Clinical Management of Psoriatic Arthritis and Psoriasis

Fourth Edition

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CHAPTER **1**

Genetics and Pathogenesis of Psoriasis and Psoriatic Arthritis

Despite the long history of psoriasis and psoriatic arthritis (PsA), until recently, little had been known of their underlying genetics and pathogenesis. Without this knowledge, rational clinical management and drug development for this disease was limited. Thus, prior to undertaking a review of the management of this disease, it is critical to survey what is understood about the mechanisms that govern psoriasis.

The propensity for psoriasis to be more prominent in families has been known for some time. Early studies of the inheritance of psoriasis suggested that the prevalence of psoriasis in individuals with a first-degree relative with psoriasis is about four times that of the general population. Twin studies suggested about a 60% rate of concordance between monozygotic twins compared with 15% in dizygotic twins.[1] Similarly, PsA has a strong familial component; in Moll and Wright's original series, the prevalence of PsA in first-degree relatives of probands was 5.5%.[2] This actually corresponds to a much higher relative risk for PsA than for psoriasis. There are no published twin studies in PsA.

While these data suggest a high level of genetic influence on psoriasis and PsA, the correlations are not 100%. Additionally, no single gene has emerged to suggest a simple Mendelian inheritance pattern. Most now assume that the etiology of these diseases, like many others, is multifactoral, and that both complex genetics and environmental factors play a role in their pathogenesis.

Genetics of Psoriasis

More recent studies of psoriasis inheritance have concentrated on a polygenetic approach to disease. With more advanced genetic techniques, multiple gene loci have become associated with the inheritance of psoriasis. The most recent studies have identified about 16 to 23 main candidate genes from the screening of large numbers of patients, with over 60 minor loci identified.[3] More potentially associated genes are likely to be identified in the future. **Table 1.1** contains a brief listing of some of the candidate genes for psoriasis. According to genetic theory, the identified loci can explain a significant portion of the inheritance of psoriasis.

The most intriguing genes identified tend to be those consistent with present theories of the immunologic basis of psoriasis. The gene locus with the highest predictive value is PSORS 1, which falls within the major histocompatibility complex I (MHC I) genetic locus.[4-7] This area of the genome is particularly important in control of the activity of T lymphocytes. Likewise, more recently discovered genetic correlates include variations around the genes for receptors for interleukin (IL) 12 and 23 (IL-12 and IL-23).[8-9] The activity of these cytokines is thought to be critical in our present understanding of the pathophysiology of psoriasis.

More recently, PSORS 2, the second most clearly related genetic locus has been identified as a protein involved not in the immune response but in keratinocyte growth and maturation.[10] The protein identified by this locus, CARD14, is a signaling protein that is expressed in keratinocytes and may serve as a key factor in the role of the local cells of the skin responding to local inflammation and inducing further inflammatory responses.[11] Other candidate genes point to variations in immune function along with potential alterations in keratinocyte function as the factors that impact the likelihood of an individual developing psoriasis.

Genetics of PsA

The precise etiology of the joint disease in psoriasis, like the skin disease, remains uncertain, but, as noted, it is likely to be multifactoral. Genetic factors play a role, with a familial predisposition to PsA first noted in the studies of Moll and Wright.[2,12] More recent data have shown that as many as 40% of patients with PsA have a first-degree relative with psoriasis

or PsA, confirming the decision to include family history in the Classification of Psoriatic Arthritis (CASPAR) criteria. A number of different HLA loci have been associated with both the development of PsA and its progression. Interestingly, the genetic associations seen in psoriatic joint disease are not the same as those in skin disease.[13]

As in psoriasis, genes within the MHC 1 region have been reported to be associated with PsA, although the magnitude of this association is not as strong. Another group of genes, known as the MHC class 1 related genes (MICA) have been implicated as candidate genes in PsA, as certain MICA alleles appear to be more specific for PsA than psoriasis. The tumor necrosis factor alpha (TNF-α) gene is located near the Class 1 HLA-B region, and TNF promoter polymorphisms have also been proposed to be important in PsA susceptibility. **Figure 1.1** is a schematic illustration showing the location of a number of genes near the MHC I region that have been associated with psoriasis or PsA. The link between MHC Class II genes and PsA is not as strong. HLA-DR4 alleles, clearly linked to rheumatoid arthritis (RA), have been suggested in some studies to be linked to PsA, although this has not been widely replicated.

One of the important clinical elements of PsA is the distinction between peripheral and axial arthritis, and this distinction is reflected, to some extent, in genetic data. While the HLA-B27 locus has been associated with axial involvement, as in other axial spondyloarthropathies, other loci (HLA-B38, HLA-B39) have been reported to be associated with peripheral disease. The possibility that certain genetic factors may be associated with, or protective of, disease progression in PsA has been suggested, but there is, as yet, no consensus on which specific genes predict a worse prognosis.

Pathogenesis of Psoriasis

For most of its history, psoriasis has been thought of as a disease localized to the skin and primarily being driven by abnormalities in keratinocytes. In fact, evaluation of the clinical presentation of psoriasis and biopsies show a strong correlation with visible changes in keratinocytes. As will be discussed in more detail in later chapters, the cardinal clinical signs of psoriasis are scale, plaque elevation, and redness. This can be correlated with decreased keratinocyte maturation, increased keratinocyte

proliferation, and vascular proliferation and dilatation, respectively. Nowhere in the clinical presentation of psoriasis is there a clinical sign that associates with the inflammatory cells that inhabit biopsies from the psoriatic plaques, including T lymphocytes, monocytes, and dendritic cells. Thus, for many years, these cell types were considered to be bystanders in the pathogenesis of psoriasis.

TABLE 1.1 — Genes Associated With Psoriasis Susceptibility[a]

Gene[b]	Location	Protein Function	Pathway
IL23R	1p31	IL-23 receptor subunit	IL-23 signalling
IL28RA	1p36	IL-28 receptor subunit	IFN signalling
LCE3B/3C	1q21	Keratinocyte structural protein	Skin barrier function
REL	2p16	NF-κB subunit	NF-κB signalling
IFIH1/MDA5	2q24	Innate antiviral receptor	IFN signalling
ERAP1	5q15	Amino peptidase processing MHC class I ligands	Antigen presentation
IL4, IL13	5q31	Th2 cytokines	IL-4/IL-13 signalling
IL12B	5q33	Subunit shared by IL-12 and IL-23	IL-23 signalling
TNIP1	5q33	Inhibitor of TNF-induced NF-κB activation	NF-κB signalling
PTTG1	5q33	Anaphase promoting complex substrate	Cell cycle control
HLA-C	6p21	MHC class I antigen	Antigen presentation
TRAF3IP2	6q21	Adaptor mediating IL-17-induced NF-κB activation	IL-17/NF-κB signalling
TNFAIP3	6q23	Inhibitor of TNF-induced NF-κB activation	NF-jB signalling
CSMD1	8p23	Tumour suppressor gene	Unknown
IL23A	12q13	IL-23 subunit	IL-23 signalling
GJB2	13q11	Gap junction protein	Electrolyte transport

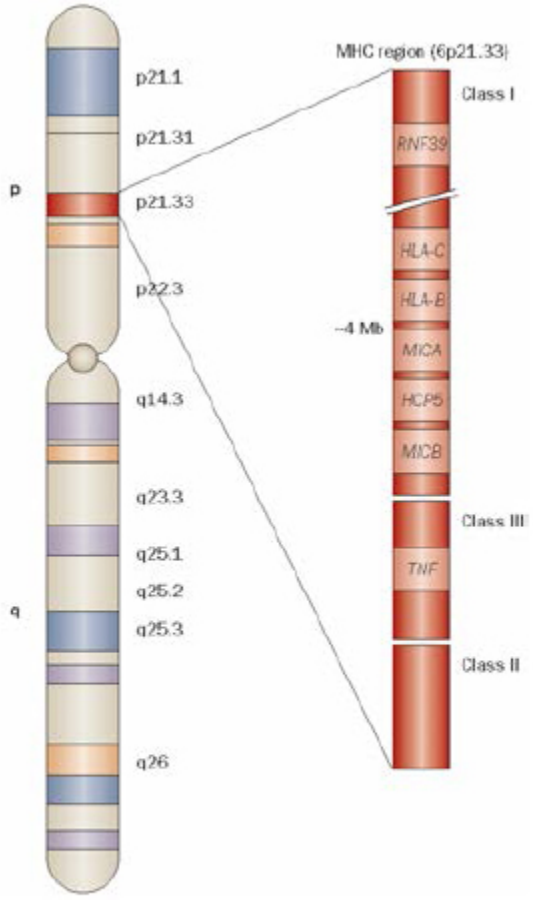
NFKBIA	14q13	Inhibitor of NF-κB activation	NF-κB signalling
FBXL19	16p11	Putative inhibitor of NF-κB activation	NF-κB signalling
NOS2	17q11	Induced nitric oxide synthase	Innate antibacterial response
SERPINB8	18q21	Serine protease inhibitor	Unknown
TYK2	19p13	Tyrosine kinase associated with cytokine receptors	IL-23 and IFN signalling
ZNF816	19q13	Zinc finger protein	Unknown
RNF114/ ZNF313	20q13	E3 ubiquitin ligase	IFN signalling

[a] All the loci included in the table showed genome-wide significant association ($P<5\times10^{-8}$) with psoriasis, in at least one genome-wide association study.
[b] Gene of interest found in the disease-associated susceptibility interval.

Capon F, Barker J. *Br J Dermatol.* 2012;166:1173-1175.

The concept of the importance of the immune cells being central in inducing the changes in psoriatic keratinocytes came with the advent of new medications that specifically targeted immune pathways and were being used initially in organ transplant rejection treatment. Patients treated for other conditions with medications like cyclosporine, that specifically targeted T cell function, were found to have profound improvements in their psoriasis. Early clinical trials of cyclosporine and other T cell specific therapies lent credence to the idea that treatment of the immune process in psoriasis could be sufficient for improving the clinical manifestations of the disease.

FIGURE 1.1 — Schematic Representation of MHC Region



Schematic representation of the MHC region, illustrating the chromosomal locations of genes and regions implicated in susceptibility to psoriasis and/or PsA.

O'Rielly DD, Rahman P. *Nat Rev Rheumatol*. 2011;7:718-732.

The most recent view of the primary role of the immune activity in the pathogenesis of psoriasis has built on these initial clinical findings. Experiments on mouse models featuring explants of human skin from psoriasis patients demonstrated that the transfer of activated T cells was sufficient for inducing early lesions of psoriasis.[14-19] Moreover, further animal modeling suggested that most of the components necessary for immune activation of the skin were present in unaffected skin in psoriasis patients.[20] Multiple cytokines were felt to be central to this process including interferon γ (IFN-γ) and TNF-α. In fact, inhibition of type I T

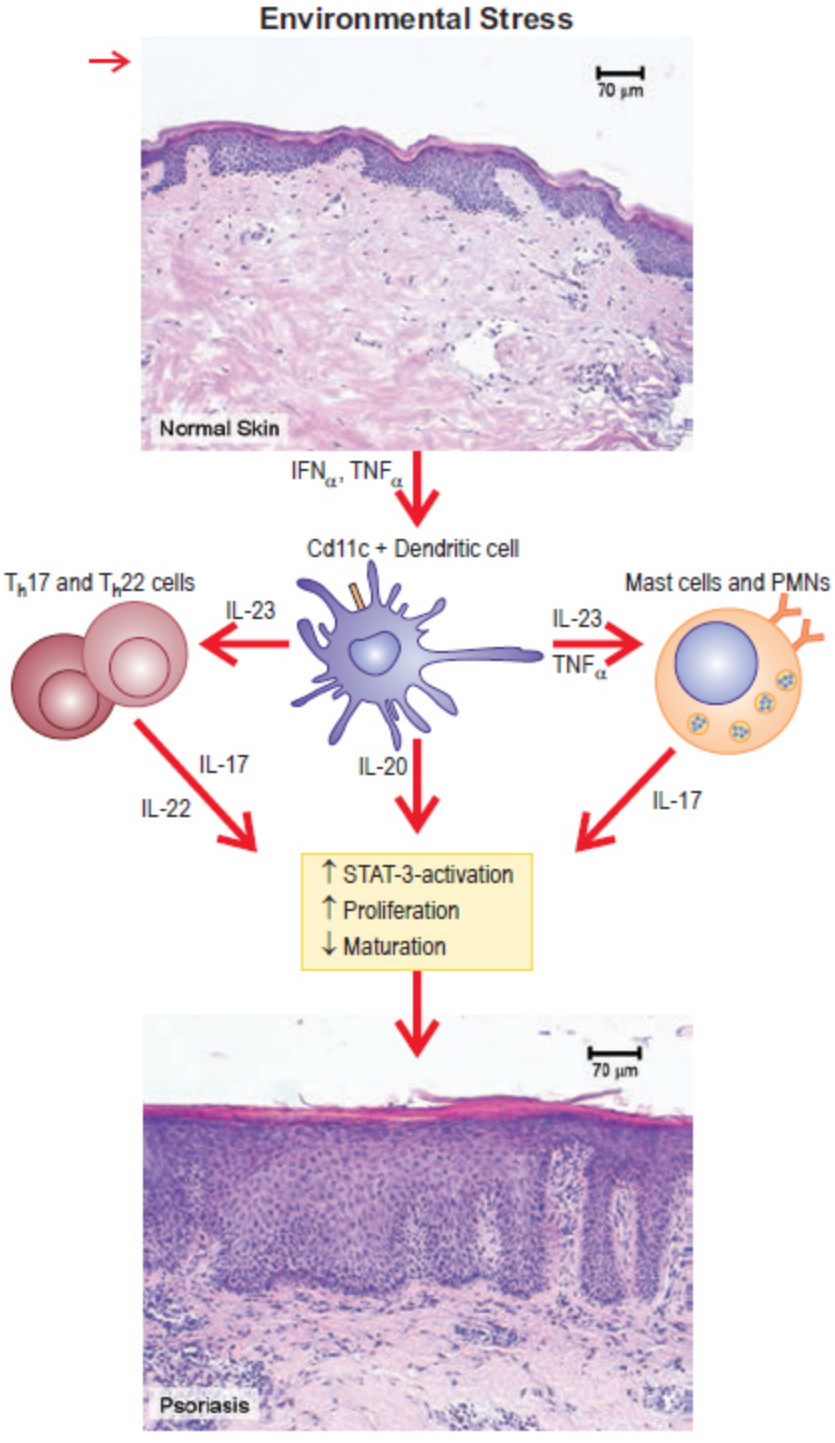
cells, the primary producers of IFN-γ, and inactivation of TNF-α showed efficacy in the treatment of psoriasis. Nonetheless, one critical element of psoriasis pathogenesis was not understood—how the immune processes directly affected the keratinocyte behavior that is representative of the clinical presentation of psoriasis.

The most recent view of the pathogenesis of psoriasis has developed from discoveries that directly connect the immune and keratinocyte findings in psoriasis. An unexpected discovery demonstrated that keratinocytes in psoriasis uniquely express high levels of an activated signal transduction protein called phosphorylated-STAT-3 (PY-STAT3) when compared with other hyperproliferative diseases of the skin.[21] From multiple other conditions, primarily epithelial cancers, it was known that PY-STAT3 was under the control of a number of cytokines that were central to a newly described immunological pathway, the IL-17 pathway.[22] Multiple cytokines were involved in the various arms of this immunologic pathway, important in the skin's ability to fight off local infections. Many of these cytokines, including IL-17, IL-20, IL-22, and IL-23, were quickly identified as being increased in psoriatic plaques when compared with uninvolved skin.[23]

Additionally, as mentioned above, some of these cytokines were connected to genetic variations that correlated to an increased propensity to develop psoriasis. Importantly, some of these cytokines, specifically IL-17, 20, and 22, have specific effects on keratinocytes that suggested a direct role of these immune proteins in the alteration of keratinocyte behavior in psoriasis. Finally, mechanisms of certain treatments such as blockade of TNF-α and inhibitors of IL-12 and IL-23 have been shown to specifically down regulate the IL-17 pathway.

The most recent model for the pathogenesis of psoriasis comes directly from the findings mentioned above and is represented in **Figure 1.2**. The sequence of events starts when some type of environmental factor initiates activation of immune cells, primarily dendritic cells or macrophages, that reside in the skin in a genetically susceptible individual. This initiation step could be local skin injury or an infection that causes skin cells to produce early response type cytokines such as interferon alpha (IFN-α), IL-1, or TNF-α. These cytokines, in turn, induce local dendritic cells to produce a critical cytokine, IL-23, that is the primary activator of the IL-17 pathway.

FIGURE 1.2 — Progression From Normal Skin to Psoriasis



Specific T cells in the skin then produce cytokines such IL-17 and IL-22 that, along with IL-20 produced by dendritic cells, have a direct impact on keratinocytes. Much of the keratinocyte response is mediated by the signaling protein, STAT-3, that is activated in response to these cytokines. Finally, many immune proteins, including IL-17 and chemokines like CCL-20, are produced, causing an upregulation and maintenance of the immune process in the skin. While this model seems complicated, a clear understanding of this sequence of events can be of great help in understanding the therapeutic pathways that are central to treatment of the cutaneous psoriasis.

Pathogenesis of PsA

In contradistinction to the skin, there has been abundant experience in other inflammatory arthritides, such as RA, to support the role of immune-mediated processes in the pathogenesis of PsA. Evidence implicates both innate and acquired immunity in the development of PsA. The common development of skin disease prior to the appearance of arthritis might suggest that pathogenic mechanisms originate in skin and then migrate to the synovium, although the evidence for this process has been limited. There is evidence for a limited T-cell receptor repertoire in both skin and joints, suggesting the possibility of an antigen-driven response, possibly due to the same antigen(s) in both locations.[24]

While the clinical appearance of involved joints in PsA may appear similar to those in RA, there are characteristic features of the disease that have been felt to be more closely related to other spondyloarthropathies than to RA. This was demonstrated in a synovial biopsy study that found that biopsies from joints in ankylosing spondylitis (AS), PsA, and undifferentiated spondyloarthopathy had greater numbers of neutrophils and CD163+ macrophages, along with fewer CD83+ dendritic cells than those from RA joints, while the RA biopsies had increased synovial lining layer hyperplasia and less vascularity than the biopsies from the spondyloarthropathy group.[25] While, as noted above, there is evidence that both psoriasis and PsA are T cell-driven diseases, synovial T cell infiltration has been reported to be less pronounced in PsA than in RA.[26]

Other authors, however, have suggested that there may be more similarities between the pathology in RA and PsA than there are differences.[27] Synovial tissue from both RA and PsA expresses high levels of pro-inflammatory cytokines, including TNF-α and IL-6, supporting the cytokine-targeting approach that has proven to be so effective in both diseases. The IL-17 pathway appears to be active in psoriatic joints as well as in skin, as ustekinumab, secukinumab, and ixekizumab, which downregulate this pathway, have been demonstrated to have activity in PsA.

One of the key pathologic distinctions between psoriatic skin and joint disease is the bone and cartilage destruction that occurs in the joints. There are abundant osteoclasts at the pannus–bone junction in PsA, with evidence that osteoclastogenesis is driven by increased expression of receptor activator of nuclear factor κB ligand (RANKL) and decreased production of osteoprotegerin in this tissue.[28] Cartilage degradation is likely mediated by matrix metalloproteinases that have been demonstrated in synovial and subsynovial tissue in PsA. Osteitis adjacent to involved joints is a commonly observed feature on imaging in PsA and other spondyloarthropathies, although little is known about the precise histopathology in these lesions.

Enthesitis is another unique clinical feature seen in PsA and other spondyloathropathies. Again, little is known about the mechanisms of this manifestation, although some authors have hypothesized that the predilection for lower extremity involvement may indicate an etiologic role for tissue microtrauma.[29] Local trauma has also been reported to foster the development of psoriatic synovitis.

Finally, the role of other environmental influences, such as infections, on the development of PsA, continues to be the subject of speculation. While a direct connection, such as that between streptococcal infection and guttate psoriasis, has not been observed, the partially restricted T-cell receptor repertoire observed in psoriatic synovial tissue has been suggested as evidence for an antigenic, possibly infectious, trigger. There has also been an interesting observation that patients infected with human immunodeficiency virus (HIV) can develop a particularly severe form of psoriasis and PsA. Psoriatic disease has been noted to worsen with progressive loss of CD4+ T cells, and may improve with HIV therapy that restores circulating CD4 cell counts.

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