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REVIEW

The Pathogenesis and Genetics of Psoriasis☆

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Abstract Psoriasis vulgaris and psoriatic arthritis are interrelated disorders with an important genetic component. While linkage studies have identified several candidate *loci* and genes, only recent technological advances and extensive genome-wide association studies have provided robust evidence of associations between psoriasis and several genes inside and outside the major histocompatibility complex. Most of these genes can be incorporated into an integrated pathogenic model of psoriatic disease comprising distinct signaling networks affecting skin barrier function (LCE3, DEFB4, GJB2), innate immune responses involving nuclear factor-κB signaling (TNFAIP3, TNIP1, NFKBIA, REL, FBXL19, TYK2, NOS2, CARD14), and adaptive immune responses involving CD8 T cells and interleukin 23 (IL-23)/IL-17-mediated lymphocyte signaling (HLA-C, IL12B, IL23R, IL23A, TRAF3IP2, ERAP1). A better understanding of the potential gene/gene and gene/environment interactions and of the functions of altered transcripts will undoubtedly have nosologic, therapeutic and prognostic implications.

PALABRAS CLAVE
Genética;
Patogenia;
Psoriasis;
Artritis psoriásica

Psoriasis: bases genéticas y patogenéticas

Resumen La psoriasis vulgar y la artritis psoriásica son trastornos relacionados entre sí, con un importante componente genético. Aunque los estudios de ligamiento han llevado a la identificación de diversos *loci* y genes de susceptibilidad, ha sido el reciente progreso tecnológico y la realización de estudios de asociación genómica extensos lo que ha permitido demostrar asociaciones robustas de la psoriasis con diversos genes, asociados o no al complejo mayor de histocompatibilidad. La mayoría de estos genes se pueden incorporar en un modelo patogénico integrado que comprende distintas redes de señalización que afectan la función barrera de la piel *(LCE3, DEFB4, GJB2)*, la respuesta inmune innata implicando al sistema de señales del factor nuclear-κB *(TNFAIP3, TNIP1, NFKBIA, REL, FBXL19, TYK2, NOS2, CARD14)*, y la respuesta inmune adaptativa implicando a linfocitos T CD8 y las señales de la vía interleucina 23 (IL-23)/IL-17 *(HLA-C, IL12B, IL23R, IL23A, TRAF3IP2, ERAP1)*. La mejor comprensión de las potenciales

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interacciones entre los genes implicados y de estos con factores ambientales, así como el conocimiento de las alteraciones en las funciones de las proteínas codificadas tendrán sin duda implicaciones nosológicas, terapéuticas y pronósticas.

Introduction

Evidence suggests that psoriasis vulgaris is not a genetically homogenous disease but rather several different disease phenotypes associated with different genetic variants. For example, purely palmoplantar pustulosis can be considered a separate entity from psoriasis vulgaris, which in turn is genetically more closely associated with guttate psoriasis.[1] Psoriasis vulgaris is a chronic inflammatory disease that shows a clear association with certain alleles of the *HLA-C* gene, and specifically with the *HLA-Cw6* allele (known as *HLA-Cw*0602* when identified through high-resolution genotyping), present in 30% of psoriasis patients (compared with between 10% and 15% in the general population). The relative risk of developing the disease is 2.5 greater in homozygous individuals than in heterozygous ones.[2] *HLA-Cw6*-positive patients have certain clinical characteristics defined by an early onset of the disease, presence of more extensive plaques, and a higher incidence of the Koebner phenomenon. In addition, more frequent streptococcal throat infection and high sensitivity to sunlight may be trigger factors and markers of more severe disease. *HLA-Cw6*-negative patients, in contrast, have a higher frequency of nail disorders and psoriatic arthritis.[2,3]

Before detailing the most important genetic aspects of the disease, we will review the underlying immunopathogenic mechanisms to enable a more integrated overview of the major therapeutic advances in recent years. These advances will then be described in detail.

Immunopathogenesis of Psoriasis

Psoriasis is characterized by marked epidermal proliferation and abnormal differentiation with immune activation of keratinocytes, accompanied by numerous inflammatory and immune disorders, in which both innate and acquired immunity participate.[4–6] The efficacy of cyclosporin, demonstrated more than 25 years ago, pointed to the fundamental role of T-lymphocytes.[7] Subsequently, the efficacy of selective T-cell modulators further confirmed the importance of these types of cells.[8–10] The marked efficacy of biologic agents that target tumor necrosis factor alfa (TNF-α) has also been demonstrated recently.[11] This cytokine acts as a pleiotropic mediator of different types of inflammation. Likewise, anti-p40 antibodies, which block differentiation and expansion of Th1 and Th17 lymphocytes through interleukin (IL) 12 and IL-23, respectively, have also been found to be effective.[12]

The role of TNF-α and skin-resident T-lymphocytes has been confirmed in an experimental model with AGR129 mice, which lack the genes that encode interferon (IFN) and natural-killer (NK) cells, and so are unable to reject human skin.[13] When apparently healthy skin from patients with psoriasis was grafted onto these mice, they spontaneously developed psoriasis plaques without the addition of $CD4^+$ T lymphocytes. Serial biopsies showed that human T lymphocytes resident in the grafts proliferate and produce TNF-α, and treatment with human anti-CD3 antibodies, which impede T-lymphocyte proliferation, or TNF-α inhibitors (infliximab or etanercept), prevented conversion of the prepsoriatic skin into psoriasis lesions.[13] Moreover, blockade of the exocytosis of T lymphocytes to the epidermis with an anti-integrin $\alpha1\beta1$ antibody limits lesion development. When T lymphocytes are already present in the epidermis, inhibition is partial, and treatment is ineffective when fully developed psoriasis lesions are grafted, thereby confirming the role of resident T lymphocytes and their migration to the epidermis in the development of psoriasis lesions.[14]

The recent discovery of a subpopulation of T lymphocytes that express IL-17, and whose expression is determined by the action of IL-23 produced by antigen-presenting cells and dendritic cells on naïve T-cell precursors,[15] has greatly changed our understanding of the pathogenesis of psoriasis. A marked expansion of cytotoxic T lymphocytes, which independently express IL-17 and IL-22 in the psoriatic epidermis, has been reported.[16,17] The expansion of Th1 lymphocytes feeds back into this process by stimulating synthesis of IL-12 and IL-23 by antigen-presenting cells through production of IFN-γ.[16]

Genetic Linkage Studies of Psoriasis

In the 1990s, several groups started gene linkage studies which analyzed the cosegregation of microsatellite genetic markers in families with members with psoriasis. At least 6 loci of susceptibility to psoriasis, denoted PSORS1 through PSORS6, were identified.[18–21] The main genetic determinant of psoriasis (PSORS1), located in the 6p21 chromosomal region, accounts for between 30% and 50% of genetic susceptibility to the disease and probably corresponds to the *HLA-Cw*0602* allele, although the determinant is not associated with cases of late-onset psoriasis.[20] This allele has been postulated to allow the presentation of a putative epitope present in type-I keratins, specifically, those whose expression is upregulated in psoriasis. This epitope may act as an autoantigen, present cross-reactivity with streptococcal protein M, and perpetuate autoimmune response (and perhaps $CD4^+$ response with NK receptors) mediated by $CD8^+$ cells, which are able to recognize the major histocompatibility complex (MHC) class I, leading to chronic lesions.[19] The second locus of susceptibility to psoriasis, PSORS2, identified through linkage studies in different families, is located in the 17q24-q25 region, where a susceptibility locus has also been identified for atopic dermatitis, and the putative genes are implicated in regulating the immunological