Psoriasis Bench to Bedside

Genetics Meets Immunology

MORE THAN 25 years of accumulating evidence strongly implicates the immune system in the pathogenesis of psoriasis, including both acquired immunity (T cells) and innate host defense (macrophages, antigen-presenting cells, and keratinocytes). Psoriasis also has a strong genetic component, but the identity of the genes involved has largely remained obscure. In a study recently published in *Nature Genetics*,[1] these 2 themes of psoriasis—genetics and immunology—come together in a coherent and clinically relevant way.

The genetic makeup 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.[2] However, previous searches for psoriasis genes outside the HLA region yielded no consistent, reproducible evidence of linkage (ie, consistent transmission of a genetic marker with psoriasis through families[3]). The same problem has been encountered in other multifactorial disorders.[4] 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, in which individual genes typically make only modest contributions to risk. In this setting, tests of association are much more powerful than tests of linkage.[5] Association studies are also easier to execute, as there is no need to collect family members. However, association studies require approximately 500 000 genetic markers to survey the genome comprehensively compared with the approximately 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 represent subtle differences in the DNA code that normally exist between individuals. With the advent of the HapMap,[6] which provides a dense map of millions of SNPs, along with the development of microarray-based genotyping technologies that allow up to 1 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, whose objective was to carry out a genome-wide association scan.[1] In the initial scan, we tested 438 670 SNPs in 1359 psoriasis cases and 1400 healthy controls. We found significant associations at 3 genetic regions that had previously been associated with psoriasis (*HLA-C*, *IL12B*, and *IL23R*).[2,7] As expected from earlier studies,[2,8-10] *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[11] (**Figure**).

Besides *HLA-C*, *IL12B*, and *IL23R*, there were many other interesting signals requiring confirmation. Working with 5 additional groups in the United States, Canada, Germany, and France, we studied 18 of the most interesting genetic regions in an additional 5048 cases and 5051 controls. Seven of the 18 regions showed consistently strong association with the development of psoriasis, and 4 of the associations were novel. One of these was *IL23A*, which encodes the p19 subunit of the cytokine interleukin (IL)-23. This study is the first to find a disease association with *IL23A* in any human disorder. Notably, 2 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). Interleukin 12 supports T_H1 cells, whereas IL-23 supports the expansion of a novel subset of T cells, called *T_H17 cells*, which protect the skin and other epithelial-lined organs, such as the gut[12] (Figure). Notably, one of the *IL23R* variants also confers risk for Crohn disease,[13] which has long been known to be clinically associated with psoriasis.[14] Moreover, 2 other reported psoriasis genetic "hotspots" contain epidermal defense genes that are highly overexpressed in psoriasis: *DEFB4* (encoding human β-defensin 2),[15] and *LCE3C/3D* (encoding late cornified envelope proteins 3B and 3C).[16,17]

Antibodies targeting p40 are highly effective against psoriasis.[18] Because p40 is common to IL-12 and IL-23, anti-p40 antibodies block both cytokines. Interleukin 23 is elevated in psoriasis lesions, but IL-12 is not,[19] suggesting that IL-23 is the primary target. Biological agents targeting tumor necrosis factor (TNF) are also highly effective against psoriasis.[20] Notably, 2 of the novel genetic signals that we found are involved in the regulation of TNF signaling: *TNFAIP3* and *TNIP1* (Figure). Together, the products of these genes function as a "brake" on immune responses triggered by TNF and by toll-like receptors, which recognize microbial agents through the innate immune system. Consistent

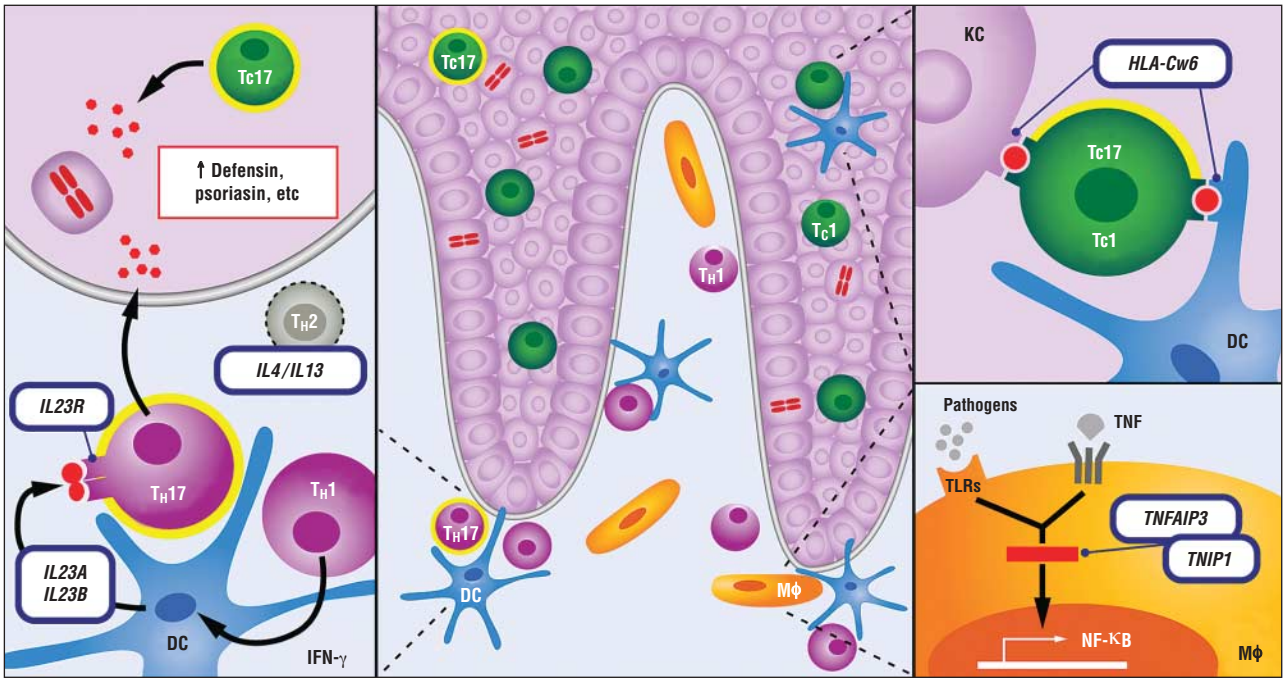

Figure. Model of psoriasis integrating genetics and immunology. The majority of dermal T cells are CD4+ (purple circles). Of these, most are T_H1, and approximately 5% express interleukin (IL)-17 (T_H17, yellow halo). Most of the T cells in the epidermis are CD8+ (green circles), and about 5% of these 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 a subunit of the receptor for IL-23. *IL4* and *IL13* may participate in tipping the balance of CD4+ T cells toward T_H2. T_H1 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 T_H17 cells. These cytokines stimulate KC proliferation (mitotic figures) and upregulate KC innate immune defense mechanisms, including defensin, psoriasin, and other proteins that are highly expressed in psoriasis lesions (etc). Macrophages (MΦ, orange) express tumor necrosis factor (TNF) receptors and toll-like receptors (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. IFN-γ indicates interferon gamma. Genetic regions implicated by this study are italicized and outlined in purple.

with a role in the control of autoimmunity, different genetic variants near *TNFAIP3* have been associated with rheumatoid arthritis and lupus.[21,22] Given that psoriasis increases risk of myocardial infarction,[23] it is notable that *Tnfaip3* influences the risk of coronary artery disease in mice.[24] These 2 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 the development of skin and join disease as well as cardiovascular complications.

The final novel genetic hotspot implicates 2 "next-door neighbor" genes—*IL4* and *IL13*—genes whose products support development of T_H2 cells. Psoriasis has traditionally been viewed as a "T_H1 disease,"[25] and genetic defects in this region may help tip the normal T_H1/T_H2 balance toward T_H1. Interestingly, interferon gamma, a major product of T_H1 cells, supports the production of IL-23 by antigen-presenting cells.[26] Together, these studies link all of these psoriasis loci together in a plausible functional pathway (Figure).

With the likely exception of *HLA-Cw6*, the causative genetic changes responsible for the association signals that we have observed remain to be determined. Our current efforts focus on pinpointing these lesions as well as on finding other associated regions in our current sample. However, further enrollment is critical. Our study involved approximately 6400 cases and 6400 controls. Research in other multifactorial autoimmune disorders has shown that the number of associated regions increases dramatically by a 2- to 3-fold increase in subjects. Potential participants can learn more about psoriasis genetics research in several ways. The 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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Financial Disclosure: None reported.

Funding/Support: This work was supported in part by awards from the National Institutes of Health, the Foundation for the National Institutes of Health, and the National Psoriasis Foundation, and by the Ann Arbor VA Hospital, the Dudley and Dawn Holmes Fund, and the Babcock Memorial Trust.

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: We are indebted to the many patients with psoriasis and controls who participated in this study, to Laura van Goor for graphics assistance, and to all the members of the Collaborative Association Study of Psoriasis.[1]

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