Published in final edited form as:
Nat Clin Pract Rheumatol. 2009 February ; 5(2): 83–91. doi:10.1038/ncprheum0987.

New insights into the pathogenesis and genetics of psoriatic arthritis

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Summary

Psoriasis (PS) and psoriatic arthritis (PSA) are inter-related heritable diseases. Psoriatic skin is characterized by hyperproliferative, poorly differentiated keratinocytes and robust mononuclear inflammation. Psoriatic joints are characterized by highly inflamed synovia and entheses with focal erosions of cartilage and bone. Recent genetic analyses have uncovered risk factors shared by both PS and PsA. With respect to common variation, the HLA class I region is the locus that predisposes most strongly to PS and PsA. Other risk factors implicate the IL23 pathway and the induction/regulation of Th17 cells in the pathogenesis of both diseases. Elaboration by cytokines such as IL22 and IL could result in the hyper-proliferative phenotype of keratinocytes and potentially synoviocytes, leading to the vicious cycle of proliferation/inflammation in both the skin and joints. In synovial tissue, disease-related cytokines may also lead to RANK ligand dependent osteoclast formation leading to bone erosion. Genetic risk factors leading specifically to PsA need to be identified. Therapies targeting TNF have frequently been highly successful in the treatment of both diseases, and genetic findings are likely to lead to the development of additional treatments tailored to an individual's genetic profile.

Introduction

Psoriasis vulgaris (PS) is a chronic inflammatory skin disease affecting 2–3% of the Caucasian population.[1, 2] It frequently develops in early adulthood between the ages of 15 and 30, although individuals of all ages can be affected. The thick scaly skin plaques observed in the psoriatic lesion reflects a number of biological changes including the reduction in the transit time a basal keratinocyte progresses to a desquamated cell (4–6 weeks to only a few days). Moreover, a large number of activated immune cells in the psoriatic dermis elaborate a complex cytokine milieu not found in normal skin.

Up to 30% of PS patients also develop psoriatic arthritis (PsA).[3] These patients complain of chronic joint pain, fatigue, and restriction of mobility, and experience a reduced quality of life compared to normal individuals.[3, 4] Some PsA patients may have an increased prevalence of cardiovascular disease and its associated risk factors than matched controls.[5–8] The same is true for PS patients, and severely affected individuals may have greater risk factors of cardiovascular disease than those with milder disease.[9] Here, we briefly review the clinical features of PsA and the treatment modalities currently available. We also describe the recently identified genetic associations that confer susceptibility to both PS and PsA that begin to

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explain the fundamental basis of the biological alterations found in these diseases and that highlight pathways to be targeted for the development of novel therapies.

Genetic and environmental contributions

PsA is a highly heritable disease. The recurrence risk (λ_S)[10] (risk to siblings/risk in the general population) of PsA is greater than 27,[11] which is far higher than for PS which is between 4 and 11.[12] Heritability is also greater for PsA than for autoimmune conditions such as rheumatoid arthritis (RA), primary Sjogren's syndrome and thyroid disease.[13] The prevalence of PS is 19 times higher among first degree relatives of probands with PsA compared with the general population.[14]

PS lesions can be triggered by a large number of factors in genetically susceptible individuals, including physical injury to the skin (the "Koebner" response), administration of interferons or other inflammation-inducing stimuli, rapid withdrawal of immunosuppressive drugs, and (systemic) infections with streptococcus or other bacteria.[15] In contrast, the trigger for PsA is not as clear although viral triggers have been suggested.[16]

Clinical features of PsA

In 1973, Moll and Wright[17] defined PsA as an inflammatory peripheral arthritis and/or spondylitis associated with PS with a negative serology test for rheumatoid factor. Since then, the wide spectrum of clinical presentations for PsA has resulted in classification criteria to help distinguish PsA from other forms of inflammatory arthritis such as rheumaoid arthritis.[18–20] These include equal sex distribution, an asymmetric arthritis particularly involving DIP joints, arthritis mutilans, spondyloarthropathy and a higher incidence of nail involvement than uncomplicated PS.[17, 21] In approximately 80% of patients, arthritis follows the development of PS by a mean of 10 years.[21, 22] In others, joint manifestations may present with or prior to the skin lesions. The arthritis, in most cases, is oligoarticular but may involve more joints over time and result in a symmetric and polyarticular destructive arthritis.[22, 23] A spinal predominant variant may present with asymmetric sacroiliitis and discontinuous spinal involvement that resembles ankylosing spondylitis. Enthesitis can help distinguish PsA from rheumatoid arthritis and osteoarthritis. This is evident in plain radiographs and MRI as periostitis, new bone formation and erosions.[24]

Current therapies for PsA

The symptoms of mild PsA are often successfully alleviated by non-steroidal anti-inflammatory drugs (NSAIDs), or by local intra-articular injections of corticosteroids.[25] However, neither of these modalities can arrest the development of structural joint damage.[26] Extensive or aggressive disease requires more potent therapy such as traditional disease-modifying anti-rheumatic drugs (DMARDs) like methotrexate and sulfasalazine.[25] Methotrexate has also been widely used to treat severe PS since the 1960s[27]. Its broad anti-inflammatory effect mediated by adenosine can neutralize neutrophils, T cells and macrophages that are all key players in PS and PsA pathogenesis.[28]

Cyclosporine, which potently inhibits T cell activation and cytokine production is effective for the rapid control of both PS and PsA.[27,29] In contrast, biological response modifiers targeting specific T cell co-stimulatory molecules such as Alefacept, a human LFA-3 (CD58)/IgG1 fusion protein, is effective for PS, but not for PsA.[30] Likewise, Efalizumab, a humanized monoclonal antibody against LFA-1 expressed by T cells, is effective for PS[31] but does not differ significantly from placebo in the treatment of PsA.[32] In some cases, treatment with Efalizumab for PS even triggers the onset of, or exacerbates, PsA.[33, 34]

Three TNFα antagonists, adalimumab, etanercept, and infliximab, have been FDA-approved for the treatment of PsA. Significant numbers of patients treated with these agents achieve ACR50 compared to placebo groups.[35,36,37] Multiple clinical trials have also demonstrated the efficacy of TNFα blockade for PS.[38, 39] Etanercept exerts its effect in PS by inhibiting inflammatory myeloid dendritic cell (DC) cytokine production and maturation, thus reducing the activity of the newly described pathogenic lineage of effector $CD4^+$ T cells, T helper(Th) 17 (T_h17) cells and the levels of their elaborated cytokines[40]. TNFα antagonists can also regulate differentiation and activation of osteoclasts[41], thus reducing bone destruction in psoriatic arthritis. Paradoxically, TNFα blockade can also induce or worsen PS, perhaps due to unopposed IFNγ production from Th1 cells or to upregulation of plasmacytoid DCs. [42] IL12/23 p40 blockade also results in a dramatic and prolonged clinical response to psoriasis[43, 44] Collectively, these data imply a pivotal role of DC and T cell interactions via TNFα and IL23/T_h17 axis in PS and potentially PsA pathogenesis that is discussed further below.

Pathogenic clues from genetic analyses

The efficacy of immune modulating therapies in the treatment of both PS and PsA implicates shared immunologic mechanisms in the pathogenesis of both diseases. Both skin and synovium are characterized by marked vascularity and robust mononuclear inflammatory infiltration that includes dendritic cells (DC), activated T cells and tissue macrophages[45–47] and multiple genetic risk factors encoded by these immune cells are beginning to be identified.

Genetic approaches for finding disease genes depend on whether they are rare mutations or common variation. The identification of rare variants responsible for Mendelian traits can be accomplished by linkage analysis followed by positional cloning as long as sufficient affected members/families are available for statistical analyses. The identification of common variation for common diseases such as PS and PsA is performed with genetic association studies. While association studies have been performed for highly plausible candidate genes (i.e those for the major histocompatibility locus antigen cluster (MHC) and IL12p40)[48, 49], recently improved technologies for genome wide association studies (GWAS) have facilitated a genome-wide and unbiased approach (see BOX).

Below we present genes/loci associated with PsA. Most were originally described to be associated with PS, and were then tested for their association with PsA. Their likely contributions to immunopathology and disease pathogenesis, particularly in the context of joint inflammation, are discussed and illustrated in Figure 1.

PSORS1 and other HLA antigens

Psoriasis susceptibility locus 1 (PSORS1) was the first PS susceptibility locus to be localized and maps to the MHC class I region. The strong association between PSORS1 and HLA-Cw6[50,51–58] is estimated to account for one-third to one-half of the genetic liability to PS[59] HLA-Cw*0602 is also increased among patients with PsA compared to controls[48] (Table 1) and leads to earlier mean age of onset of PS in PsA patients ($p = 0.003$).[48]

GWAs studies also indicate that alleles from the HLA class I region are more highly associated with PsA than any other loci in the genome are[60]. The SNPs most highly associated with PsA tag HLA-Cw*0602, but also the rarer and closely-related HLA-Cw*1203 allele.[56,57] Interestingly, and as described elsewhere, HLA-Cw*0602 and HLA-Cw*1203 may recognize the same antigen since they are identical in their alpha-2 domains and peptide binding pockets C, D, and E.[56] However, they differ by five amino acids in their alpha-1 domain, placing them in different killer cell immunoglobulin-like receptor (KIR) ligand groups. As other independent studies point to HLA-Cw*0602 alone as being the PSORS1 risk allele,[52] functional studies

may be needed to resolve this discrepancy and to conclusively rule out SNPs affecting expression of HLA-C alleles or other skin specific genes in this region such as corneodesmosin and alpha-helix coiled-coil rod homolog gene (HCR).[53, 54, 58, 61–63]

Earlier studies on PsA associations with MHC alleles were generally performed with small numbers of patients but deserve some discussion. HLA-B27 is associated with spinal involvement, whereas HLA-B38 and B39 are associated with peripheral polyarthritis.[64] These latter two alleles are highly correlated with HLA-Cw*1203, hence, this earlier finding may be due to the HLA-Cw*1203 association with PsA. The presence of the RA "shared epitope" HLA-DRB1 from the HLA class II region is reported to be associated with radiological erosions in PsA.[65] Moreover, HLA-B39 alone, HLA-B27 in the presence of HLA-DR7, and HLA-DQw3 in the absence of HLA-DR7, are reported to confer an increased risk for disease progression. Conversely, HLA-B22 is reported to be protective for disease progression.[64] Patients with both HLA-Cw6 and HLA-DRB1*07 alleles are reported to have a less severe course of arthritis than patients with HLA-C26 or HLA-DRB1*07 alone.[66] It is not clear if some of these associations are due to "linkage disequilibrium" within the MHC, reflecting a predisposing haplotype harboring a different risk factor, or are truly causative themselves.

Tumor necrosis factor alpha (*TNFA*) polymorphisms are of interest given the success of anti-TNF agents in PS and PsA. The polymorphisms that are associated with PS and PsA, such as those in the *TNFA* promoter at positions −238 and −308, have been demonstrated to be due to linkage disequilibrium with HLA-Cw*0602.[67] However, TNF*-857T, may represent a risk factor for PsA that is independent of the PSORS1 allele.[67]

In the case of PsA susceptibility, there are also important interactions with certain HLA-class I alleles and killer inhibitory receptors (KIRs) that are located on chromosome 19. Susceptibility to PsA is strongly associated with the presence of KIR2DS1 and/or KIR2DS2 plus HLA-Cw ligand group homozygosity (so that an inhibitory signal is diminished).[68,69, 70] Certain combinations of natural killer receptors and HLA-B alleles are also associated with slower time to develop AIDS, and lower risk of HIV infection in exposed uninfected individuals[71]. These include the combined genotype of *KIR3DL1* high expressing alleles and HLA-B*57 which is associated with PsA. Certain combinations of HLA and KIR are also reported to affect outcome to infection by other viruses such as hepatitis B virus, hepatitis C virus and human papilloma virus[72]. It is tempting to speculate that selection of alleles in the past that protected against viral infection lead to susceptibility to diseases such as psoriatic arthritis.

Other susceptibility genes

With the exception of the MHC, linkages and associations have not been replicated in all cohorts. This can be due to low effect size of individual genetic variation, ascertainment bias and gene-environment interactions. The following are genes that have recently been implicated in PS and PsA from genetic analyses (also summarized in Table 1).

Genes influencing the IL-23/Th17 pathway

Susceptibility to both PS and PsA is associated with alleles of the *IL12B* and IL23 receptor (*IL23R*) genes (Table 1).[49, 60, 73–75] The same *IL23R* alleles are risk factors for other inflammatory or autoimmune diseases such as Crohn's disease and ankylosing spondylitis[76, 77]. This implicates a shared inflammatory pathway mediated by IL23R in all of these diseases.[76, 78–80] A variant near *IL23A* (encoding IL-23p19) also confer PS susceptibility.[81] IL-23 is composed of two sub-units, IL-23p19 (encoded by *IL23A*) and IL-12p40 (encoded by *IL12B*), and is recognized by the heterodimeric receptor encoded by *IL23R* and *IL12RB1*. IL-12 is a heterodimer of IL12p40 and IL12p35 and binds to the heterodimeric receptor complex of

IL12Rβ2 and IL12Rβ1. These cytokines play key roles in regulating both innate and adaptive immunity. IL-12, elaborated by activated dendritic cells and macrophages during inflammation can regulate the differentiation of naïve T_h cells into IFN-γ producing T_h1 cells. IL-23 is also elaborated by dendritic cells and macrophages, and is a survival factor for T_h17 cells. The level of IL23p19 and p40 sub-units, but not IL12p35, are significantly increased in lesional compared to non-lesional skin,[82] which could be due to the direct effect of genetic risk factors such as an increased affinity for transcription factors in enhancers of these genes. Serum levels of IL12/23 p40 sub-unit is also one of the proteins that can maximally discriminate PsA patients from controls.[83]

T_h17 cells are developmentally and functionally distinct from classical T_h1 and T_h2 lineages and are characterized by the production of IL-17 and IL-22 cytokines.[84] Like the traditional T_h1 and T_h2 cells, they are proposed to have evolved to provide adaptive immunity to specific classes of pathogens, such as extracellular bacteria. Aberrant T_h17 responses are implicated in a growing list of autoimmune disorders[85] and both IL-17 and IL-22 cytokines are increased in PS lesions[40, 86]. They induce pro-inflammatory chemokines, and promote epidermal acanthosis and parakeratosis.[87–90] However, it is still unclear if this axis is similarly relevant in triggering joint disease in PsA. While activated T cells infiltrate PSA joints with similar distribution patterns as in lesional skin: CD4+ T cells predominate over CD8+ in the dermis[37] and synovial membrane[91], and the reverse in both epidermis and synovial fluid,[92, 93] the joint levels of T_h17 associated cytokines have yet to be established. These activated T cells from PsA joints can induce osteoclastogenesis and trigger bone resorption and articular damage in PsA via RANK/RANKL interactions.[94, 95] Osteoclastogenesis can be triggered by TNFα, and there is in vitro evidence that IL-23 can induce this as well, by a mechanism that is IL-17, TNFα and RANKL dependent[96, 97]. IL-17 has also been shown *in vitro* to induce the expression of RANKL in osteoblasts.[96, 97] Treatment with human IL12/23 p40 monoclonal antibody can reduce the signs and symptoms of psoriatic arthritis, supporting an important pathogenic role for IL23 and potentially T_h17 cytokines in in potentiating osteoclastogenesis and exerting a pro-erosive influence in PsA.[98]

A region of chromosome 4q27 encoding IL-2 and/or IL-21 and associated with celiac disease[99], type 1 diabetes[100], RA[101] and systemic lupus erythematosus (SLE)[102] is associated with PsA susceptibility in one study (Table 1)[60]. IL-2 is a pathogenic cytokine for PS, and blockade of the IL-2 receptor with therapeutic antibodies has led to disease resolution in some cases.[103] Together with TGFβ, IL-2 is also essential for expansion of regulatory T cells (T_{reg}).[104] IL-21 is produced by activated T cells and influences the proliferation of T and B cells, and the cytolytic activity of natural killer cells.[105] Importantly, IL-21 is produced by T_h17 cells[106] and is thought to promote and sustain T_h17 differentiation and IL-17 production in an autocrine fashion.[107–109] IL-21 can also up-regulate IL-23R[109] that, as previously mentioned, has been implicated in PS and PsA pathogenesis. However, the presence of IL-21 has yet to be demonstrated in psoriatic skin or synovium.

It is of interest that the genetic associations described above converge on cellular pathways involved in a decision of antigen-stimulated cells to differentiate into either a T_h17 or T_{reg} cell. In mice, when TGFβ is at low concentrations it synergizes with IL-6 and IL-21 to relieve FOXP3 mediated inhibition of RORγt promoting IL-23R expression and favoring T_h17 cell development[110]; a process that is dependent on histone/protein deacetylase activity[111]. Conversely, high concentrations of TGFβ repress IL-23R expression and favor the development of T_{regs}. The role of T_{regs} in PsA has not been described, but it is known that they can suppress RANKL-dependent osteoclast formation[112].

The 5q31 locus and Ps/PsA

The 5q31 region harbors genes encoding IL4, IL13 and IL5 that are upregulated in T cells committed to the T_h2 lineage[104] and certain alleles confer susceptibility to a number of inflammatory diseases including Crohn's disease (CD), asthma and PS[113–116,117] PS associated variants upstream from IL13 and within *SLC22A4/OCTN1* may both be causative[118] and independent of CD variants. However, an independent study indicated that the same OCTN1 variant is associated with both CD and PsA.[119]

The role the 5q31 locus plays in the development of PS and potentially PsA is not clear. IL-4 prevents the development of arthritis in an animal model induced by Ags or infections agents, inducing a switch from a Th1-type to a Th2-type response.[120] IL-4 and IL-13 also negatively regulate TNFα and IFNγ induced pathways in keratinocytes via activation of STAT6, suppressor of cytokine signaling (SOCS)-1 and SOCS-3. This interferes with STAT-1 and NF-kappaB signaling and activation of the beta-defensins HBD-2 and HBD-3.[121] IL4 and IL13 also play a role in the induction of T_{regs} from peripheral naïve $CD4^+$ T cells.[122] This induction is independent of the presence of TGFβ or IL-10, but is dependent on antigen-specific stimulation and B7 co-stimulation.

Other Genetic Associations

Psoriasis is also associated with allele/s of tumor necrosis factor, alpha-induced protein 3 (*TNFAIP3*), a zinc finger/ubiquitin editing enzyme, A20, and with SNPs upstream from the gene encoding its partner TNFAIP3 interacting protein 1 (TNIP1). Their encoded proteins play a role in restricting NF-κB dependent signaling and preventing inflammation. Independent polymorphisms in *TNFAIP3* are associated with rheumatoid arthritis, and systemic lupus erythematosus.[123–126,81] TNIP1 is upregulated in psoriasis lesions and uninvolved versus normal skin from controls[81] and the association of TNFAIP3 and TNIP1 with PsA needs to be examined.

Another potential avenue to explore in the genetics of PsA is the overlap between Ankylosing Spondylitis (AS) and PsA since at least some genetic risk factors are shared (e.g. HLA-B27, Il23R[77], IL-1[127]). Two regions of chromosome 2q12-13 harboring the interleukin-1 (IL-1) cytokine cluster contributed independently to risk of PsA; a region in IL1A, and a region near the end of IL1B, through IL1F7, IL1F8, and into IL1F10[127]. *ARTS1*, *TSHR* and *FCRL3* are also associated with AS[77]. Since over forty percent of patients with PsA have spondyloarthritis, patients with combinations of genetic risk factors also found in AS patients may belong to a particular subset.

Other similarities in skin and joints are worth exploring. The activated osteoclast is a $CD68^+$ blood-derived, macrophage-like cell that lives normally in an unactivated state on the bone cortex or outer surface.[128] $CD68^+/CD11c^+$ dendritic cells are also present in the dermal-epidermal junction of lesional psoriatic skin and are the main producers of IL-20.[129] IL-20 production can be stimulated by TNFα[95] that is produced by myeloid leukocytes including DCs and macrophages. Hence, genetic factors that contribute to the differentiation, activation, or down-regulation of myeloid cells may be important for the $CD68^+$ osteoclasts in PSA and also for the $CD68^+/CD11c^+$ dendritic cells in PS.

Conclusion

The immune system is a tightly regulated network of cells and cytokines, and genetic factors that lead to immune alterations may likely tip the balance towards inflammation in the skin and synovium of PS and PsA, respectively. Noteworthy shared associations in PS and PsA involve components of the IL-23/Th17 pathway, namely, *IL23R*, *IL12B*, and potentially

IL23A and *IL21*. As it is known that the different T_h subsets can counter-regulate each other,[130, 131] further dissection of the contribution and interaction of different T_h subsets in PsA is of extreme interest. It will also be of interest to determine if they also play a role in osteoclastogenesis. It is also important to identify specific genetic factors that differentiate PsA from PS.

Genetic risk factors generally have odds ratios below 2 and frequently between 1.1 and 1.5. Even for the MHC, the OR is < 4.0. Hence, multiple genes of low risk effect may be involved in susceptibility to PS and PsA. This is similar to CD where ~30 genes with low risk effects (generally <1.3) have been identified, and where there are predicted to be possibly 100 risk factors with even lower risk effects (<1.1).[132]

Many questions are left unanswered that, we hope, genetics can further elucidate. Can we stratify patients into different subpopulations based on genetic risk factors and tailor therapy? Which genetic risk factors can predict response to treatment? What role does the environment play in triggering disease? Answering these questions will require much larger patient populations, and well-annotated clinical databases, than those studied so far.

BOX

These approaches search for association of a disease with single nucleotide polymorphisms (SNPs); variations in DNA sequence that exists in two forms (alleles) in a population. Such markers (~500,000 or more) have been selected throughout the genome by the International HapMap project[134] as representatives of the sequence that surround them. When an "association" between a SNP and a disease exists, the frequency of the alleles differs in cases compared to healthy controls. The marker is usually not the "cause" of the trait, but identifies the general locale of the offending alteration.

Acknowledgments

Supported in part by NIH grant R01 AR050266 (AMB) and the Clinical Scholars Program at The Rockefeller University (KEN). We thank Drs. James Krueger and Michelle Lowes for critical comments on the review.

References

1. Gelfand JM, et al. The prevalence of psoriasis in African Americans: results from a population-based study. J Am Acad Dermatol 2005;52:23–6. [PubMed: 15627076]
2. Menter A, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol 2008;58:826–50. [PubMed: 18423260]
3. Zachariae H, et al. Quality of life and prevalence of arthritis reported by 5,795 members of the Nordic Psoriasis Associations. Data from the Nordic Quality of Life Study. Acta Derm Venereol 2002;82:108–13. [PubMed: 12125937]
4. Husted JA, Gladman DD, Farewell VT, Cook RJ. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. Arthritis Rheum 2001;45:151–8. [PubMed: 11324779]
5. Han C, et al. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol 2006;33:2167–72. [PubMed: 16981296]
6. Kimhi O, et al. Prevalence and risk factors of atherosclerosis in patients with psoriatic arthritis. Semin Arthritis Rheum 2007;36:203–9. [PubMed: 17067658]
7. Gonzalez-Juanatey C, et al. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. Arthritis Rheum 2007;57:1074–80. [PubMed: 17665475]

8. Tam LS, et al. Cardiovascular risk profile of patients with psoriatic arthritis compared to controls--the role of inflammation. Rheumatology (Oxford) 2008;47:718–23. [PubMed: 18400833]
9. Neimann AL, et al. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55:829–35. [PubMed: 17052489]
10. Martin MP, et al. Innate partnership of HLA-B and KIR3DL1 subtypes against HIV-1. Nat Genet 2007;39:733–40. [PubMed: 17496894]
11. Gladman DD, Farewell VT, Pellett F, Schentag C, Rahman P. HLA is a candidate region for psoriatic arthritis. evidence for excessive HLA sharing in sibling pairs. Hum Immunol 2003;64:887–9. [PubMed: 12941544]
12. Bhalerao J, Bowcock AM. The genetics of psoriasis: a complex disorder of the skin and immune system. Hum Mol Genet 1998;7:1537–45. [PubMed: 9735374]
13. Myers A, Kay LJ, Lynch SA, Walker DJ. Recurrence risk for psoriasis and psoriatic arthritis within sibships. Rheumatology (Oxford) 2005;44:773–6. [PubMed: 15757963]
14. Rahman P, et al. Association of SEEK1 and psoriatic arthritis in two distinct Canadian populations. Ann Rheum Dis 2005;64:1370–2. [PubMed: 15708881]
15. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet 2007;370:263–71. [PubMed: 17658397]
16. Palazzi C, et al. Hepatitis C virus infection in psoriatic arthritis. Arthritis Rheum 2005;53:223–5. [PubMed: 15818717]
17. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55–78. [PubMed: 4581554]
18. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis (PSA)--an analysis of 220 patients. Q J Med 1987;62:127–41. [PubMed: 3659255]
19. McGonagle D, Conaghan PG, Emery P. Psoriatic arthritis: a unified concept twenty years on. Arthritis Rheum 1999;42:1080–6. [PubMed: 10366099]
20. Fournie B, et al. Proposed classification criteria of psoriatic arthritis. A preliminary study in 260 patients. Rev Rhum Engl Ed 1999;66:446–56. [PubMed: 10567972]
21. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64(Suppl 2):ii14–7. [PubMed: 15708927]
22. Myers WA, Gottlieb AB, Mease P. Psoriasis and psoriatic arthritis: clinical features and disease mechanisms. Clin Dermatol 2006;24:438–47. [PubMed: 16966023]
23. Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology (Oxford) 2003;42:1460–8. [PubMed: 14523223]
24. McGonagle D. Imaging the joint and enthesis: insights into pathogenesis of psoriatic arthritis. Ann Rheum Dis 2005;64(Suppl 2):ii58–60. [PubMed: 15708939]
25. Nash P, Clegg DO. Psoriatic arthritis therapy: NSAIDs and traditional DMARDs. Ann Rheum Dis 2005;64(Suppl 2):ii74–7. [PubMed: 15708943]
26. Gottlieb A, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol 2008;58:851–64. [PubMed: 18423261]
27. Warren RB, Griffiths CE. Systemic therapies for psoriasis: methotrexate, retinoids, and cyclosporine. Clin Dermatol 2008;26:438–47. [PubMed: 18755362]
28. Chan ES, Cronstein BN. Molecular action of methotrexate in inflammatory diseases. Arthritis Res 2002;4:266–73. [PubMed: 12106498]
29. Salvarani C, Cantini F, Olivieri I. Disease-modifying antirheumatic drug therapy for psoriatic arthritis. Clin Exp Rheumatol 2002;20:S71–5. [PubMed: 12463452]
30. Mease PJ, Gladman DD, Keystone EC. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. Arthritis Rheum 2006;54:1638–45. [PubMed: 16646026]
31. Dubertret L, et al. CLinical experience acquired with the efalizumab (Raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial. Br J Dermatol 2006;155:170–81. [PubMed: 16792770]

32. Papp KA, Caro I, Leung HM, Garovoy M, Mease PJ. Efalizumab for the treatment of psoriatic arthritis. J Cutan Med Surg 2007;11:57–66. [PubMed: 17374316]
33. Bang B, Gniadecki R. Severe exacerbation of psoriatic arthritis during treatment with efalizumab. A case report. Acta Derm Venereol 2006;86:456–7. [PubMed: 16955198]
34. Viguier M, et al. Onset of psoriatic arthritis in patients treated with efalizumab for moderate to severe psoriasis. Arthritis Rheum 2008;58:1796–802. [PubMed: 18512820]
35. Mease PJ, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385–90. [PubMed: 10972371]
36. Mease PJ, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52:3279–89. [PubMed: 16200601]
37. Antoni C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64:1150–7. [PubMed: 15677701]
38. Woolacott NF, Khadjesari ZC, Bruce IN, Riemsma RP. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review. Clin Exp Rheumatol 2006;24:587–93. [PubMed: 17181932]
39. Ravindran V, Scott DL, Choy EH. A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. Ann Rheum Dis 2008;67:855–9. [PubMed: 17827183]
40. Zaba LC, et al. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. J Exp Med 2007;204:3183–94. [PubMed: 18039949]
41. Fantuzzi F, Del Giglio M, Gisondi P, Girolomoni G. Targeting tumor necrosis factor alpha in psoriasis and psoriatic arthritis. Expert Opin Ther Targets 2008;12:1085–96. [PubMed: 18694376]
42. Collamer AN, Guerrero KT, Henning JS, Battafarano DF. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: a literature review and potential mechanisms of action. Arthritis Rheum 2008;59:996–1001. [PubMed: 18576309]
43. Leonardi CL, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665–74. [PubMed: 18486739]
44. Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675–84. [PubMed: 18486740]
45. Rottman JB, Smith TL, Ganley KG, Kikuchi T, Krueger JG. Potential role of the chemokine receptors CXCR3, CCR4, and the integrin alphaEbeta7 in the pathogenesis of psoriasis vulgaris. Lab Invest 2001;81:335–47. [PubMed: 11310827]
46. Kruithof E, et al. Synovial histopathology of psoriatic arthritis, both oligo- and polyarticular, resembles spondyloarthropathy more than it does rheumatoid arthritis. Arthritis Res Ther 2005;7:R569–80. [PubMed: 15899044]
47. Ritchlin C. Psoriatic disease--from skin to bone. Nat Clin Pract Rheumatol 2007;3:698–706. [PubMed: 18037929]
48. Gladman DD, Cheung C, Ng CM, Wade JA. HLA-C locus alleles in patients with psoriatic arthritis (PsA). Hum Immunol 1999;60:259–61. [PubMed: 10321964]
49. Tsunemi Y, et al. Interleukin-12 p40 gene (IL12B) 3′-untranslated region polymorphism is associated with susceptibility to atopic dermatitis and psoriasis vulgaris. J Dermatol Sci 2002;30:161–6. [PubMed: 12413772]
50. Tiilikainen A, Lassus A, Karvonen J, Vartiainen P, Julin M. Psoriasis and HLA-Cw6. Br J Dermatol 1980;102:179–84. [PubMed: 7387872]
51. Fan X, et al. Comparison of clinical features of HLA-Cw*0602-positive and -negative psoriasis patients in a Han Chinese population. Acta Derm Venereol 2007;87:335–40. [PubMed: 17598037]
52. Nair RP, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet 2006;78:827–51. [PubMed: 16642438]
53. Chang YT, et al. Psoriasis vulgaris in Chinese individuals is associated with PSORS1C3 and CDSN genes. Br J Dermatol 2006;155:663–9. [PubMed: 16965413]

54. Orru S, Giuressi E, Carcassi C, Casula M, Contu L. Mapping of the major psoriasis-susceptibility locus (PSORS1) in a 70-Kb interval around the corneodesmosin gene (CDSN). Am J Hum Genet 2005;76:164–71. [PubMed: 15529278]
55. Holm SJ, et al. HLA-Cw*0602 associates more strongly to psoriasis in the Swedish population than variants of the novel 6p21.3 gene PSORS1C3. Acta Derm Venereol 2005;85:2–8. [PubMed: 15848982]
56. Helms C, et al. Localization of PSORS1 to a haplotype block harboring HLA-C and distinct from corneodesmosin and HCR. Hum Genet 2005;118:466–76. [PubMed: 16235096]
57. Veal CD, et al. Family-based analysis using a dense single-nucleotide polymorphism-based map defines genetic variation at PSORS1, the major psoriasis-susceptibility locus. Am J Hum Genet 2002;71:554–64. [PubMed: 12148091]
58. Asumalahti K, et al. Coding haplotype analysis supports HCR as the putative susceptibility gene for psoriasis at the MHC PSORS1 locus. Hum Mol Genet 2002;11:589–97. [PubMed: 11875053]
59. Elder JT. PSORS1: linking genetics and immunology. J Invest Dermatol 2006;126:1205–6. [PubMed: 16702966]
60. Liu Y, et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. PLoS Genet 2008;4:e1000041. [PubMed: 18369459]
61. Allen M, et al. Corneodesmosin expression in psoriasis vulgaris differs from normal skin and other inflammatory skin disorders. Lab Invest 2001;81:969–76. [PubMed: 11454986]
62. Martinez-Borra J, et al. Psoriasis vulgaris and psoriatic arthritis share a 100 kb susceptibility region telomeric to HLA-C. Rheumatology (Oxford) 2003;42:1089–92. [PubMed: 12730526]
63. Martinez-Borra J, et al. The region of 150 kb telometic to HLA-C is associated with psoriasis in the Jewish population. J Invest Dermatol 2005;125:928–32. [PubMed: 16297191]
64. Gladman DD, Farewell VT. HLA studies in psoriatic arthritis: current situation and future needs. J Rheumatol 2003;30:4–6. [PubMed: 12508382]
65. Korendowych E, McHugh N. Genetic factors in psoriatic arthritis. Curr Rheumatol Rep 2005;7:306–12. [PubMed: 16045834]
66. Ho PY, et al. HLA-Cw6 and HLA-DRB1*07 together are associated with less severe joint disease in psoriatic arthritis. Ann Rheum Dis 2007;66:807–11. [PubMed: 17223660]
67. Reich K, et al. TNF polymorphisms in psoriasis: association of psoriatic arthritis with the promoter polymorphism TNF*-857 independent of the PSORS1 risk allele. Arthritis Rheum 2007;56:2056–64. [PubMed: 17530646]
68. Martin MP, et al. Cutting edge: susceptibility to psoriatic arthritis: influence of activating killer Ig-like receptor genes in the absence of specific HLA-C alleles. J Immunol 2002;169:2818–22. [PubMed: 12218090]
69. Williams F, et al. Activating killer cell immunoglobulin-like receptor gene KIR2DS1 is associated with psoriatic arthritis. Hum Immunol 2005;66:836–41. [PubMed: 16112031]
70. Nelson GW, et al. Cutting edge: heterozygote advantage in autoimmune disease: hierarchy of protection/susceptibility conferred by HLA and killer Ig-like receptor combinations in psoriatic arthritis. J Immunol 2004;173:4273–6. [PubMed: 15383555]
71. Boulet S, et al. A combined genotype of KIR3DL1 high expressing alleles and HLA-B*57 is associated with a reduced risk of HIV infection. Aids 2008;22:1487–91. [PubMed: 18614872]
72. Martin MP, Carrington M. Immunogenetics of viral infections. Curr Opin Immunol 2005;17:510–6. [PubMed: 16084708]
73. Cargill M, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet 2007;80:273–90. [PubMed: 17236132]
74. Nair RP, et al. Polymorphisms of the IL12B and IL23R genes are associated with psoriasis. J Invest Dermatol 2008;128:1653–61. [PubMed: 18219280]
75. Capon F, et al. Sequence variants in the genes for the interleukin-23 receptor (IL23R) and its ligand (IL12B) confer protection against psoriasis. Hum Genet 2007;122:201–6. [PubMed: 17587057]
76. Duerr RH, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006;314:1461–3. [PubMed: 17068223]

77. Burton PR, et al. Association scan of 14,500 nonsynonymous SNPs in four diseases identifies autoimmunity variants. Nat Genet 2007;39:1329–37. [PubMed: 17952073]
78. Taylor KD, et al. IL23R haplotypes provide a large population attributable risk for Crohn's disease. Inflamm Bowel Dis. 2008
79. Lakatos PL, et al. ATG16L1 and IL23 receptor (IL23R) genes are associated with disease susceptibility in Hungarian CD patients. Dig Liver Dis. 2008
80. Rueda B, et al. The IL23R Arg381Gln non-synonymous polymorphism confers susceptibility to ankylosing spondylitis. Ann Rheum Dis. 2008
81. Nair RP, Callis-Duffin KC, Helms C, et al. Genome-wide Scan Reveals Association of Psoriasis with IL-23 and NF- B Pathways. submitted
82. Lee E, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. J Exp Med 2004;199:125–30. [PubMed: 14707118]
83. Szodoray P, et al. Circulating cytokines in Norwegian patients with psoriatic arthritis determined by a multiplex cytokine array system. Rheumatology (Oxford) 2007;46:417–25. [PubMed: 16936328]
84. McGeachy MJ, Cua DJ. Th17 cell differentiation: the long and winding road. Immunity 2008;28:445–53. [PubMed: 18400187]
85. Awasthi A, Murugaiyan G, Kuchroo VK. Interplay Between Effector Th17 and Regulatory T Cells. J Clin Immunol. 2008
86. Lowes MA, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol 2008;128:1207–11. [PubMed: 18200064]
87. Boniface K, et al. IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of human keratinocytes. J Immunol 2005;174:3695–702. [PubMed: 15749908]
88. Wolk K, et al. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. Eur J Immunol 2006;36:1309–23. [PubMed: 16619290]
89. Sa SM, et al. The effects of IL-20 subfamily cytokines on reconstituted human epidermis suggest potential roles in cutaneous innate defense and pathogenic adaptive immunity in psoriasis. J Immunol 2007;178:2229–40. [PubMed: 17277128]
90. Nograles K. Brit J Dermatol. in press
91. Veale D, Farrell M, Fitzgerald O. Mechanism of joint sparing in a patient with unilateral psoriatic arthritis and a longstanding hemiplegia. Br J Rheumatol 1993;32:413–6. [PubMed: 7684307]
92. Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. Ann Rheum Dis 2005;64(Suppl 2):ii30–6. [PubMed: 15708932]
93. Costello P, Bresnihan B, O'Farrelly C, FitzGerald O. Predominance of CD8+ T lymphocytes in psoriatic arthritis. J Rheumatol 1999;26:1117–24. [PubMed: 10332977]
94. Colucci S, et al. Lymphocytes and synovial fluid fibroblasts support osteoclastogenesis through RANKL, TNFalpha, and IL-7 in an in vitro model derived from human psoriatic arthritis. J Pathol 2007;212:47–55. [PubMed: 17370327]
95. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. Nature 2003;423:337–42. [PubMed: 12748652]
96. Yago T, et al. IL-23 induces human osteoclastogenesis via IL-17 in vitro, and anti-IL-23 antibody attenuates collagen-induced arthritis in rats. Arthritis Res Ther 2007;9:R96. [PubMed: 17888176]
97. Kotake S, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. J Clin Invest 1999;103:1345–52. [PubMed: 10225978]
98. Gottlieb A. abstract. Academy Clinical Rheumatology Annual meeting. 2007
99. van Heel DA, et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. Nat Genet 2007;39:827–9. [PubMed: 17558408]
100. Todd JA, et al. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet 2007;39:857–64. [PubMed: 17554260]
101. Zhernakova A, et al. Novel association in chromosome 4q27 region with rheumatoid arthritis and confirmation of type 1 diabetes point to a general risk locus for autoimmune diseases. Am J Hum Genet 2007;81:1284–8. [PubMed: 17999365]

102. Sawalha AH, et al. Genetic association of interleukin-21 polymorphisms with systemic lupus erythematosus. Ann Rheum Dis 2008;67:458–61. [PubMed: 17720724]
103. Krueger JG, et al. Successful in vivo blockade of CD25 (high-affinity interleukin 2 receptor) on T cells by administration of humanized anti-Tac antibody to patients with psoriasis. J Am Acad Dermatol 2000;43:448–58. [PubMed: 10954656]
104. Skapenko A, Schulze-Koops H. Analysis of Th1/Th2 T-cell subsets. Methods Mol Med 2007;136:87–96. [PubMed: 17983142]
105. Parrish-Novak J, Foster DC, Holly RD, Clegg CH. Interleukin-21 and the IL-21 receptor: novel effectors of NK and T cell responses. J Leukoc Biol 2002;72:856–63. [PubMed: 12429707]
106. Butt C, et al. Association of functional variants of PTPN22 and tp53 in psoriatic arthritis: a case-control study. Arthritis Res Ther 2006;8:R27. [PubMed: 16507123]
107. Huffmeier U, et al. Male restricted genetic association of variant R620W in PTPN22 with psoriatic arthritis. J Invest Dermatol 2006;126:932–5. [PubMed: 16456530]
108. Wei L, Laurence A, Elias KM, O'Shea JJ. IL-21 is produced by Th17 cells and drives IL-17 production in a STAT3-dependent manner. J Biol Chem 2007;282:34605–10. [PubMed: 17884812]
109. Zhou L, et al. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nat Immunol 2007;8:967–74. [PubMed: 17581537]
110. Zhou L, et al. TGF-beta-induced Foxp3 inhibits T(H)17 cell differentiation by antagonizing RORgammat function. Nature 2008;453:236–40. [PubMed: 18368049]
111. Koenen HJ, et al. Human CD25highFoxp3pos regulatory T cells differentiate into IL-17-producing cells. Blood 2008;112:2340–52. [PubMed: 18617638]
112. Zaiss MM, et al. Treg cells suppress osteoclast formation: a new link between the immune system and bone. Arthritis Rheum 2007;56:4104–12. [PubMed: 18050211]
113. Onnie C, et al. Sequence variation, linkage disequilibrium and association with Crohn's disease on chromosome 5q31. Genes Immun 2006;7:359–65. [PubMed: 16724073]
114. Wills-Karp M. The gene encoding interleukin-13: a susceptibility locus for asthma and related traits. Respir Res 2000;1:19–23. [PubMed: 11667960]
115. Kauppi P, et al. A second-generation association study of the 5q31 cytokine gene cluster and the interleukin-4 receptor in asthma. Genomics 2001;77:35–42. [PubMed: 11543630]
116. Holloway JW, et al. Linkage analysis of the 5q31-33 candidate region for asthma in 240 UK families. Genes Immun 2001;2:20–4. [PubMed: 11294563]
117. Chang YT, et al. Cytokine gene polymorphisms in Chinese patients with psoriasis. Br J Dermatol 2007;156:899–905. [PubMed: 17388919]
118. Li Y, et al. The 5q31 variants associated with psoriasis and Crohn's disease are distinct. Hum Mol Genet. 2008
119. Ho P, et al. Evidence for common genetic control in pathways of inflammation for Crohn's disease and psoriatic arthritis. Arthritis Rheum 2005;52:3596–602. [PubMed: 16255050]
120. Finnegan A, Mikecz K, Tao P, Glant TT. Proteoglycan (aggrecan)-induced arthritis in BALB/c mice is a Th1-type disease regulated by Th2 cytokines. J Immunol 1999;163:5383–90. [PubMed: 10553063]
121. Albanesi C, et al. IL-4 and IL-13 negatively regulate TNF-alpha- and IFN-gamma-induced beta-defensin expression through STAT-6, suppressor of cytokine signaling (SOCS)-1, and SOCS-3. J Immunol 2007;179:984–92. [PubMed: 17617590]
122. Skapenko A, Kalden JR, Lipsky PE, Schulze-Koops H. The IL-4 receptor alpha-chain-binding cytokines, IL-4 and IL-13, induce forkhead box P3-expressing CD25+CD4+ regulatory T cells from CD25−CD4+ precursors. J Immunol 2005;175:6107–16. [PubMed: 16237107]
123. Graham RR, et al. Genetic variants near TNFAIP3 on 6q23 are associated with systemic lupus erythematosus. Nat Genet. 2008
124. Musone SL, et al. Multiple polymorphisms in the TNFAIP3 region are independently associated with systemic lupus erythematosus. Nat Genet. 2008
125. Plenge RM, et al. Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. Nat Genet 2007;39:1477–82. [PubMed: 17982456]

126. Thomson W, et al. Rheumatoid arthritis association at 6q23. Nat Genet 2007;39:1431–3. [PubMed: 17982455]

127. Rahman P, et al. Association between the interleukin-1 family gene cluster and psoriatic arthritis. Arthritis Rheum 2006;54:2321–5. [PubMed: 16918024]

128. Athanasou NA, Puddle B, Quinn J, Woods CG. Use of monoclonal antibodies to recognise osteoclasts in routinely processed bone biopsy specimens. J Clin Pathol 1991;44:664–6. [PubMed: 1890200]

129. Wang F, et al. Prominent production of IL-20 by CD68+/CD11c+ myeloid-derived cells in psoriasis: Gene regulation and cellular effects. J Invest Dermatol 2006;126:1590–9. [PubMed: 16645593]

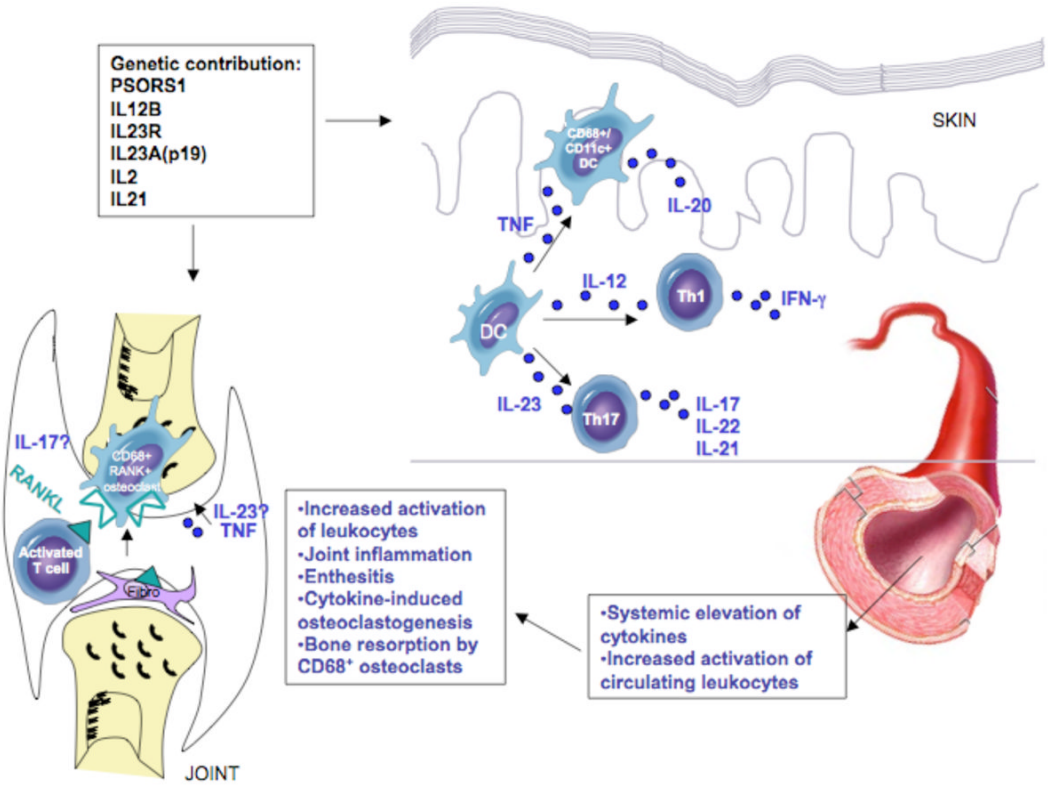
130. Nakae S, Iwakura Y, Suto H, Galli SJ. Phenotypic differences between Th1 and Th17 cells and negative regulation of Th1 cell differentiation by IL-17. J Leukoc Biol 2007;81:1258–68. [PubMed: 17307864]

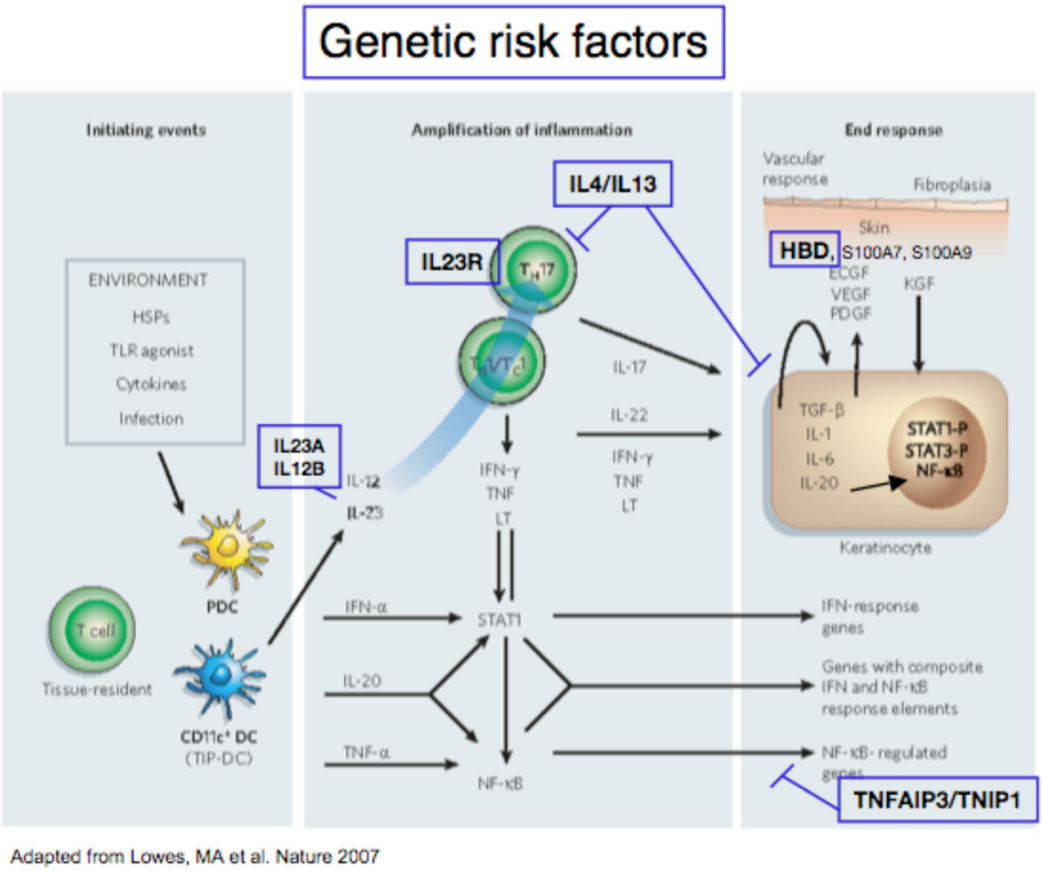
131. Harrington LE, Mangan PR, Weaver CT. Expanding the effector CD4 T-cell repertoire: the Th17 lineage. Curr Opin Immunol 2006;18:349–56. [PubMed: 16616472]

132. Barrett JC, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat Genet 2008;40:955–62. [PubMed: 18587394]

133. Huffmeier U, et al. Genetic Variants of the IL-23R Pathway: Association with Psoriatic Arthritis and Psoriasis Vulgaris, but No Specific Risk Factor for Arthritis. J Invest Dermatol. 2008

134. A haplotype map of the human genome. Nature 2005;437:1299–320. [PubMed: 16255080]





Adapted from Lowes, MA et al. Nature 2007

Figure 1. Model of the relationship between skin and joint inflammation

Genes with variants (box) contributing to psoriasis and/or psoriatic arthritis susceptibility. While infiltrating leukocytes and their cytokine products are currently better characterized in the skin than in the inflamed joint, they may be similar in both sites. Leukocytes and cytokines originating in the skin may play a direct or indirect role in the development of arthritis. Alternatively, they may originate in the synovium in a similar manner to their development in the skin.

Gene variants (blue boxes) that predispose to psoriasis influence pro-inflammatory pathways, notably the Th1 and Th17 pathways. Model of cytokine networks in psoriasis adapted from Lowes, MA et al, 2007. The role of the 5q31 region harboring IL4/IL13 is speculative at this stage. HBD (beta defensin) is upregulated in keratinocytes as a result of stimulation by IL20 and other cytokines. An increase in the number of copies of gene family members is also associated with psoriasis.

Table 1

Genes/SNPs associated with PsA. Numbers of cases/controls used for each study along with corresponding odds ratios (ORs) and P values are shown.

Gene	Chs	SNP	Case	Control	OR	P	Ref
IL12B	5q33	rs6887695	576	480	1.1	0.0013	60
			748	937	1.5	4.72×10^{-7}	133
		rs3212227	748	937	1.48	2.1×10^{-5}	133
IL23R	1p31	rs11209026	576	480	1.70	8×10^{-4}	60
			748	937	1.59	0.002	133
IL2/IL21	4q27	rs13151961	576	480	1.37	0.002	60
IL-1 gene cluster	2q13	rs3811047	212	159	1.82		127
TNF-alpha	6p21	−857	375	376	1.96	0.0025	67
HLA class I6p21 rs10484554			576	480	2.4	6.9×10^{-11}	60
	6p21	HLA-Cw6	94				48
HLA class I - HCP5	6p21	rs2395029	576	480	3.2	1.9×10^{-10}	60
Killer inhibitory receptor (2DS1 and/or 2DS2) + HLA-Cw ligand group homozygosity	19q/6p21		366/75			$P < 0.0001$	68–70