Molecular Dissection of Psoriasis: Integrating Genetics and Biology

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Psoriasis is a common and debilitating disease of the skin, nails, and joints, with an acknowledged but complex genetic basis. Early genome-wide linkage studies of psoriasis focused on segregation of microsatellite markers in families; however, the only locus consistently identified resided in the major histocompatibility complex. Subsequently, several groups mapped this locus to the vicinity of *HLA-C*, and two groups have reported *HLA-Cw6* itself to be the major susceptibility allele. More recently, the development of millions of single-nucleotide polymorphisms, coupled with the development of high-throughput genotyping platforms and a comprehensive map of human haplotypes, has made possible a genome-wide association approach using cases and controls rather than families. Taking advantage of these developments, we participated in a collaborative genome-wide association study of psoriasis involving thousands of cases and controls. Initial analysis of these data revealed and/or confirmed association between psoriasis and seven genetic loci—*HLA-C, IL12B, IL23R, IL23A, IL4/IL13, TNFAIP3*, and *TNIP1*—and ongoing studies are revealing additional loci. Here, we review the epidemiology, immunopathology, and genetics of psoriasis, and present a disease model integrating its genetics and immunology.

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Abbreviations: Ag, antigen; APC, antigen-presenting cell; CASP, Collaborative Association Study of Psoriasis; DC, dendritic cell; EDC, epidermal differentiation complex; GWAS, genome-wide association study; KC, keratinocyte; KIR, killer immunoglobulin-like receptors; LCE, late cornified envelope; LD, linkage disequilibrium; MHC, major histocompatibility complex; pDC, plasmacytoid dendritic cells; PsA, psoriatic arthritis; PSORS1*, psoriasis susceptibility-1; SNP, single-nucleotide polymorphism; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α*

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EPIDEMIOLOGY OF PSORIASIS: AN OVERVIEW

Psoriasis is a common disease, affecting about 2% of Americans at a cost of over 3 billion dollars a year (Sander *et al.*, 1993). Psoriasis has a major impact on the quality of life (Gupta *et al.*, 1993; Choi and Koo, 2003), leading psoriatics to report a reduction in physical and mental functioning comparable with that seen in cancer, arthritis, hypertension, heart disease, diabetes, and depression (Rapp *et al.*, 1999). More than 150,000 new diagnoses of psoriasis are made each year in the United States. Most of these are made in persons under 30 years of age, with more than 10,000 being less than 10 years old (Krueger *et al.*, 1984). A total of 10–40% of psoriatics develop psoriatic arthritis (PsA), which is severe and deforming in about 5% of patients (Gladman, 1994; Gelfand *et al.*, 2005).

The clinical and genetic epidemiology of psoriasis and PsA has been reviewed previously, and will be considered only briefly here (Elder *et al.*, 1994; Rahman and Elder, 2005; Gudjonsson and Elder, 2007b). Disease onset is most commonly observed in the early twenties. It has been proposed that two forms of psoriasis can be recognized (type I and type II), with type I psoriasis, characterized by onset age $\leqslant$40 years, being more likely to be familial, severe, and strongly associated with *HLA-Cw6* (Henseler and Christophers, 1985; Stuart *et al.*, 2002). The prevalence of psoriasis is approximately the same in males and females, though PsA has been suggested to be preferentially transmitted from male parents (Rahman *et al.*, 1999; Karason *et al.*, 2003).

Substantial genetic epidemiological data, including studies of twins, pedigrees, and relatives of unrelated index patients suggest that psoriasis is multifactorial, that is, influenced by multiple genes as well as environmental factors including stress, trauma, and infections, notably Streptococcal pharyngitis (Lomholt, 1963; Watson *et al.*, 1972; Gudjonsson and Elder, 2007a). Genetic epidemiological studies of PsA indicate that this disorder is even more strongly influenced by genes than is cutaneous psoriasis (Moll *et al.*, 1973; Chandran *et al.*, 2007a).

Several different forms of cutaneous psoriasis can be observed in the same person, either simultaneously or over time. These include chronic plaque, guttate, inverse, seborrheic, and localized and generalized pustular psoriasis, as well as palmoplantar pustulosis. Of these, chronic plaque disease is the most common. Guttate psoriasis is characterized by the rapid and generalized development of many small papules, which resolve spontaneously in about half the cases, and progress to chronic plaque psoriasis in the rest.

Psoriatic arthritis typically presents between the ages of 35 and 45 years, usually but not always after onset of skin disease (Gladman *et al.*, 1987). The Moll and Wright classification of PsA has been widely used (Moll and Wright, 1973). They defined PsA as a rheumatoid factor-negative inflammatory arthritis involving (a) distal interphalangeal predominant arthritis of hands and feet, (b) symmetric polyarthritis, (c) symmetric oligoarticular arthritis, (d) predominant axial spondylitis, and/or (e) arthritis mutilans. As seen for cutaneous psoriasis, the clinical manifestations of PsA can change considerably over time in any given patient (Jones *et al.*, 1994; Marsal *et al.*, 1999). More recently, the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria have emerged as a sensitive, specific, and reproducible tool for making a diagnosis of PsA (Taylor *et al.*, 2006). These criteria are based on both genetic and clinical features, and define PsA as the presence of inflammatory articular disease with at least 3 points from the following items: current psoriasis (2 points), a personal history of psoriasis (1 point, unless current psoriasis is present), a family history of psoriasis (1 point, unless current psoriasis was present or there was a personal history of psoriasis), dactylitis, juxta-articular new bone formation, rheumatoid factor negativity, and nail dystrophy (1 point each). These criteria have been shown to be sensitive and specific, not only in the original study (Taylor *et al.*, 2006) but also in early arthritis clinic, in early PsA clinic, and in family medicine clinics (Taylor *et al.*, 2006; Chandran *et al.*, 2007b). The presence of enthesitis (inflammation of ligament, tendon, and capsular insertions into bone) has been proposed as a unifying factor in the pathogenesis of PsA (McGonagle *et al.*, 1999).

Approximately half of psoriasis patients develop nail changes, including pitting, ''oil drop'' spotting, and onychodystrophy. Nail changes are strongly associated with PsA (Wright, 1959; Baker *et al.*, 1964; Eastmond and Wright, 1979; Gladman *et al.*, 1986; Lavaroni *et al.*, 1994; Williamson *et al.*, 2004), possibly because of the close proximity of the nail folds to the ''entheseal unit'' of the distal interphalangeal joint region (Tan *et al.*, 2007).

IMMUNOPATHOGENESIS OF PSORIASIS

In pathophysiological terms, psoriasis is characterized by markedly increased epidermal growth and altered differentiation, many biochemical, immunological, inflammatory, and vascular abnormalities, and a poorly understood relationship to nervous system function (Gudjonsson and Elder, 2007a). There is a large body of literature on the immunopathogenesis of psoriasis, which has been comprehensively reviewed recently (Lowes *et al.*, 2007; Nickoloff *et al.*, 2007). Many observations suggest that psoriasis is a T-cell-mediated disease driven at least in part by a positive feedback loop from activated T cells to antigen-presenting cells (APCs) that is mediated by IFN-γ, IL-1, and tumor necrosis factor-α (TNF-α). Moreover, there are important contributions of innate immune mechanisms involving the epidermis and macrophages (Buchau and Gallo, 2007). In psoriatic lesions, there is a distinct compartmentalization of T cells between the anatomic layers of the skin: CD4+ T cells are found predominantly in the upper dermis, whereas CD8+ T cells mostly localize to the epidermis (Baker *et al.*, 1984). The functional importance of T cells is emphasized by the high therapeutic efficacy of cyclosporine A, a T-cell-selective immunosuppressant (Ellis *et al.*, 1986), as well as other T-cell-selective immunomodulators, including anti-CD4 antibodies (Prinz *et al.*, 1991), CTLA4Ig (Abrams *et al.*, 2000), alefacept (Sugiyama *et al.*, 1993), and DAB389IL-2 (Gottlieb *et al.*, 1995). The role of hematopoietic cells in psoriasis is further highlighted by cases of psoriasis caused by or cured by bone marrow transplants, depending on whether the donor or recipient had psoriasis (Gardembas-Pain *et al.*, 1990; Kanamori *et al.*, 2002). Biologics that block TNF-α are also highly effective, reflecting important roles for this multifunctional cytokine in antigen (Ag) presentation, macrophage activation, and leukocyte trafficking (for review, see Gudjonsson and Elder, 2007a).

The recent discovery of a new subset of human T cells expressing IL-17 (Steinman, 2007) has led to the suggestion that these cells have a major role in psoriasis (Lowes *et al.*, 2008) as well as other autoimmune epithelial disorders such as Crohn's disease (Neurath, 2007). Although the mechanisms involved in the differentiation of IL-17-expressing T cells from naïve precursors remain controversial (Steinman, 2007), it is clear that the expansion and survival of these cells are driven by IL-23, largely produced by dendritic APC acting on the IL-23 receptor on T cells. We recently showed that IFN-γ causes myeloid APC to produce IL-1 and IL-23 and thereby stimulate the expansion of IL-17+ T cells (Kryczek *et al.*, 2008) (Figure 1). In this study, we also found a marked expansion of CD8+ T cells expressing IL-17 in psoriatic epidermis. Nearly all of the epidermal IL-17-producing T cells were CD8+, whereas such cells were essentially absent from normal epidermis (Kryczek *et al.*, 2008). More recently, we and others (Nograles *et al.*, 2009) have made similar observations for IL-22. Unlike mouse T cells, in which IL-17 and IL-22 are typically co-expressed, we found little overlap between T cells expressing IL-17 and those expressing IL-22 in normal or psoriatic skin (Rubin *et al.*, 2009). As we will discuss in more detail later, these intriguing cells form an important link in the chain connecting the genetics and immunology of psoriasis.

Another key link in this chain is provided by an elegant series of experiments by Nestle and colleagues, making use of a xenograft model in which nonlesional psoriatic skin is grafted onto highly immunocompromised AGR mice. In this model, local activation of human immunity occurs within the graft, possibly as a result of the trauma of grafting. Using this model, they initially showed that local proliferation of human T cells within the grafted skin itself, rather than trafficking of circulating immunocytes into the skin, is sufficient for the development of psoriasis (Boyman *et al.*, 2004). These studies also established a strong correlation between the presence of epidermal T cells and the development of epidermal hyperplasia (Boyman *et al.*, 2004). In subsequent experiments, they used a mAb against very late activation Ag-1 (α1β1 integrin), which is required for T-cell interaction with the epidermal basement membrane and subsequent

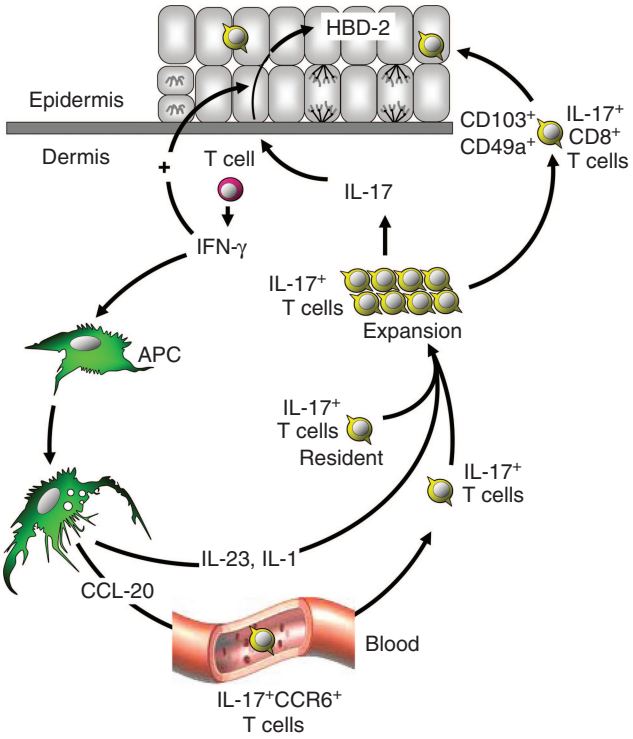

Figure 1. Proposed mechanism for Th1-mediated support of IL-17-producing T cells. Th1 cells produce IFN-γ, which stimulates myeloid antigen-presenting cells (APCs) to secrete IL-23. Together with IL-1, IL-23 promotes the survival and expansion of CD4+ and CD8+ T cells expressing IL-17. (The same mechanism expands to a largely non-overlapping population of T cells expressing IL-22, not shown). The entry of IL-17- and IL-22-producing CD8+ T cells into the epidermis promotes epidermal hyperplasia and an innate keratinocyte defense response involving proteins such as human β-defensin 2 (HBD-2), which are highly overexpressed in psoriasis. Obtained with permission from Kryczek *et al.*, 2008.

emigration of T cells into the epidermis, to ask whether this emigration was necessary for lesion development. Indeed, antibody treatment blocked accumulation of T cells within the epidermis, and this blockade inhibited psoriatic lesion development to the same extent as observed after neutralization of TNF-α. The anti–very late activation Ag antibodies were less effective, however, when some T cells were already present in the grafted epidermis, and were ineffective when fully-developed psoriatic lesions were grafted (Conrad *et al.*, 2007). These studies are highly relevant to the genetics of psoriasis, because most epidermal T cells are CD8+ and are therefore likely to respond to Ags presented in the context of major histocompatibility complex (MHC) Class I molecules, such as HLA-Cw6. Consistent with this notion, many of the clonally expanded epidermal T cells in chronic psoriatic plaques are CD8+ (Chang *et al.*, 1994).

GENETIC LINKAGE STUDIES OF PSORIASIS

Psoriasis is one of the most common and most heritable of the common diseases that display familial aggregation (Vyse and Todd, 1996). The epidemiological rationale for considering psoriasis to be a multifactorial (polygenic and environmentally influenced) genodermatosis was discussed earlier. However, these studies did not identify the specific genes involved. In 1990, Risch showed that polygenic disorders could be studied for allele sharing in a practical number (hundreds) of chosen families, as long as λ_1 (the overall excess risk of disease in a first-degree relative of an affected person) was at least 4, and as long as at least one of these loci was of major effect (that is, as long as the excess risk was not more or less evenly divided between hundreds of genes) (Risch, 1990). As λ_1 has been estimated to be in the range of 3–6 (Elder *et al.*, 1994) and as high as 10 for juvenile-onset psoriasis (Elder *et al.*, 2001), and with the emergence of microsatellites as practical genetic markers, in the 1990s, several groups embarked on a search for genetic determinants of psoriasis (Matthews *et al.*, 1996; Nair *et al.*, 1997; Trembath *et al.*, 1997; Samuelsson *et al.*, 1999; Capon *et al.*, 1999b; Karason *et al.*, 2000; Lee *et al.*, 2000; Fischer, 2001; Lesueur *et al.*, 2007). These studies relied on genetic linkage techniques (that is, either consistent co-segregation of a particular genetic marker with disease or sharing of alleles in affected sibling pairs). However, with the exception of the *psoriasis susceptibility-1* (*PSORS1*) locus, these studies yielded no consistent evidence for linkage to specific non-MHC loci that could be robustly replicated (reviewed in Capon *et al.*, 2004). The same problem has been encountered in a variety of other complex genetic disorders (Altmuller *et al.*, 2001). We now appreciate that this was due to the high population frequency of disease alleles in many complex genetic disorders (Risch and Merikangas, 1996).

PSORIASIS GENETICS AND THE MHC

Human leukocyte antigen associations with psoriasis have been known for over 35 years (Russell *et al.*, 1972), and earlier studies had localized the disease determinant to the Class I end of the MHC (Schmitt-Egenolf *et al.*, 1996; Jenisch *et al.*, 1998). More recently, several groups reached the conclusion that *PSORS1* was in the vicinity of *HLA-C*, but other nearby genes could not be excluded (for review, see Capon *et al.*, 2004). Despite the somewhat disappointing results of genome-wide linkage studies, the many psoriasis families we and others chose proved to be very useful for detailed mapping of *PSORS1*. As the defined genetic relationships between family members make it possible to determine the phases of the microsatellite genotypes (that is, to determine which marker alleles were on which chromosome), it is possible to infer recombinant ancestral haplotypes (that is, to infer meiotic crossover events that occurred many generations ago). We initially carried out an analysis of MHC haplotypes using 62 microsatellite markers (Nair *et al.*, 2000), which mapped *PSORS1* to the proximal MHC Class I region in the vicinity of *HLA-C*, and similar results were reported by Trembath and colleagues (Veal *et al.*, 2002). In 2006, we reported a more detailed recombinant ancestral haplotype mapping of the region in 678 families, along with DNA sequencing of the critical interval in two disease and five normal chromosomes. This analysis strongly implicated *HLA-C* rather than any of the 10 other nearby genes, and identified *HLA-Cw6* as very likely to be the disease allele at *PSORS1* (Nair *et al.*, 2006). Our conclusions were recently

confirmed by a large study of Han Chinese psoriatics, many of whom do not carry the same extended haplotypes found in psoriatics of Northern European descent (Fan *et al.*, 2008).

GENOME-WIDE ASSOCIATION STUDIES OF PSORIASIS

Unlike many Mendelian disorders in which the disease alleles are rare and of catastrophic effect, the alleles underlying complex genetic disorders are relatively common and make only modest individual contributions to disease risk, rendering them difficult to identify by linkage (Botstein and Risch, 2003). In this setting, tests of association are much more powerful than tests of linkage, provided causal variants or proxies for them can be genotyped (Risch and Merikangas, 1996). However, in contrast to linkage studies, association studies require at least 100,000 genetic markers to comprehensively survey the genome (Kruglyak, 1999; International HapMap Consortium, 2003). For this reason, genome-wide association studies (GWAS) were not feasible in the 1990s, and genetic association studies were limited to candidate genes or regions. In this decade, however, the HapMap has provided millions of genetic markers in the form of single-nucleotide polymorphisms (SNPs) (Altshuler *et al.*, 2005). Concurrently, technologies were developed for high-throughput genotyping, allowing 100,000–1,000,000 SNPs to be typed in thousands of individuals at a reasonable cost. Anticipating these developments, we decided to focus our collection efforts on unrelated cases and controls, instead of families. This made it much easier to enroll subjects through dermatology clinics, allowing a rapid increase in sample size. In 2006, we initiated a multicenter collaboration with Dr Anne Bowcock at the Washington University of St Louis and Dr Gerald Krueger of the University of Utah to carry out a GWAS of psoriasis, which we named the Collaborative Association Study of Psoriasis (CASP). Our initial results were published recently (Nair *et al.*, 2009b).

After quality control filtering of the data, we analyzed 438,670 SNPs typed for 1,359 cases and 1,400 controls. As shown in Figure 2, the discovery GWAS revealed strong associations not only at the established susceptibility loci *HLA-C*, *IL12B*, and *IL23R* (Tsunemi *et al.*, 2002; Capon *et al.*, 2007; Cargill *et al.*, 2007; Nair *et al.*, 2008b) but also showed promising association signals that fell short of genome-wide significance at numerous other loci. With additional colleagues from Canada, Germany, and France, we carried out a replication analysis of the GWAS results, genotyping 21 SNPs representing 19 independent loci in 6 independent samples of European origin, numbering 5,048 cases and 5,051 controls. We confirmed association at seven loci (with $P<10^{-3}$ in the replication study and $P<5\times10^{-8}$ overall). In addition to the three loci previously associated with psoriasis, namely, *HLA-C*, *IL12B*, and *IL23R*, we identified novel genetic signals located near four plausible psoriasis candidate genes: *IL23A*, *IL4/IL13*, *TNFAIP3*, and *TNIP1*. These will be discussed in more detail below.

Four other GWAS of psoriasis have been reported (Cargill *et al.*, 2007; Capon *et al.*, 2008; Liu *et al.*, 2008; Zhang *et al.*, 2009). All of them detected strong associations in the vicinity of *HLA-Cw6*, and additional signals in genes whose products are components of the IL-23 ligand–receptor complex. One of them detected a very strong association to the vicinity of the late cornified envelope (LCE) genes located in the epidermal differentiation complex (Zhang *et al.*, 2009). This finding was simultaneously reported in a study focusing on copy number variation in psoriasis, which showed that increased risk of psoriasis is associated with deletion of the *LCE3B* and *LCE3C* genes (de Cid *et al.*, 2009). This interesting family of genes, which we initially identified in 1997 by positional cloning (Zhao and Elder, 1997), is involved in the terminal stages of epidermal maturation (Jackson *et al.*, 2005). Although *LCE3B* and *LCE3C* are not expressed in normal skin, they are highly expressed in psoriasis and after epidermal injury produced by tape stripping (de Cid *et al.*, 2009). Another locus identified in one of these GWAS maps to chromosome 20q13 near the *ZNF313* gene. *ZNF313* is strongly expressed in the skin and, similar to *TNFAIP3* and *TNIP1* (see below), encodes a ubiquitin ligase (Capon *et al.*, 2008). Recently, we were able to confirm this association in a sample of 2,140 cases and 1,922 controls (OR = 1.19, $P=8.9\times10^{-5}$) (Nair *et al.*, 2008a). Other genetic signals for which replication has been claimed include SNPs in the vicinity of *PTPN22* other than the R620W mutation known to increase risk in several other autoimmune diseases (Chung and Criswell, 2007), and several SNPs in the *CDKAL1* region. We find confirmatory associations with SNPs in the *CDKAL1* region in the CASP primary GWAS data set ($P=0.0001$), but not with SNPs in the *PTPN22* region (data not shown).

An interesting feature of the GWAS results obtained thus far in psoriasis and other complex genetic disorders is that the risk allele is often the most common allele in the population. There are several possible explanations for this. The disease allele may be ancestral, as is the case for lactose intolerance. Alternatively, the ''disease'' allele may be beneficial in certain contexts (that is, defense against pathogens), as is the case for hemoglobinopathies increasing resistance to malaria, or at least be selectively neutral with respect to reproduction. It is also possible that the rare variant may actually encode a protective function. Finally, the actual functional variant may be rare, but carried on a common haplotype tagged by the observed variant. Fine mapping and functional studies of disease-associated variants are in their early stages in psoriasis and in many other complex genetic disorders. With time, the outcome of these studies should allow us to distinguish between these possibilities.

INTEGRATING THE GENETICS AND IMMUNOLOGY OF PSORIASIS

With the likely exception of *HLA-Cw6* (Nair *et al.*, 2006), the disease-predisposing variants responsible for the genetic signals we and others have observed in psoriasis remain to be identified. Nevertheless, our results suggest roles for several key immunological pathways in disease susceptibility. Here, we present a model integrating the genetics and immunology of psoriasis emphasizing the functional relationships between the genetic loci that have been implicated to date. Some aspects of this model have been presented previously (Elder, 2009; Nair *et al.*, 2009a).

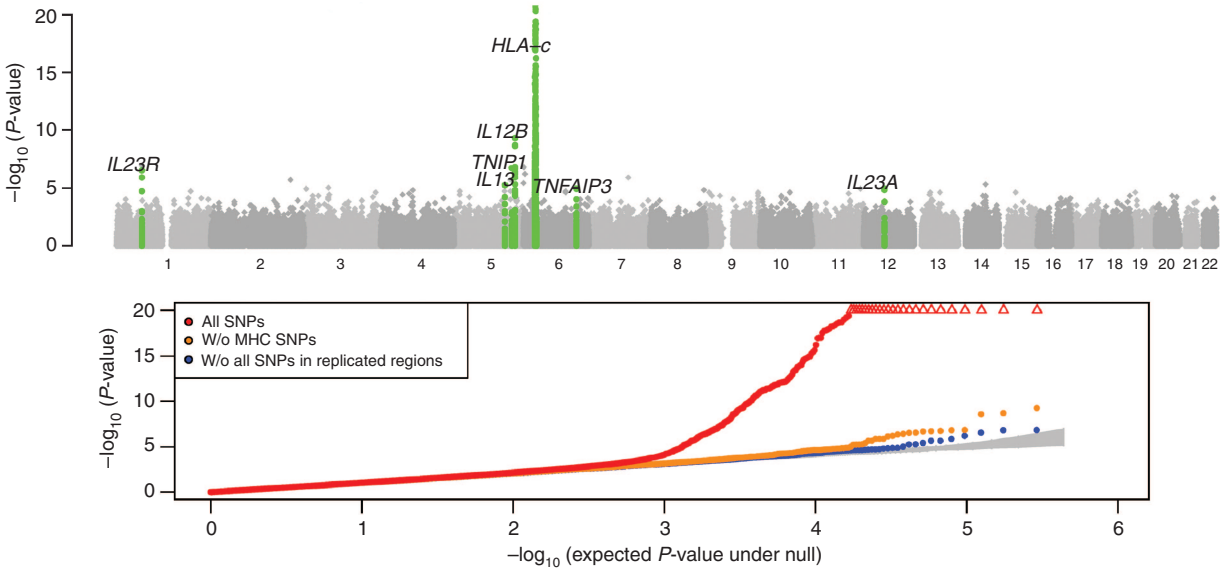

Figure 2. Results of the discovery phase of the Collaborative Association Study of Psoriasis genome-wide association study. The upper panel is a ''Manhattan plot'' summarizing the association results obtained for 438,670 genotyped single-nucleotide polymorphisms (SNPs), plotted against chromosomal position. Seven of the 19 regions that were followed up yielded convincing evidence of association in the replication study, as indicated by green coloration. The lower panel presents a quantile-quantile plot comparing observed *versus* expected *P*-values obtained for the 438,670 genotyped SNPs. Red symbols represents all SNPs, orange symbols represent the results after excluding major histocompatibility complex (MHC) SNPs, and blue symbols represent the results after excluding SNPs at all replicated loci. The gray area represents the 90% confidence interval expected under a null distribution of *P*-values. Note that all panels are truncated at a $-\log_{10}$(*P*-value) of 20; markers near *HLA-C* exceed this threshold considerably ($P \approx 10^{-53}$). Adapted from Nair *et al.*, 2009b, with permission.

HLA-Cw6

As expected from our earlier work (Nair *et al.*, 2006), the MHC yielded by far the strongest association signals in the CASP study (Figure 2). The SNP that yielded the strongest association with psoriasis (rs12191877, $OR_{replication} = 2.64$, $P_{combined} << 10^{-100}$) was in strong linkage disequilibrium (LD) with *HLA-Cw6* ($r^2 = 0.63$). In cases and controls for which *HLA-Cw6* typing was available, *HLA-Cw6* was much more highly associated with psoriasis than any single SNP. However, neither rs12191877 (Nair *et al.*, 2009b) nor *HLA-Cw6* itself (Feng *et al.*, 2009) could fully account for the MHC association signals. To search for additional disease-associated variants, we carried out a forward selection procedure, yielding a model with three imputed SNPs. Two of these were in strong LD with *HLA-Cw6* and are likely to be surrogates for it. However, the third SNP (rs2022544, *P*-value $= 10^{-7}$) maps between the MHC Class III region and the *HLA-DR* gene cluster and exhibits only weak LD with *HLA-Cw6* ($r^2 = 0.01$). These results confirm the predominance of *HLA-Cw6* in terms of the magnitude of its genetic effect, but suggest that at least one additional psoriasis susceptibility determinant remains to be identified in the MHC.

Guttate psoriasis is very strongly associated with *HLA-Cw6*, and in one study, this allele was present in 100% of guttate psoriasis cases (Mallon *et al.*, 2000). Guttate psoriasis is frequently preceded by Streptococcal pharyngitis (Gudjonsson and Elder, 2007a), and this is the only infection that has been shown to trigger psoriasis in a prospective cohort study (Gudjonsson *et al.*, 2003). Further suggestive of a critical role for the tonsils, other streptococcal infections of the skin, such as impetigo or erysipelas, do not have the same propensity to trigger psoriasis. Tonsillar T cells recognize activated skin capillary endothelium (Akagi *et al.*, 1992) and express the skin-specific homing molecule CLA (cutaneous lymphocyte antigen). During an episode of Streptococcal pharyngitis, we envision that Streptococcal Ags are presented in the context of HLA-Cw6 to naïve T cells in the tonsils, causing them to proliferate, differentiate into an effector/memory phenotype, and acquire skin-homing capacity. In addition, innate immune mechanisms may serve to polyclonally activate existing skin-homing memory T cells during the initial infection. On the basis of the observation of peptidoglycan-containing macrophages in the papillary and perivascular infiltrates of guttate and chronic plaque psoriasis, it has been suggested that peptidoglycan, a major constituent of the Streptococcal cell wall, may function to activate T cells in psoriasis through a Toll-like receptor (TLR)-mediated and cytokine-dependent mechanism (Baker *et al.*, 2006).

After homing to the skin, polyclonally activated T cells may provoke the initial development of the small but widespread lesions that are characteristic of guttate psoriasis. In one study, a lack of clonal TCR gene rearrangement coupled with skewing of TCR Vβ chain usage was observed in acute flares of guttate psoriasis, suggesting that superantigens might be involved in the development of guttate flares (Leung *et al.*, 1995). In contrast, studies of chronic plaque psoriasis have identified oligoclonal TCR rearrangements, suggesting the involvement of nominal Ags rather than superantigens (Chang *et al.*, 1994; Prinz *et al.*, 1999;

Lin *et al.*, 2001; Vollmer *et al.*, 2001; Diluvio *et al.*, 2006). Importantly, the same clonal expansions of skin-homing T cells are found in the tonsils and in lesional skin of psoriatic patients (Diluvio *et al.*, 2006). These findings suggest that over time, a relatively small number of Streptococcus-specific, skin-homing T cells begin to recognize self-Ags, leading to the development of chronic plaque psoriasis (Gudjonsson *et al.*, 2004). Consistent with an ongoing role for HLA-Cw6 in the chronic phase of the process, both chronic plaque and generalized pustular psoriasis are also strongly associated with *HLA-Cw6* (Ozawa *et al.*, 1998).

In at least half of guttate psoriasis cases, the disease resolves spontaneously and recurs only rarely if at all. What determines which patients will progress to chronic plaque disease? Presumably, with the resolution of active infection, pathogen-derived innate immune stimulants such as peptidoglycan are cleared. However, for a response to self-Ags to develop leading to chronic plaque disease, there must be a prolonged loss of immunological tolerance. One genetic determinant of tolerance could be that certain self-Ags might be presented in the context of HLA-Cw6 in such a way as to overcome or bypass normal tolerance. However, the precise nature of the Ag(s) involved has remained elusive. One study found that HLA-Cw6 preferentially presented peptides common to Streptococcal M protein and the hyperproliferative keratin K17 to skin-homing CD8+ T cells (Johnston *et al.*, 2004). This mechanism has been suggested to explain the preferential reactivity of these cells for peptides with structural homology between Streptococcal M protein and the hyperproliferative keratins, K16 and K17 (Johnston *et al.*, 2004). Another study attempted to identify psoriasis Ags by expression cloning of RNA derived from psoriatic skin (Jones *et al.*, 2004). However, at variance with expectation, T cells from the blood of normal controls were as strongly reactive as T cells derived from the blood of psoriatic patients. Although our model focuses on HLA-Cw6 as the key MHC determinant of immunological self-tolerance in psoriasis, considerable evidence supports the notion that *HLA-B* alleles that are not in LD with *HLA-Cw6* are also associated with psoriasis and PsA, notably with *HLA-B27*, *HLA-B38*, *HLA-B39* (Espinoza *et al.*, 1982), and *HLA-B46* (Choonhakarn *et al.*, 2002; Nair *et al.*, 2009c). It is possible that these additional associations could reflect loss-of-tolerance events similar to those we envision for *Streptococcus pyogenes* and HLA-Cw6, except that different microorganisms provide the initial Ags.

Loss of tolerance could also involve the sudden appearance of proteins that are strongly expressed in psoriasis but not in normal skin. When processed, peptides derived from such proteins could serve as neoantigens. In addition to the keratins K16 and K17 discussed above, other proteins that are strongly upregulated in psoriasis include human β-defensin-2 (encoded by *DEFB4*), psoriasin (*S100A7*), calgranulin (*S100A8* and *S100A9*), small proline-rich region proteins (*SPRR*), and *LCE* proteins. Interestingly, many of these proteins are encoded by genes located in the epidermal differentiation complex located on human chromosome 1q21.3, in which genetic linkage and association to psoriasis have been reported (Bhalerao and Bowcock, 1998; Capon *et al.*, 1999a, 2001; de Cid *et al.*, 2009; Zhang *et al.*, 2009).

Psoriatic lesions manifest a complex and highly active proteolytic environment, particularly in the more differentiated layers in which proteins encoded in the epidermal differentiation complex are most highly expressed (Zeeuwen *et al.*, 2009). It is possible that this aberrant proteolytic environment might also contribute to the development of neoantigenic peptides. Alternatively, proteases could be involved in the generation of innate defense peptides with altered antimicrobial and/or inflammatory properties, as has been observed for cathelicidins in rosacea (Yamasaki *et al.*, 2007).

Many of these potentially neoantigenic proteins are intracellular components of keratinocytes (KCs) and yet must be presented on the surface of dendritic APC for effective Ag presentation, suggesting a requirement for cross-presentation (Heath *et al.*, 2004). The fact that cross-presentation is dependent on CD4+ T cell might explain the observed dependence of psoriasis on CD4+ T cells in the severe combined immunodeficient mouse xenograft model (Nickoloff and Wrone-Smith, 1999). However, it remains possible that Ag-driven CD4+ T cells have a more direct role, as many of the observed TCR rearrangements observed in psoriatic dermis arise in CD4+ cells (Chang *et al.*, 1994). Moreover, Streptococcus-specific CD4+ T-cell lines from psoriatic patients responded in an HLA-DR-restricted fashion, ruling out mitogenic or superantigenic stimulation (Baker *et al.*, 2006). It has been suggested that Streptococcal peptidoglycan may function both as an Ag and as a stimulus for innate immunity by TLR activation (Baker *et al.*, 2006). In any event, it is important to note that the vast majority of T cells in psoriatic skin are not clonally expanded, indicating that additional, non-Ag-specific mechanisms are involved in maintaining the psoriatic infiltrate.

HLA-C also serves as a ligand for killer immunoglobulin-like receptors (KIRs), which can either inhibit or stimulate natural killer cells. Interestingly, the *KIR* locus has been reported to be associated with PsA (Nelson *et al.*, 2004; Williams *et al.*, 2005). Natural killer cells are major producers of IFNs and serve as a bridge between innate and acquired immunity. Inhibitory KIRs negatively regulate natural killer cell activation by interacting with a dimorphic allotype (Asn80/Lys80) of HLA-C (Long and Rajagopalan, 2000). *HLA-Cw6* is one of several ''group 2'' alleles carrying Lys at position 80. Thus, if this mechanism were responsible for the observed association of HLA-Cw6 with psoriasis, it would be expected that a combination of all ''group 2'' alleles would provide a stronger association signal in individuals carrying the cognate inhibitory KIR genotype than does HLA-Cw6, but this was not the case in PsA (Nelson *et al.*, 2004). Further increasing complexity, because the KIR locus has an evolutionary history of expansion and contraction, for some inhibitory receptors, an individual may encode receptor only, ligand only, both receptor and ligand, or neither one. Thus, the role of *HLA-Cw6* as a genetic regulator of natural killer cell activity in psoriasis remains to be clarified.

NF-κB signaling

A20 and ABIN1 are the products of the *TNFAIP3* and *TNIP1* genes, respectively. These proteins interact with each other and participate in the ubiquitin-mediated destruction of IKKγ/NEMO, thereby regulating a key nexus of NF-κB signaling (Mauro *et al.*, 2006). The degradation of several other components of the TNF signaling pathway is also regulated by A20 (Mauro *et al.*, 2006). TNF-α blockade markedly improves psoriasis-like pathology in a mouse model of psoriasis induced by injection of IL-23 (Chan *et al.*, 2006), and a region of mouse chromosome 10 containing *Tnfaip3* promotes psoriasis in a TNF-α-dependent manner in another mouse model (Wang *et al.*, 2008). Given that atherosclerosis is a major co-morbidity of psoriasis (Gelfand *et al.*, 2006), it is notable that susceptibility to atherosclerosis has also been associated with the same region of mouse chromosome 10 (Idel *et al.*, 2003). Moreover, SNPs near *TNFAIP3* yield genome-wide significant associations with rheumatoid arthritis (Plenge *et al.*, 2007; Thomson *et al.*, 2007) and systemic lupus erythematosus (Graham *et al.*, 2008; Musone *et al.*, 2008). These polymorphisms were not associated with psoriasis in the CASP study (all $P > 0.30$) and are not in LD with the psoriasis-associated alleles ($r^2 < 0.03$), suggesting that different alleles of *TNFAIP3* increase susceptibility to systemic lupus erythematosus, rheumatoid arthritis, and psoriasis. Given that each of these diseases can be associated with arthritis, it is interesting that the NF-κB inhibitor parthenolide abrogated IL-23-mediated stimulation of receptor activator of NF-κB (RANK) ligand on CD4+ T cells in an arthritogenic mouse model (Ju *et al.*, 2008).

Tissue macrophages also have an important role in mouse models of psoriasis, even in the absence of T cells (Stratis *et al.*, 2006; Wang *et al.*, 2006). As many events in macrophage and dendritic cell (DC) activation and function are NF-κB dependent, genetic variation in *TNFAIP3* and *TNIP1* could influence the balance between a self-limited response in which tolerance is eventually restored, and a self-sustaining one in which it is not. Clonal expansion of T cells requires the active participation of APC, especially DCs, which are intimately involved in the regulation of immunological tolerance at least in part through the Ag-specific stimulation of regulatory T cells (Yamazaki and Steinman, 2009). As discussed below, an increasingly complex network of resident and inflammatory DCs with tolerogenic as well as immunostimulatory capacities is emerging in psoriasis and other inflammatory skin disorders.

IL-23 signaling

Three psoriasis-associated genetic signals map to components of the IL-23 ligand–receptor complex (Nair *et al.*, 2009b). One is found near *IL12B* (which encodes the p40 subunit common to IL-23 and IL-12), another is located near *IL23A* (which encodes the p19 subunit of IL-23), and a third resides near *IL23R* (which encodes a subunit of the IL-23 receptor). This was the first study to implicate genetic variants near *IL23A* as conferring susceptibility to any human autoimmune disorder. 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 (Bettelli *et al.*, 2007). These results lead us to speculate that aberrant IL-23 signaling renders certain individuals susceptible to inappropriate immune responses targeting epithelial cells, thus contributing to the chronic and relatively skin-specific inflammation seen in psoriasis. This speculation is supported by the excellent antipsoriatic efficacy of biologics targeting the p40 subunit (Krueger *et al.*, 2007), coupled with the fact that *IL12B* and *IL23A* are markedly overexpressed in psoriatic lesions, whereas *IL12A* is not (Lee *et al.*, 2004).

Given that the epithelial linings of the skin and the gut are somewhat similar, it is notable that one of the same genetic variations in the *IL23R* gene that increases risk for psoriasis also confers risk for Crohn's disease (Duerr *et al.*, 2006), a condition that is strongly associated with psoriasis clinically (Najarian and Gottlieb, 2003). We also showed genome-wide significant associations between PsA and *IL12B* (Nair *et al.*, 2009b), and we and others have reported strong associations between PsA and *IL23A* and/or *IL23R* (Liu *et al.*, 2008; Huffmeier *et al.*, 2009; Nair *et al.*, 2009b). Given that PsA is a highly destructive form of arthritis associated with increased RANK-positive myeloid osteoclast precursors (Ritchlin *et al.*, 2003), it is notable that IL-23 promotes osteoclast formation by upregulation of RANK in myeloid precursor cells (Chen *et al.*, 2008), while inducing expression of RANK ligand on CD4+ T cells (Ju *et al.*, 2008).

Th1–Th2–Th17 balance

One of the genetic signals we identified contains the *IL13*, *IL4*, *IL-5*, and *RAD50* genes in a region of strong LD. Although the most highly significant signals reside closer to *IL4* and *IL13*, a locus control region that regulates the transcription of *IL13*, *IL4*, and *IL5* resides in the *RAD50* gene (Lee *et al.*, 2003). Thus, it is possible that the functional variant may influence the expression of *IL4*, *IL5*, and/or *IL13*. These cytokines act at several levels to regulate allergic responses and defense against extracellular pathogens. In addition to biasing the T-cell repertoire toward Th2 differentiation, IL-4 and IL-13 inhibit the development of Th17 cells from naïve T cells (Harrington *et al.*, 2005; Newcomb *et al.*, 2009). Furthermore, IL-4 was shown to instruct DCs to produce IL-12 and promote Th1 development when present during the initial activation of DCs by infectious agents (Biedermann *et al.*, 2001). This unexpected result may be explained by the more recent observation that the levels of IL-4 present during DC differentiation regulate their polarizing effects on T-cell differentiation, with low levels promoting Th2 and higher levels promoting Th1 (Guenova *et al.*, 2008). IL-4 and IL-13 are markedly overexpressed in atopic dermatitis skin relative to normal skin, but not in psoriasis (Van der Ploeg *et al.*, 1997; Nomura *et al.*, 2003). Treatment of psoriasis with IL-4 results in significant clinical improvement (Ghoreschi *et al.*, 2003), which has recently been shown to be accompanied by reduced expression of IL-23 and reduced numbers of Th17 cells (Guenova *et al.*, 2009). The fact that we observe genetic signals at both ends of this

polarizing spectrum (IL-23 on the one hand, and IL-4/IL13 on the other) suggests that Th1–Th2–Th17 balance is likely to be a key functional and genetic determinant of psoriasis.

Putting it all together: from initiation of lesions to generation of the epidermal response

Recently, plasmacytoid DCs (pDCs) have been implicated in the initiation of psoriasis lesions (Nestle *et al.*, 2005). pDCs are a specialized subset of DCs that are increased in number in psoriatic lesions and characterized by the production of large amounts of IFN-α (Wollenberg *et al.*, 2002). IFN-α had been suspected to have a role in psoriasis based on reports of exacerbations in psoriatic patients receiving intravenous IFN-α (Quesada and Gutterman, 1986) and patients treated with the topical TLR7 agonist imiquimod (Gilliet *et al.*, 2004). IFN-α has multiple pro-inflammatory biological functions including upregulation of MHC class I expression (Hermann *et al.*, 1998), inducing cross-presentation of self-Ags to CD8+ T cells (Le Bon *et al.*, 2003), and activation of T cells (Nestle *et al.*, 2005). Activation of these cells can occur through binding of the antimicrobial peptide LL-37 in complexes with host DNA, with intracellularly expressed TLR9 (Lande *et al.*, 2007). LL-37 is a secreted peptide that is abundantly expressed in established psoriatic lesions (Frohm *et al.*, 1997), providing a plausible mechanism for pDC activation. TLR7 signaling occurs in part through the NF-κB pathway (Tamura *et al.*, 2008) and this could be one of the means by which the psoriasis risk variants in *TNFAIP3* and *TNIP1* influence psoriasis risk.

In addition to pDC, there is a very complex population of myeloid DCs in psoriatic skin, including epidermal Langerhans cells, inflammatory dendritic epidermal cells, as well as resident and inflammatory dermal DCs (Nickoloff *et al.*, 2007; Zaba *et al.*, 2009b). The myeloid DC population is expanded and activated in psoriasis (Baadsgaard *et al.*, 1989; Nestle *et al.*, 1994), with a marked increase in the numbers of immature DCs producing inflammatory cytokines and capable of stimulating T cells producing IL-17 and IFN-γ (Kryczek *et al.*, 2008; Zaba *et al.*, 2009a). Experiments undertaken in the uninvolved skin xenograft model suggest that the induction of myeloid DC maturation and/or activation is a key intermediary through which IFN-α produced by pDCs leads to T-cell activation by myeloid DC (Nestle *et al.*, 2005). Again, variants in the *IL12B*, *IL23A*, *IL23R*, *TNFAIP3*, and/or *TNP1* genes could all have plausible role(s) in this process.

As T cells respond clonally to Ags (self-derived or foreign) in the context of HLA-Cw6, and/or more broadly to cytokines produced by activated DC and/or macrophages, they will differentiate, expand, and activate their effector functions. Some of these will be naïve T cells being stimulated to develop into different lineages, such as Th1, Th2, or the progenitor(s) of T cells expressing IL-17 and/or IL-22 (Mills, 2008), whereas others will be skin-homing memory T cells (Clark *et al.*, 2006) or regulatory T cells (Sakaguchi, 2004). Subsets of memory CD4+ and CD8+ T cells will expand locally in the dermis in response to IL-23 and IL-1, which in turn are produced by DC in response to stimuli such as IFN-γ (Kryczek *et al.*, 2008) (Figure 1). Genetically mediated hyperfunction of IL-23 itself (through variants of *IL12B* and *IL23A*) and/or of its receptor (through *IL23R*) could enhance the expansion of T cells expressing IL-17 and/or IL-22. Whether through direct effects on T cells or altered DC programming, genetically mediated abnormalities in the expression or function of IL-4 and/or IL-13 could lead to development of Th1 bias, leading to increased expression of IFN-γ and DC-mediated expansion of T cells producing IL-17 and/or IL-22 (Figure 3).

Intraepidermal CD8+ T cells producing IL-17 and/or IL-22 can be predicted to have a particularly important role in promoting the psoriatic epidermal response, as there would be no need for IL-17 and IL-22 produced by these cells to diffuse from the dermis into the epidermis. IL-17 and IL-22 strongly upregulate KC-derived effectors of innate defense known to be highly overexpressed in psoriasis, including the defensins hBD-2 and hBD-3, CCL20, S100A7, S100A8, and S100A9 (Boniface *et al.*, 2005; Wilson *et al.*, 2007; Zheng *et al.*, 2007; Guttman-Yassky *et al.*, 2008; Kryczek *et al.*, 2008; Ma *et al.*, 2008). Interestingly, all these molecules have been shown to have chemotactic as well as antimicrobial activity, and are all induced in response to epidermal insult (Schauber and Gallo, 2007). This could explain the well-known tendency of psoriasis to flare at sites of skin injury (the Koebner phenomenon). Thus, it would appear that T-cell-derived cytokines have a key role not only in stimulating the antimicrobial activities of KCs but also in their ability to promote the influx of inflammatory cells. We have recently shown that this response is activated more often in uninvolved psoriatic skin than it is in site-matched skin from normal individuals, in concert with a decrease in expression of genes involved in lipid biosynthesis (Gudjonsson *et al.*, 2009). We speculate that this subtle but highly coordinated response might represent the incipient epidermal response to T cells whose normal task is skin immunosurveillance.

Despite decades of study, the mechanism(s) by which cutaneous inflammation provokes epidermal hyperplasia in psoriasis have remained enigmatic. Early studies suggested that psoriatic KCs are refractory to cAMP-dependent growth regulatory signals (Voorhees and Duell, 1971) or that KCs are more responsive to psoriatic fibroblasts than to normal fibroblasts (Saiag *et al.*, 1985). Once it became clear that the T-cell-specific immunosuppressant cyclosporine rapidly and markedly reduced psoriatic epidermal hyperplasia (Ellis *et al.*, 1986) and cytokine expression (Elder *et al.*, 1993; Kojima *et al.*, 1994), and that several other T-cell-selective immunomodulators were clinically effective (Prinz *et al.*, 1991; Sugiyama *et al.*, 1993; Gottlieb *et al.*, 1995; Abrams *et al.*, 2000), the focus shifted to T cells. These clinical observations prompted the use of *in vitro* and animal models of psoriasis, which further supported a critical role for T cells. Making use of short-term cultures of human monolayer KCs, it was reported that T-cell clones could produce soluble factors that were mitogenic for KCs (Prinz *et al.*, 1994), and that psoriatic KCs are hyperresponsive to the effects of T-cell-derived cytokines, at least one of which was IFN-γ

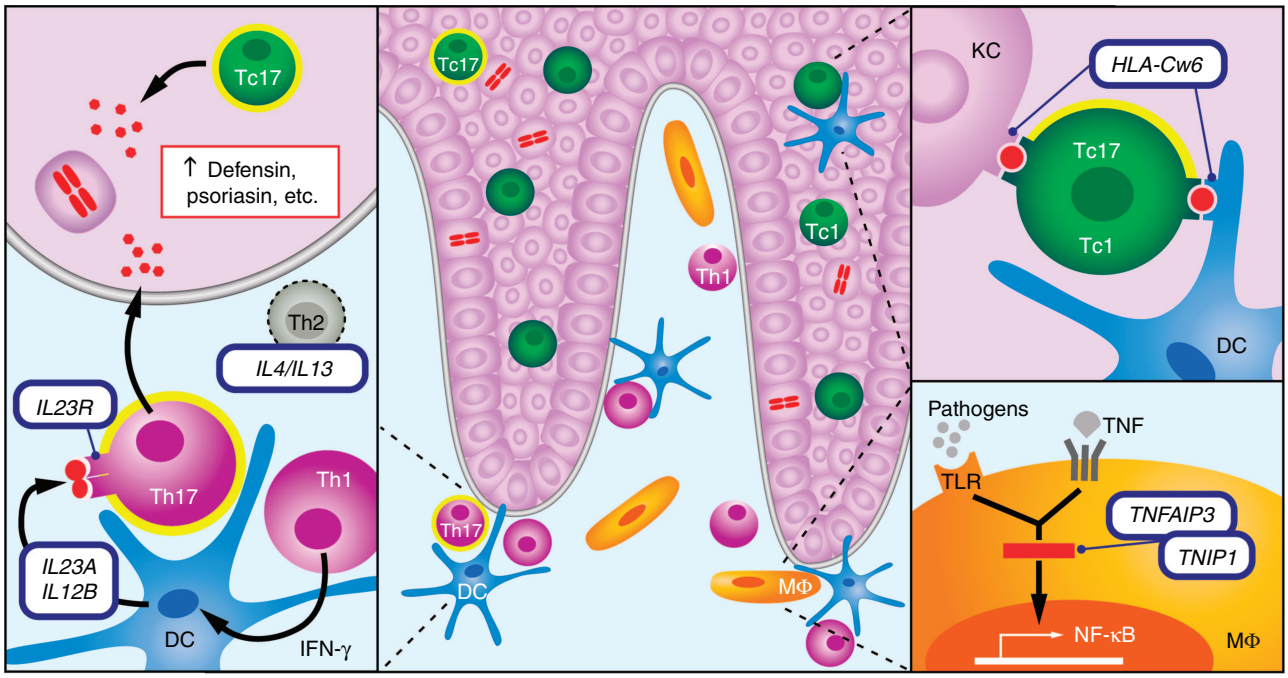

Figure 3. Model integrating the genetics and immunology of psoriasis. Genes identified as psoriasis-associated by the Collaborative Association Study of Psoriasis genome-wide association study are italicized. The majority of dermal T cells are CD4+ (purple); most of these are Th1, but ~5% of them produce IL-17 (Th17, yellow halo). Most epidermal T cells are CD8+ (green circles) and about 5% of them express IL-17 (Tc17, yellow halo). Upper right panel—HLA-Cw6 may increase susceptibility to psoriasis by presenting antigens to CD8+ T cells from the surface of dendritic cells (DCs, blue), and/or by presenting keratinocyte antigens to activated CD8+ T cells. As indicated by the partial yellow halo, some of these T cells may express IL-17. Lower right panel—macrophages (Mϕs, orange) and DCs express TNF receptors and Toll-like receptors (TLRs) that signal through IKK-γ to promote translocation of NF-κB to the nucleus. The proteins encoded by *TNFAIP3* (A20) and *TNIP1* (ABIN1) are capable of binding to each other, and cooperatively block this signaling by altering patterns of protein ubiquitylation. Lower left panel—*IL23A* and *IL12B* encode the subunits of IL-23. *IL23R* encodes one subunit of the receptor for IL-23. *IL4* and *IL13* may participate in psoriasis by directly skewing the differentiation of CD4+ T cells toward Th2, or by altering the cytokine profile of DCs in such a way as to favor Th1 differentiation. As shown in Figure 1, Th1 cells stimulate the production of IL-23 by DCs. In turn, IL-23 stimulates the production of IL-17 and/or IL-22 by Th17 cells. Upper left panel—IL-17 and IL-22 upregulate keratinocyte innate immune defense mechanisms, including defensins, psoriasin (S100A7), and other proteins that are highly expressed in psoriasis lesions. In addition, IL-22 may promote keratinocyte proliferation and/or alter keratinocyte differentiation. Reproduced from Nair *et al.*, 2009a, with permission.

(Bata-Csorgo *et al.*, 1995). However, it is difficult to extrapolate from monolayer KC cultures to the *in vivo* situation, because KCs rapidly become hyperproliferative in culture. This experimental problem was overcome when it was shown that injection of T cells can provoke epidermal hyperplasia in pre-psoriatic skin grafted onto severe combined immunodeficient mice (Nickoloff and Wrone-Smith, 1999) and that the entry of T cells into the epidermis is necessary for spontaneous development of the epidermal hyperplasia in the AGR xenograft model (Conrad *et al.*, 2007). Another approach has been the use of skin equivalent models. However, despite their ability to stratify, these models retain an innate immune gene expression response very similar to psoriasis (McFarland *et al.*, 2008), and do not fully recapitulate the distinctive cellular milieu of psoriatic lesions. Despite these limitations, IL-22 has been shown to promote epidermal thickening and altered KC differentiation, along with marked upregulation of the innate defense response, in three independent studies (Boniface *et al.*, 2005; Sa *et al.*, 2007; Nograles *et al.*, 2008). However, actual KC hyperproliferation was seen in only one of these studies (Sa *et al.*, 2007). Interestingly, in this study it was necessary to block the EGFR to observe the hyperproliferative effect of IL-22 (Sa *et al.*, 2007).

In addition to these cytokine-driven mechanisms, CD8+ T cells might also promote epidermal hyperplasia by inflicting cytotoxic injury on KCs. Epidermal CD8+ T cells in psoriasis express perforin, and therefore could directly damage KCs in the traditional cytotoxic manner (Kastelan *et al.*, 2004; Prpic Massari *et al.*, 2007). This damage might be sublethal in nature, as frank cytolysis of KCs is not a prominent feature of psoriasis. It has been suggested that psoriatic KCs are relatively resistant to apoptotic damage because they exhibit exaggerated features of senescence (Nickoloff, 2001). KCs are known to respond to Fas ligand-mediated apoptotic insult by elaborating the epidermal growth factor-like growth factor, amphiregulin, thereby encouraging the proliferation and survival of their neighbors despite their own demise (Iordanov *et al.*, 2005). These findings leave open the long-suggested possibility that autocrine EGFR activation may have an important role in the elicitation of psoriatic epidermal hyperplasia (Elder *et al.*, 1989). Of course, CD8+ T cells could also trigger KCs to release a variety of other soluble factors, including cytokines

such as TNF-α, chemokines such as IL-8 and CCL20, eicosanoids, and/or growth factors, which could further increase local inflammation and stimulate KC proliferation.

Despite the evident experimental complexities presented by the psoriatic tissue response, we now have the beginnings of a genetic ''Rosetta stone'' pointing us toward molecular pathways that will help us finally understand why such a distinctive pattern of cutaneous inflammation develops in psoriasis, and how this inflammation provokes its equally distinctive epidermal response. Although this stone requires further extensive polishing (that is, the identification of additional genetic signals and the elucidation of causative genetic variants outside the MHC), it should be valuable for years to come.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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