-17+ T-cells via APC-derived IL-23, and that negative regulation of inflammatory signaling through the NF-κB axis is impaired due to genetic variants of *TNFAIP3* and *TNIP1*.

Keywords

Psoriasis; dermatology; human genetics; interleukins; NF-κB; immunology

Epidemiology of Psoriasis: An Overview

Psoriasis vulgaris (PsV) is a common inflammatory and hyperproliferative skin disease, affecting over 4 million Americans (about 2%) at an estimated cost of $1.6 to $3.2 billion annually [1]. The cutaneous manifestations of psoriasis are unpleasant and obvious, with a very negative impact on quality of life [2]. The majority of the 150,000 new U.S. cases diagnosed annually arise in individuals <30 years of age, and 10,000 of these are in individuals <10 years old [3]. Moreover, up to 40% of psoriatics develop psoriatic arthritis (PsA), and in 5% of them the arthritis is severe and deforming [4].

The clinical and genetic epidemiology of psoriasis has been reviewed in detail [5-8] and will be only briefly considered here. Two forms of psoriasis differing in age of onset have been proposed, with early onset disease (onset ≤ 40 years) more likely to be familial, severe, and associated with *HLA-Cw6*[9]. The peak age of disease onset is the early twenties. Twin studies, pedigree studies, and recurrence risk analysis support a multifactorial model of inheritance, with a major susceptibility locus (psoriasis susceptibility 1 or *PSORS1*) residing within the MHC, with other loci throughout the genome. There is clearly a role for environmental factors

such as trauma, stress, and infections such as streptococcal pharyngitis (for review, see [5]). PsA is even more strongly influenced by genes, than is PsV [10; 11].

The clinical variants of psoriasis include chronic plaque psoriasis, guttate psoriasis, localized pustular psoriasis, inverse psoriasis, sebopsoriasis and generalized pustular psoriasis, as well as palmoplantar pustulosis. Chronic plaque disease is by far the most common form. The clinical manifestations of psoriasis can change over time in any given person. Nail changes (pitting, onychodystrophy, and/or "oil drop" spotting) are found in around 50% of psoriasis patients. Guttate psoriasis is characterized by the sudden appearance of hundreds of small papules, with spontaneous resolution in approximately half of cases, with the other half progressing to chronic plaque psoriasis. The association of guttate psoriasis with *HLA-Cw6* is even stronger than it is for chronic plaque psoriasis [12]. Generalized pustular psoriasis manifests the same HLA associations found in plaque-type psoriasis [13]. In contrast, palmoplantar pustulosis is not associated with *HLA-Cw6* [14] and is only rarely associated with typical psoriatic plaques. Therefore, it appears to be a distinct entity. PsA typically presents between the ages of 35 and 45, usually but not always after onset of skin disease. Disease is oligoarticular and asymmetrical in over 80% of patients.

The Th1 —Th17 axis: New Insights into Psoriasis Pathogenesis

Recently, there has been a major expansion knowledge that may provide specific insights into the link between immunocytic infiltration and epidermal hyperplasia. A new subset of T-cells expressing IL-17 appears to play a major role in psoriasis [15] as well as other inflammatory autoimmune disorders including multiple sclerosis [16] and Crohn's disease (CD) [17]. IL-23 drives this novel immune circuit. It is produced by myeloid cells and acts on T-cells via its cognate receptor. IL-12 and IL-23 share the p40 subunit, encoded by the *IL12B* gene. The p40 subunit heterodimerizes with p19 to for IL-12 and with p35 to form IL-23. The IL-12 and IL-23 receptors share the common IL12rRβ1 subunit, which binds to IL12Rβ2 to form the IL-12 receptor and to the product of the *IL23R* gene to form the IL-23 receptor. In mice, injection of IL-23 leads to epidermal hyperplasia mediated by IL-22 produced by IL-17-expressing T-cells [18; 19], and consistent if not identical phenomena are observed in humans [20]. Keratinocytes express high levels of IL-22 receptors, and are highly responsive to IL-22 as well as other cytokines of the IL-20 subfamily including IL-19, IL-20, and IL-24 [21; 22]. IL-22 is distinctive among these cytokines in that it is primarily expressed by activated T-cells and not keratinocytes [23] and is therefore well-positioned as a bridge between the two. We have recently implicated IFN-γ as a key stimulus causing CD14+ macrophages to stimulate the proliferation of IL-17+ T-cells, via their production of IL-1 and IL-23 [24] (Figure 1). We also identified a population of CD8+ IL-17-expressing cells in the epidermis of psoriatic lesions. Essentially all of the IL-17 producing T-cells in psoriatic epidermis were CD8+, whereas there were no such cells in normal epidermis [24]. these cells may play a causal role in provoking epidermal hyperplasia in psoriasis, as recent studies in xenografted mice have shown that entry of T-cells into the epidermis is necessary for development of the epidermal hyperplastic response [25].

Genome-wide Association Scan of Psoriasis

With the advent of the HapMap [26], we now have a dense map of millions of SNPs to choose from, and massive throughput genotyping technologies allow 100,000-1,000,000 SNPs to be characterized economically in thousands of individuals. Anticipating these developments, in 2003 we refocused our experimental approach from linkage to association, opting to collect large numbers of cases and controls rather than families. In 2006 we formed a multicenter collaboration with Dr. Anne Bowcock at Washington University of St. Louis and Dr. Gerald Krueger of the University of Utah, to carry out a GWAS of psoriasis(the Collaborative Association Study of Psoriasis, or CASP). We were funded by the Genetic Association

Information Network (GAIN), a public-private partnership formed to facilitate the execution of GWAS and the rapid dissemination of their results [27]. We also linked up with five additional groups of collaborators interested in PsV and PsA, in order to carry out a powerful replication study based on the GAIN results. The results of this study have recently been published [28] but will be briefly reviewed here.

We carried out a GWAS of 1,409 Caucasian psoriasis cases and 1,436 Caucasian controls, making use of a Perlegen Sciences microarray platform that types a large number of SNPs with known effects on protein structure and gene expression, and allows for efficient incorporation of HapMap tag SNPs. After removing SNPs and samples with low genotype call rates, screening for related individuals, and removing markers with strong deviations from Hardy-Weinberg equilibrium (HWE), we carried out our initial association analysis on 438,670 SNPs in 1,539 cases and 1,400 controls. By far, the strongest association signals mapped to the MHC (Figure 2). SNP rs12191877, the marker demonstrating the strongest association with psoriasis ($f_{control}$ = 0.15, f_{case} = 0.30, $OR_{follow\text{-}up}$ = 2.64, $p_{combined} << 10^{-100}$), was in linkage disequilibrium (LD) with *HLA-Cw6* (r^2 = 0.63). Nearly equally strong signals were observed in the vicinity of CDSN, as expected from our earlier studies of the MHC in psoriasis families [29]. In a subset of cases and controls with *HLA-Cw6* typing, this allele was more strongly associated with psoriasis than any genotyped or imputed SNP, but could not fully account for all observed association signals. We used a forward selection procedure to assess the possibility that multiple psoriasis susceptibility alleles might exist within the MHC. This analysis resulted in a model with three imputed SNPs. The first two of these (rs12204500 and rs13191343, forward selection p-values of 8×10^{-57} and 2×10^{-10}, respectively) are close to and in strong LD with *HLA-Cw6* (r^2 = 0.78 and 0.52, respectively). However, the third SNP (rs2022544, p-value = 10^{-7}) maps closer to the *HLA-DR* gene cluster in the C6orf10 gene and exhibits only weak LD with *HLA-Cw6* (r^2 = 0.01). These results confirm the predominance of the PSORS1 in terms of the magnitude of its genetic effect, and suggest that at least one additional determinant of psoriasis susceptibility resides within the MHC. This would be consistent with studies demonstrating a higher risk associated with an extended ancestral haplotype carrying HLA-Cw6, HLA-B57, and HLA-DR4, relative to other HLA-Cw6-bearing haplotypes [29; 30].

Based on our initial genome-scan results, 21 SNPs representing 18 independent loci were genotyped in independent samples totaling 5,048 cases and 5,051 controls (1,642 cases and 1,101 Caucasian controls from the Michigan, 718 cases and 1,464 controls from Kiel, Germany) 981 cases and 925 controls from Celera Genomics, 302 cases and 500 controls from St. Louis, 691 cases and 217 controls from Toronto, and 368 cases and 358 controls from Newfoundland) as well as a pedigree-based collection from France (1130 individuals from 45 families ranging from 5 to 60 members). Follow-up genotyping results confirmed association at 7 loci (with $p < 10^{-3}$ in the replication study and $p < 10^{-8}$ overall), including three loci previously associated with psoriasis, *HLA-C*, *IL12B*, *IL23R* [28; 31-33], and four new loci located near plausible psoriasis candidate genes: *IL23A*, *IL4/IL13*, *TNFAIP3*, and *TNIP1*. We next assessed the risk of PsA conferred by these replicated loci. As shown in Table 1, three loci reached genome-wide significance for PsA compared to normal controls (*HLA-C*, *IL12B*, and *TNIP1*), and one came close (*IL4 / IL13*). Three loci manifested a statistically significant difference ($p < 0.05$) between PsA and purely cutaneous psoriasis: *HLA-C*, *IL12B*, and *IL23R*.

With the probable exception of *HLA-Cw6* [29], the precise genetic variants responsible for the remaining six observed associations remain to be determined. Nevertheless, our results suggest roles for several key immunologic pathways in disease susceptibility.

HLA-Cw6

HLA-C plays a key role in the presentation of antigens to CD8+ T-cells, which predominate in the epidermis of psoriatic lesions. Guttate eruptions frequently follow attacks of Streptococcal pharyngitis [5]. Other streptococcal skin infections such as erysipelas, impetigo, or cellulitis do not seem to trigger psoriasis, suggesting a critical role for the tonsils. Tonsillar T-cells recognize activated skin endothelium [34], and home to the skin. Indeed, the same skin-homing T-cell clones present in the tonsils are also found in the lesional skin of psoriatic patients [35]. Many of these clonally exapanded T-cells are CD8+ [36]. Several other studies have also identified oligoclonal TCR rearrangements in psoriasis [35-39]. These findings support the notion that T-cells originally stimulated in the tonsils may traffic into the skin, where some of them become clonally expanded due to antigenic stimulation. However, the identity of the antigen(s) has remains elusive. One study identified several potential psoriasis antigens by expression cloning from psoriatic skin RNA [40]. However, peripheral blood T-cells from normal controls reacted as strongly as T-cells derived from psoriatic patients [40], making the results hard to interpret. In another study, HLA-Cw6 preferentially presented cross-reactive peptides derived from Streptococcal M protein and the hyperproliferative keratin K17 to skin-homing CD8+ T cells [41], suggesting that the evolution of guttate into chronic plaque psoriasis might reflect a transition from a self-limited response to Streptococcus initiated in the tonsils, to a sustained response to homologous peptides derived from hyperproliferative skin keratins [41]. It has also been suggested that peptidoglycan (PG), the major constituent of the streptococcal cell wall, acts as a T cell activator in psoriasis [42]. PG-containing cells were detected in CD68+ macrophages in the dermal papillae and cellular infiltrates of guttate and chronic plaque skin lesions [42]. Based on these results, it has been proposed that macrophages may serve as a vehicle for transportation of PG from the tonsils to the skin, where it may serve both as an antigen and as a stimulus for Toll-like receptor (TLR) mediated stimulation of innate immunity [43]. Whatever the antigen(s) may be, it is important to realize that most T-cells present in psoriatic skin are not clonally expanded, indicative of important roles for additional mechanisms to maintain the psoriatic infiltrate.

HLA-C also plays a role in binding to killer immunoglobulin-like receptors (KIRs) on natural killer (NK) cells, and *KIR* genes have previously been associated with PsA[44; 45]. NK cells are major producers of interferons and serve as a bridge between innate and acquired immunity. KIR molecules can either inhibit or stimulate NNK cells, and inhibitory KIR genes interact with a dimorphic allotype (Asn80/Lys80) present on HLA-C molecules [46]. HLA-Cw6 is one of several “group 2” alleles carrying Lys at position 80, thus one might expect that a combination of all “group 2” alleles would provide a stronger association signal than does HLA-Cw6, but this is not the case (unpublished data). Thus, at present, the role of HLA-Cw6 as a mediator of in NK cell activity in psoriasis remains to be genetically clarified through typing of both KIRs and HLA-C in a large dataset.

IL-23 signaling

Three SNPs exhibiting strong evidence of association map near *IL12B* (encoding the p40 subunit of IL-23 and IL-12), *IL23A* (encoding the p19 subunit of IL-23), and *IL23R* (encoding a subunit of the IL-23 receptor) (see 28 for details). Our study implicated genetic variants in the *IL23A* locus for the first time in psoriasis and for that matter in any human autoimmune disorder. Interestingly, our GWAS identified no associations with either of the IL-12-specific genes *IL12B* or *IL12RB2*, and psoriasis lesions markedly overexpress IL-12/23 p40 and IL-23 p19, but not IL-12 p35 [47]. IL-23 signaling promotes cellular immune responses by promoting the survival and expansion of a recently identified subset of T-cells expressing IL-17 that protects epithelia against microbial pathogens [48]. Dysregulated IL-23 signaling could lead to inappropriate, chronic immune responses that target epithelial cells, perhaps helping to explain the relatively skin-specific inflammation seen in psoriasis. One of the same genetic variations

in the *IL23R* gene that increases risk for psoriasis also confers risk for Crohn's Disease [49], a disorder that has long been known to be clinically associated with psoriasis [50]. It is possible that this clinical association reflects the similarities between the epithelial linings of the skin and the gut.

NF-κB signaling

The products of the *TNFAIP3* and *TNIP1* genes (A20 and ABIN1/Naf1α, respectively), physically interact with each other to influence the ubiquitin-mediated destruction of IKKγ / NEMO, a central nexus of NF-κB signaling [51]. A20 also regulates the degradation of several other components of the TNF signaling pathway [51]. TNF-α blockade improves symptoms in a mouse model of psoriasis induced by administration of IL-23 [52] and a region of mouse chromosome 10 encompassing *Tnfaip3* promotes psoriasis in a TNF-α dependent manner in another mouse model [53]. This region of the mouse genome has been also associated with atherosclerosis [54], a major co-morbidity of psoriasis [55].

Of particular interest in the context of this meeting, common polymorphisms near *TNFAIP3* have recently been associated with systemic lupus erythematosus (SLE) [56; 57] and with rheumatoid arthritis RA [58; 59]. Notably, the polymorphisms implicated in RA and SLE show no association with psoriasis in our sample (all $p > 0.30$) and are not in linkage disequilibrium (LD, all $r^2 < 0.03$) with the psoriasis associated alleles, suggesting that each of these common autoimmune diseases is driven by a different variant of the *TNFAIP3* gene. Some of the polymorphisms implicated in RA and SLE reside far upstream from the gene (~200 kb), suggesting that they might reflect the existence of regulatory variants. Of note, we have also found an association between PsA and SNPs in this upstream region (unpublished data).

Th2-predisposing genes

IL-13 and IL-4 are products of Th2 cells that play a multifaceted role in allergic reactions and in the immune response to extracellular pathogens. Both IL-13 and IL-4 are expressed at high levels in atopic dermatitis, but only at very low levels in psoriasis [60]. IL-4 treatment has led to significant clinical improvement of psoriasis [61]. The *IL13* and *IL4* genes are located within 12.5 kb of each other on human chromosome 5q31.1, just telomeric to the *RAD50* gene, within a block of linkage disequilibrium (LD). While our most positive signals reside near *IL4* and *IL13*, positive signals are also found in *RAD50*. Thus, the functional variant could influence not just *IL13* but alternatively or in addition might influence *IL4* and *RAD50*. Interestingly, a locus control region that regulates the transcription of both *IL13* and *IL4* within the *RAD50* gene [62].

Immuno-Genetic Model for the Development of Psoriasis

During an initial flare of guttate psoriasis following a strep throat, we envision that T-cells encounter streptococcal antigens presented in the context of HLA-Cw6 in the tonsils, where they proliferate, differentiate into an effector / memory phenotype, and acquire skin homing capability (i.e., become CLA+). Upon entering the skin, these cells encounter a locally activated dermal environment characterized by capillary dilatation and edema [63-66] and the presence of plasmacytoid dendritic cells [67; 68]. We suspect that this "pre-psoriatic environment" may be initiated by focal mast cell degranulation and activation of plasmacytoid dendritic cells and macrophages, with release of TNF-α and interferon leading to induction of adhesion molecules on the endothelial cell surface, facilitating entry of T-cells into the dermis. These events might be triggered by circulating pathogen-derived factors such as PG [43] and/or innate immune mediators induced by them. Many of the signaling pathways are mediated by TNF-α, toll-like receptors, or other ligands and receptors of the TNF receptor family that pass through NF-κB, often by way of IKK-γ. Thus, genetically-mediated defects in *TNFAIP3* and *TNIP1* could

enhance this early inflammatory stage of lesion development by interfering with normal negative feedback regulation of NF-κB signaling.

At this early stage of lesional evolution epidermal changes are subtle, but include a modest increase in keratinocyte DNA synthesis, widened extracellular spaces between keratinocytes, and biochemical alterations in the stratum corneum indicative of altered differentiation, despite a lack of visible parakeratosis [69]. These epidermal changes may be provoked by macrophage-derived proteases creating holes in the epidermal basement membrane [70; 71], allowing permeation of fibronectin [72] and cytokine-laden mast cell granules into the epidermis [73]. These events could be hyperactive in psoriasis due to defective negative feedback regulation of signaling by *TNFAIP3* and *TNIP1*. Keratinocyte hyperplasia results the activation of a set of genes involved in regenerative hyperplasia, including keratins K6, K16 and K17 [74; 75], along with many other genes involved in innate immunity, including human β-defensin-2 (hBD-2), psoriasin (S100A7), S100A8, and S100A9, small proline-rich region (SPRR) proteins, and late cornified envelope (LCE) proteins [76; 77]. Many of the most strongly up-regulated genes in psoriasis are located in the epidermal differentiation complex on chromosome 1q21.3, also known as *PSORS4* because of several reports of genetic linkage and association of this region to psoriasis [78-82]. It is also notable that the defensin gene cluster on human chromosome 8p exists in different numbers of copies in different individuals, and psoriasis has been associated with increasing defensin gene copy number [83]. Once their expression has been turned on, peptides derived from these regenerative hyperplasia-associated proteins might serve as neoantigens on the surface of epidermal keratinocytes in the context of HLA Class I molecules, such as HLA-Cw6. It is also possible that Strep-derived PG could be delivered from the tonsils to the skin by macrophages, where they would be recognized as foreign antigens and/or promote innate immune responses via binding to TLR2 [43]. In the latter setting, downstream inflammatory signals could again be amplified as a consequence of *TNFAIP3* and/or *TNIP1* hypofunction.

As a consequence of Streptococcal infection, the pool of T-cells responding to Streptococcal antigens will be expanded and activated. CD4+ and CD8+ T-cells will enter the dermis via the inflamed endothelium. A subset of both CD4+ and CD8+ cells will express IL-17 and/or IL-22 due to stimulation by IL-23 and IL-1. Genetically-mediated hyperfunction of IL-23 and/or of its receptor could enhance the production of IL-17-expressing T-cells. Moreover, development of Th1 bias might be facilitated genetically-mediated hypofunction of the *IL4* and *IL13* genes. This would be predicted to lead to overproduction of IFN-γ, a major product of Th1 cells. We have shown that IFN-γ markedly stimulates the production of IL-23 by myeloid APC [24], and IL-23 in turn supports the development of T-cells expressing IL-17 and/or IL-22 (Figure 1).

Many of the CD8+ cells entering the skin will selectively traffic to the epidermis, because they express VLA-1 as well as integrin $a_E\beta_7$, which binds to E-cadherin expressed by keratinocytes [25; 84]. Once in the epidermis, a subset of Strep-reactive CD8+ T-cells is predicted to recognize self-derived or Streptococcal peptides in the context of HLA-Cw6, thus maintaining immunologic activation in an antigen-driven manner. We envision that a transition of reactivity from Strep-derived to self proteins might be necessary for the transition from guttate to chronic plaque psoriasis. Whatever the nature of the antigen, entry of CD8+ T-cells into the epidermis would trigger more extensive epidermal hyperplasia, possibly by means of cytokines such as IL-17 and/or IL-22 produced by epidermal CD8+ T-cells [18-20; 24]. Macrophages may also participate in this process, as suggested by two different mouse models of psoriasis [85; 86], but it is important to remember that the development of extensive epidermal hyperplasia in the human skin xenograft model requires entry of T-cells into the epidermis [25]. CD8+ T-cells could also trigger the local release a variety of soluble factors other than or in addition to IL-17 and/or IL-22, including cytokines such as TNF-α, chemokines such as IL-8 and CCL20, eicosanoids, and/or other innate immune mediators, which could further increase local

inflammation and stimulate keratinocyte proliferation [87]. Whether mediated by soluble factors or by actual physical damage, keratinocytes could respond to T-cell insult by elaborating growth factors such as amphiregulin, thereby encouraging their own proliferation and survival [88]. Concomitant with the induction of increased epidermal hyperplasia, there will be further up-regulation of keratinocyte-derived innate immune peptides with antimicrobial and chemotactic activity such as human β-defensin 2, CCL20, S100A7, S100A8, and S100A9, thus further increasing the number of immune and inflammatory cells entering the lesion, including neutrophils.

As summarized in Figure 3, we envision the psoriatic tissue reaction as a multi-stage process, with the recognition of antigen in the context of HLA-Cw6 by CD8+ T-cells playing a major role. This recognition probably takes place not only on antigen-presenting cells, but also on the surface of keratinocytes. Genetic alterations in the *TNFAIP3* and *TNIP1* genes may play very important roles in APC and macrophages due to the central role of these genes in regulating NF-κB signaling. Genetic variation in *IL12B*, *IL23A*, and *IL23R* may contribute to hyperexpansion of T-cells expressing IL-17 and/or IL-22, and this process is further supported by IFN-γ-producing Th1 cells whose polarization is influenced by genetically-mediated hypofunction of IL-4 and/or IL-13. Entry of CD8+ T-cells expressing IL-17 and/or IL-22 into the epidermis may provoke epidermal hyperplasia, leading to the overexpression by keratinocytes of many proteins involved in innate immunity. At least some of these may serve a source of antigen as well. Thus, the epidermal response "feeds back" into all earlier stages of the psoriatic developmental process, amplifying the psoriatic tissue response. Based on the model shown in Figure 3, the psoriasis susceptibility genes that we and others have identified so far seem to fit very well with current concepts of its immunopathogenesis.

Future Prospects

Much additional work is required to identify the actual disease-predisposing variants of these genes, and to understand how they contribute to pathology. Moreover, as can be seen in Figure 2, additional genes remain to be discovered. Currently, we are carrying out a deeper follow-up scan of approximately 10,000 SNPs in approximately 3,000 cases and 3,000 controls to identify additional psoriasis loci. Moreover, we expect that the number of psoriasis genes that can be found will increase substantially as sample size grows through collaboration and continued subject enrollment. For example, work on lipids progressed from one new locus in a ~2,800 sample GWAS [89], to 7 new loci in an ~8,800 sample GWAS [90; 91] and now 7-9 additional loci from a ~20,000 sample GWAS (unpublished data). Another example is human height, where two initial GWAS identified one gene each [92; 93] and subsequent larger GWAS and meta-analysis [92; 94] expanded the number of loci to nearly 40. Similar stories are playing out for other traits, notably Crohn's disease where a recent study of ~14,000 samples identified a total of 32 confirmed loci, 21 of which were new [95]. Even if the risk conferred by the variants uncovered by larger GWAS is relatively small, these genes may constitute very good therapeutic targets. We already know that monoclonal antibodies directed against TNF-α and IL/12/23 p40 provide highly efficacious therapeutic regimens for many psoriasis patients [96; 97], meaning that five of the genes implicated in our GWAS (*IL12B*, *IL23A*, *IL23R*, *TNFAIP3*, and *TNIP1*) play key roles in pathways targeted by therapeutic interventions. We expect that as new psoriasis susceptibility genes are identified, that many of them will further illuminate these pathways, and discover new ones amenable to therapeutic intervention. Moreover, once the full catalog of psoriasis genes have been identified, it may be possible to generate a "psoriasis gene profile" that can accurately predict one's risk of developing psoriasis. We have already been able to demonstrate a 25-fold difference in risk depending upon how many disease alleles one inherits at the *HLA-C* and *IL12B* loci [98]. Finally, as illustrated by *IL23R* in Crohn's disease and *TNFAIP3* in RA and SLE, genetic insights into psoriasis may

contribute to the better understanding of a variety of autoimmune and inflammatory disorders. Thus, continuing the search for psoriasis genes seems well worthwhile.

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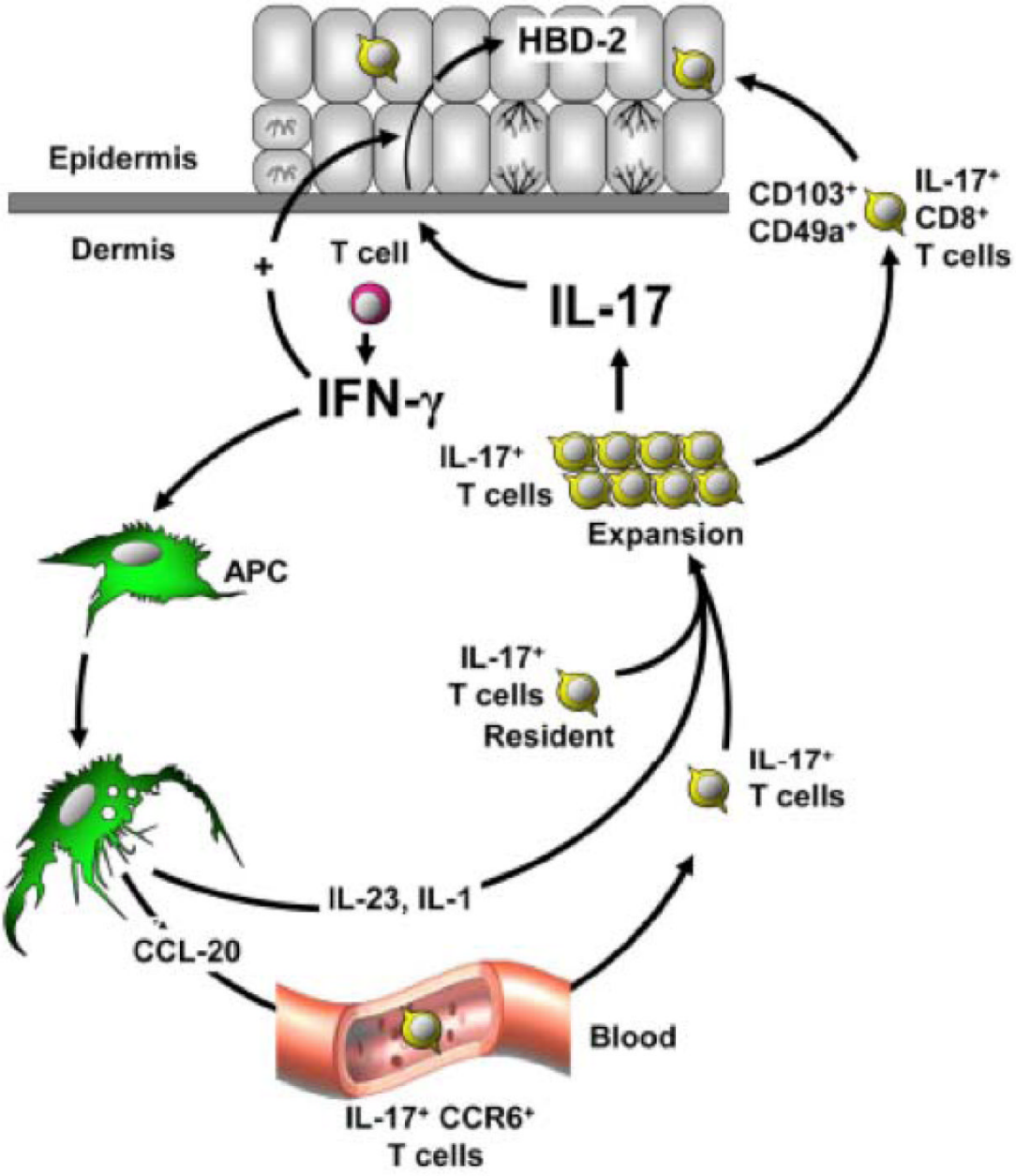

Figure 1.

Interplay between IFN-γ producing Th1 cells and IL-17-producing T-cells in psoriatic lesions. Interferon-γ produced by Th1 cells stimulates myeloid APCs and/or macrophages to produce IL-23, which together with IL-1, stimulates the survival and expansion of T-cells expressing IL-17 and/or IL-22. The entry of CD8+ T-cells expressing these cytokines into the epidermis is associated with increased epidermal hyperplasia and the production of innate immune peptides such as human β—defensin 2 (HBD-2). From [24], with permission.

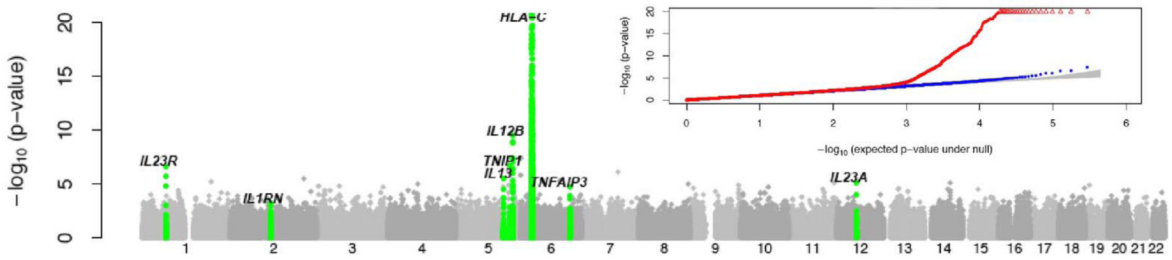

Figure 2.

CASP GWAS results plotted against chromosomal position; the inset presents quantile-quantile plots. Loci that were followed up and showed convincing evidence of association in the replication study are labeled in green. In the inset, red represents all the SNPs; blue symbols represent results after excluding SNPs at replicated loci and the gray area corresponds to the 90% confidence region for a null distribution of p-values. All panels are truncated at $-\log_{10}$(p-value) = 20, markers near *HLA-C* exceed this threshold. Adapted from [28], with permission.

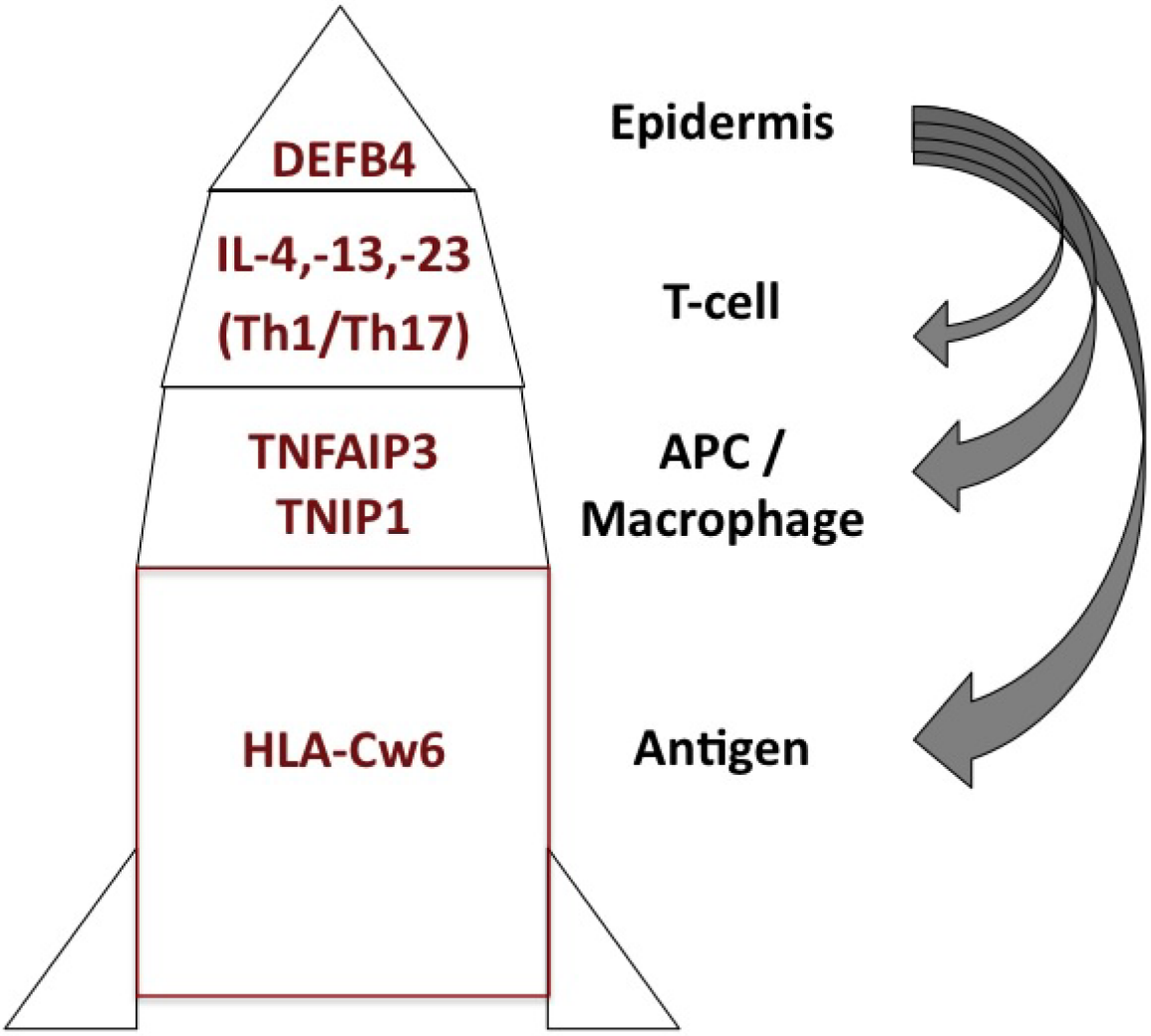

Figure 3.
Multi-stage model integrating genetics and immunology of psoriasis. See text for details.

Table 1

Association of replicated CASP GWAS signals with PsA.

				PsC vs. control (3523 cases, 5942 controls)				PsA vs. control (1755 cases, 5942 controls)				PsA vs. PsC (1755 cases, 3523 controls)			
Position (bld 36.1)	Nearby Notable Gene	Alleles (risk/ nonrisk)	.	freq cases	freq controls	meta OR	meta allelic p-value	freq cases	freq controls	meta OR	meta allelic p-value	freq cases	freq controls	meta OR	meta allelic p-value
3.1E+O7	HLA-C	T/C		0.316	0.139	2.87	2.98E-178	0.260	0.139	2.34	6.26E-62	0.260	0.316	0.87	6.14E-03
I.6E+O8	1L12B	G/A		0.846	0.797	1.42	4.57E-18	0.861	0.797	1.63	3.90E-16	0.861	0.846	1.19	9.51E-03
1.5E+O8	TNIP1	A/G		0.083	0.054	1.56	1.40E-13	0.100	0.054	1.78	2.32E-14	0.100	0.083	1.15	7.43E-02
1.3E+O8	IL23	G/A		0.821	0.787	1.24	3.77E-08	0.833	0.787	1.34	1.35E-07	0.833	0.821	1.10	1.13E-01
1.4E+08	TNFAIP3	G/T		0.364	0.318	1.23	3.O7E-1O	0.362	0.318	1.18	2.94E-04	0.362	0.364	0.98	6.70E-01
5.5E+O7	IL2RA	C/G		0.949	0.932	1.33	1.9OE-O5	O.955	0.932	1.55	9.49E-06	0.955	0.949	1.15	2.25E-01
6.7E+07	IL2RB	G/A		0.340	0.295	1.23	1.75E-1O	0.318	0.295	1.07	1.42E-01	0.318	0.340	0.89	1.50E-02