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Psoriasis Bench to Bedside – Genetics Meets Immunology

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COMMENTARY

Over 25 years of accumulating evidence strongly implicates the immune system in the pathogenesis of psoriasis, including both acquired immunity (T-cells) and innate host

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defense (macrophages, antigen-presenting cells, and keratinocytes) [2]. Psoriasis also has a strong genetic component, but the identity of the genes involved has remained largely obscure. In a study recently published in Nature Genetics 1, these two themes of psoriasis genetics and immunology come together in a coherent and clinically-relevant way.

The genetics of psoriasis is multifactorial: multiple genes and the environment conspire to increase one's risk of developing psoriasis. Like several other multifactorial autoimmune disorders, psoriasis manifests strong HLA associations. In 2006, *HLA-Cw6* was found to be the likely cause of these HLA associations in psoriasis [3]. However, previous searches for psoriasis genes outside the HLA region yielded no consistent, reproducible evidence of *linkage* (i.e., consistent transmission of a genetic marker with psoriasis through families; reviewed in Capon et al. 4). The same problem has been encountered in other multifactorial disorders 5. We now appreciate that while linkage studies are very good for finding genes that make large contributions to risk, they are less powerful in multifactorial disorders, where individual genes typically make only modest contributions to risk. In this setting, tests of association are much more powerful than tests of linkage 6. Association studies are also easier to execute, as there is no need to collect family members. However, association studies require ~500,000 genetic markers to comprehensively survey the genome, compared to the ~300 markers needed to perform a linkage scan.

With the dawning of the new millennium, sequencing of the human genome provided the needed markers. Called single nucleotide polymorphisms (SNPs), these markers are subtle differences in the DNA code that normally exist between individuals. With the advent of the HapMap [7] providing a dense map of millions of SNPs along with the development of microarray-based genotyping technologies allowing up to a million SNPs to be tested at once, the impossible became possible. To take advantage of these developments, in 2006 we initiated the Collaborative Association Study of Psoriasis (CASP), whose objective was to carry out a genome-wide association scan 1. In the initial scan, we tested 438,670 SNPs on 1,359 psoriasis cases and 1,400 healthy controls. We found significant associations at three genetic regions that had previously been associated with psoriasis (*HLA-C*, *IL12B*, and *IL23R*) [3, 8]. As expected from earlier studies [3, 9–11] , *HLA-C* produced by far the strongest genetic signal. While its precise role in psoriasis remains unknown, it has been postulated that it may be involved in antigen presentation to CD8+ T-cells, whose migration into the epidermis appears to be required for the development of psoriatic lesions [12] (Figure 1).

Besides *HLA-C*, *IL12B*, and *IL23R*, there were many other interesting signals requiring confirmation. Working with five additional groups in the United States, Canada, Germany, and France, we studied 18 of the most interesting genetic regions in an additional 5,048 cases and 5,051 controls. In all, seven of the 18 regions showed consistently strong association with the development of psoriasis, and four of the associations were novel. One of these was *IL23A*, which encodes the p19 subunit of the cytokine IL-23. This study is the first to find a disease association with *IL23A* in any human disorder. Notably, two of the previously identified psoriasis genes encode proteins that bind to p19. *IL23R* encodes a component of the IL-23 receptor, and IL12B encodes p40, a component of both IL-12 and IL-23 (Figure 1). IL-12 supports Th1 cells, whereas IL-23 supports the expansion of a novel subset of T-cells, called Th17 cells, that protect the skin and other epithelial-lined organs such as the gut [13] (Figure 1). Notably, one of the *IL23R* variants also confers risk for Crohn's Disease [14], which has long been known to be clinically associated with psoriasis [15]. Moreover, two other psoriasis genetic "hotspots" contain epidermal defense genes that are highly overexpressed in psoriasis: *DEFB4* (encoding human β-defensin-2) [16], and *LCE3C/3D* (encoding late cornified envelope proteins 3B and 3C) [17, 18].

Antibodies targeting p40 are highly effective against psoriasis [19]. Because p40 is common to IL-12 and IL-23, anti-p40 antibodies block both cytokines. IL-23 is elevated in psoriasis lesions but IL-12 is not [20], suggesting that IL-23 is the primary target. Biologicals targeting TNF-α are also highly effective against psoriasis [21]. Notably, two of the novel genetic signals we found are involved in the regulation of TNF-α signaling: *TNFAIP3* and *TNIP1* (Figure 1). Together, the products of these genes function as a "brake" on immune responses triggered by TNF-α and by Toll-like receptors, which recognize microbial agents through the innate immune system. Consistent with a role in the control of autoimmunity, different genetic variants near *TNFAIP3* have been associated with rheumatoid arthritis and lupus [22, 23]. Given that psoriasis increases risk of myocardial infarction [24], it is notable that *Tnfaip3* influences the risk of coronary artery disease in mice [25]. These two genes provide novel targets for therapeutic intervention. Moreover, as our genetic toolbox of psoriasis risk markers expands, we may be able to predict which patients will respond best to various therapies, and, even if imperfectly, begin to predict who is at risk for development of skin and join disease, as well as cardiovascular complications.

The final novel genetic "hotspot" implicates two "next-door neighbor" genes, *IL4* and *IL13*, genes that support development of Th2 cells. Psoriasis has traditionally been viewed as a "Th1 disease" [26], and genetic defects in this region may help tip the normal Th1 / Th2 balance toward Th1. Interestingly, interferon-γ, a major product of Th1 cells, supports the production of IL-23 by antigen-presenting cells [27]. Together, these studies link all of these psoriasis loci together in a plausible functional pathway (Figure 1).

With the likely exception of *HLA-Cw6*, the causative genetic changes responsible for the association signals we have observed remain to be determined. Our current efforts focus on pinpointing these lesions, as well as finding other associated regions in our current sample. However, further enrollment is critical. Our study involved approximately 6,400 cases and 6,400 controls. Research in other multifactorial autoimmune disorders has shown that the number of associated regions increases dramatically by a two- to three-fold increase in subjects. Potential participants can learn more about psoriasis genetics research in several ways. Dr. Elder's Psoriasis Genetics Laboratory maintains a web site (www.psoriasis.umich.edu) and a toll-free number (800-356-2840). Other resources include the Utah Psoriasis Initiative (http://uuhsc.utah.edu/psoriasis/) and the National Psoriasis Foundation (www.psoriasis.org).

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References

1. Nair RP, Duffin KC, Helms C, et al. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. Nat Genet 2009 Feb;41(2):199–204. [PubMed: 19169254]
2. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature 2007 Feb 22;445(7130):866–873. [PubMed: 17314973]
3. Nair RP, Stuart PE, Nistor I, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet 2006 May;78(5):827–851. [PubMed: 16642438]

4. Capon F, Trembath RC, Barker JN. An update on the genetics of psoriasis. Dermatol Clin 2004 Oct; 22(4):339–347. vii. [PubMed: 15450331]
5. Altmuller J, Palmer LJ, Fischer G, Scherb H, Wjst M. Genomewide scans of complex human diseases: true linkage is hard to find. Am J Hum Genet 2001;69(5):936–950. [PubMed: 11565063]
6. Botstein D, Risch N. Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. Nat Genet 2003;33 Suppl:228–237. [PubMed: 12610532]
7. Altshuler D, Brooks LD, Chakravarti A, Collins FS, Daly MJ, Donnelly PA. haplotype map of the human genome. Nature 2005 Oct 27;437(7063):1299–1320. [PubMed: 16255080]
8. Cargill M, Schrodi SJ, Chang 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 Feb;80(2):273–290. [PubMed: 17236132]
9. Trembath RC, Clough RL, Rosbotham JL, et al. Identification of a major susceptibility locus on chromosome 6p and evidence for further disease loci revealed by a two stage genome-wide search in psoriasis. Hum Mol Genet 1997;6(5):813–820. [PubMed: 9158158]
10. Nair RP, Henseler T, Jenisch S, et al. Evidence for two psoriasis susceptibility loci (HLA and 17q) and two novel candidate regions (16q and 20p) by genome-wide scan. Hum Mol Genet 1997;6(8): 1349–1356. [PubMed: 9259283]
11. Liu Y, Helms C, Liao W, et al. A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. PLoS Genet 2008 Mar;4(3) e1000041.
12. Conrad C, Boyman O, Tonel G, et al. Alpha1beta1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. Nat Med 2007 Jul;13(7):836–842. [PubMed: 17603494]
13. Bettelli E, Oukka M, Kuchroo VK. T(H)-17 cells in the circle of immunity and autoimmunity. Nat Immunol 2007 Apr;8(4):345–350. [PubMed: 17375096]
14. Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006 Dec 1;314(5804):1461–1463. [PubMed: 17068223]
15. Najarian DJ, Gottlieb AB. Connections between psoriasis and Crohn's disease. J Am Acad Dermatol 2003 Jun;48(6):805–821. quiz 822-804. [PubMed: 12789169]
16. Hollox EJ, Huffmeier U, Zeeuwen PL, et al. Psoriasis is associated with increased beta-defensin genomic copy number. Nat Genet 2008 Jan;40(1):23–25. [PubMed: 18059266]
17. de Cid R, Riveira-Munoz E, Zeeuwen PL, et al. Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. Nat Genet 2009 Feb;41(2):211–215. [PubMed: 19169253]
18. Zhang XJ, Huang W, Yang S, et al. Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21. Nat Genet 2009 Feb;41(2):205–210. [PubMed: 19169255]
19. Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. N Engl J Med 2007 Feb 8;356(6):580–592. [PubMed: 17287478]
20. Lee E, Trepicchio WL, Oestreicher JL, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. J Exp Med 2004 Jan 5;199(1):125–130. [PubMed: 14707118]
21. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003 Nov 20;349(21):2014–2022. [PubMed: 14627786]
22. Plenge RM, Cotsapas C, Davies L, et al. Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. Nat Genet 2007 Dec;39(12):1477–1482. [PubMed: 17982456]
23. Graham RR, Cotsapas C, Davies L, et al. Genetic variants near TNFAIP3 on 6q23 are associated with systemic lupus erythematosus. Nat Genet 2008 Aug 1;40:1059–1061. [PubMed: 19165918]
24. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. Jama 2006 Oct 11;296(14):1735–1741. [PubMed: 17032986]
25. Idel S, Dansky HM, Breslow JL. A20, a regulator of NFkappaB, maps to an atherosclerosis locus and differs between parental sensitive C57BL/6J and resistant FVB/N strains. Proc Natl Acad Sci U S A 2003 Nov 25;100(24):14235–14240. [PubMed: 14614151]

26. Uyemura K, Yamamura M, Fivenson D, Modlin R, Nickoloff B. The cytokine network in lesional and lesion-free psoriatic skin is characterized by a T-helper type 1 cell-mediated response. J Invest Dermatol 1993;101:701–705. [PubMed: 7693825]

27. Kryczek I, Bruce AT, Gudjonsson JE, et al. Induction of memory IL-17+ T cell trafficking and expansion by IFN-gamma: Mechanism and pathological relevance. Journal of Immunology 2008;181:4733–4741.

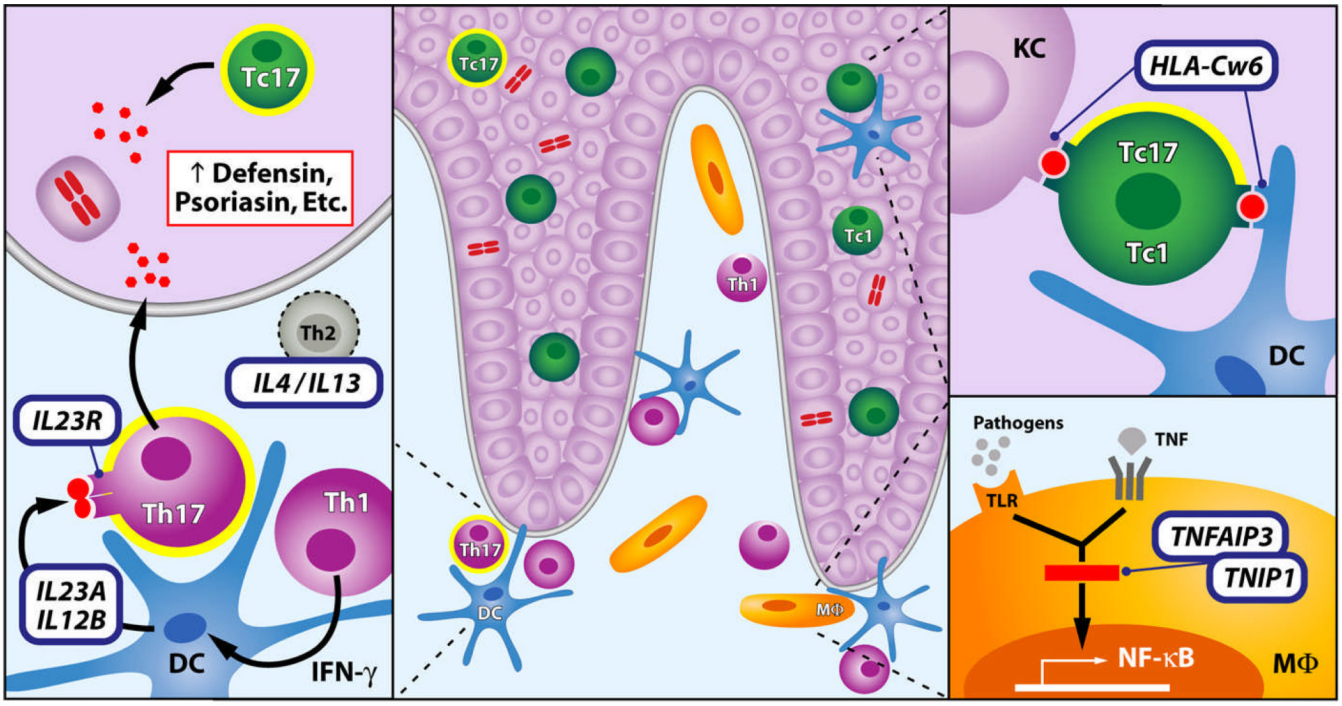

Figure 1.

Model of psoriasis integrating genetics and immunology. Genes identified by our study are *italicized*. The majority of dermal T-cells are CD4+ (purple circles). Of these, most are Th1 and about 5% express IL-17 (Th17, yellow halo). Most of the T-cells in the epidermis are CD8+ (green circles) and about 5% of these express IL-17 (Tc17, yellow halo). HLA-Cw6 may be involved in the activation of CD8+ T-cells by dendritic cells (DC, blue), and activated CD8+ T-cells may recognize keratinocyte (KC) antigens presented in the context of HLA-Cw6. Some of these T-cells are likely to be Tc17 cells. *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 tipping the balance of CD4+ T-cells towards Th2. Th1 cells stimulate the production of IL-23 by DC. In turn, IL-23 stimulates the production of IL-17 (and other cytokines such as IL-22) by Th17 cells. These cytokines stimulate keratinocyte proliferation (mitotic figures) and up-regulate keratinocyte innate immune defense mechanisms, including defensins, psoriasin, and other proteins that are highly expressed in psoriasis lesions. Macrophages (Mφ, orange) express TNF receptors and TLRs, which signal to NF-κB in the nucleus. The proteins encoded by TNFAIP3 and TNIP1 bind to each other and block this signaling. Similar signaling pathways may also be active in other types of skin cells.