REVIEW ARTICLE

MECHANISMS OF DISEASE

Psoriasis

Frank O. Nestle, M.D., Daniel H. Kaplan, M.D., Ph.D., and Jonathan Barker, M.D.

From St. John's Institute of Dermatology, National Institute for Health Research Biomedical Research Centre, Cutaneous Medicine Theme and Federation of Clinical Immunology Societies Centre of Excellence at King's College London and Guy's and St. Thomas' Foundation Trust, London (F.O.N., J.B.); and the Department of Dermatology, Center for Immunology, University of Minnesota, Minneapolis (D.H.K.). Address reprint requests to Dr. Nestle at St. John's Institute of Dermatology, Fl. 9, Guy's Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, United Kingdom, or at frank.nestle@kcl.ac.uk.

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Psoriasis is important to the clinician because it is common and has treatment implications beyond the care of skin lesions. It is important to the physician-scientist because it serves as a model for studies of mechanisms of chronic inflammation. It is important to the clinical-trial investigator because it is increasingly a first-choice disease indication for proof-of-principle studies of new pathogenesis-based therapeutic strategies.

In recent years, substantial advances have been made in elucidating the molecular mechanisms of psoriasis. However, major issues remain unresolved, including the primary nature of the disease as an epithelial or immunologic disorder, the autoimmune cause of the inflammatory process, the relevance of cutaneous versus systemic factors, and the role of genetic versus environmental influences on disease initiation, progression, and response to therapy.

This review summarizes recent progress in our understanding of the molecular and immunologic basis of psoriasis and shows how improved insight into disease mechanisms has already resulted in tangible benefits for patients, including the introduction of new targeted therapies.

EPIDEMIOLOGIC FEATURES AND CLINICOPATHOLOGICAL CORRELATIONS

"Lepra is easily distinguished from most other eruptions: from Psoriasis by the regular circular form of the patches, which in the latter disease are always irregular, and in which, also, the borders are neither elevated nor inflamed. . . ."[1] These important remarks by Thomas Bateman, which were based on original descriptions by the British dermatologist Robert Willan, ended hundreds of years of confusion and laid the foundation for establishing psoriasis as a disease entity that is separate from leprosy. In addition, Willan's observations inaugurated a new way to classify and diagnose skin disease, based on accurate descriptions of skin lesions.

Psoriasis is a common, chronic skin disease, affecting approximately 2% of the population.[2] Most scientific research refers to the common clinical variant termed psoriasis vulgaris, which affects approximately 85 to 90% of all patients with the disease.[3] Psoriasis is associated with a high degree of morbidity; patients are embarrassed about the appearance of their skin, and there are side effects of medications. In addition, patients with psoriasis, like those with other major medical disorders, have reduced levels of employment and income as well as a decreased quality of life.[4,5] The combined costs of long-term therapy and social costs of the disease have a major impact on health care systems and on society in general.

The disease is usually manifested as raised, well-demarcated, erythematous oval plaques with adherent silvery scales (Fig. 1). The scales are a result of a hyperproliferative epidermis with premature maturation of keratinocytes and incomplete cornification with retention of nuclei in the stratum corneum (parakeratosis). The

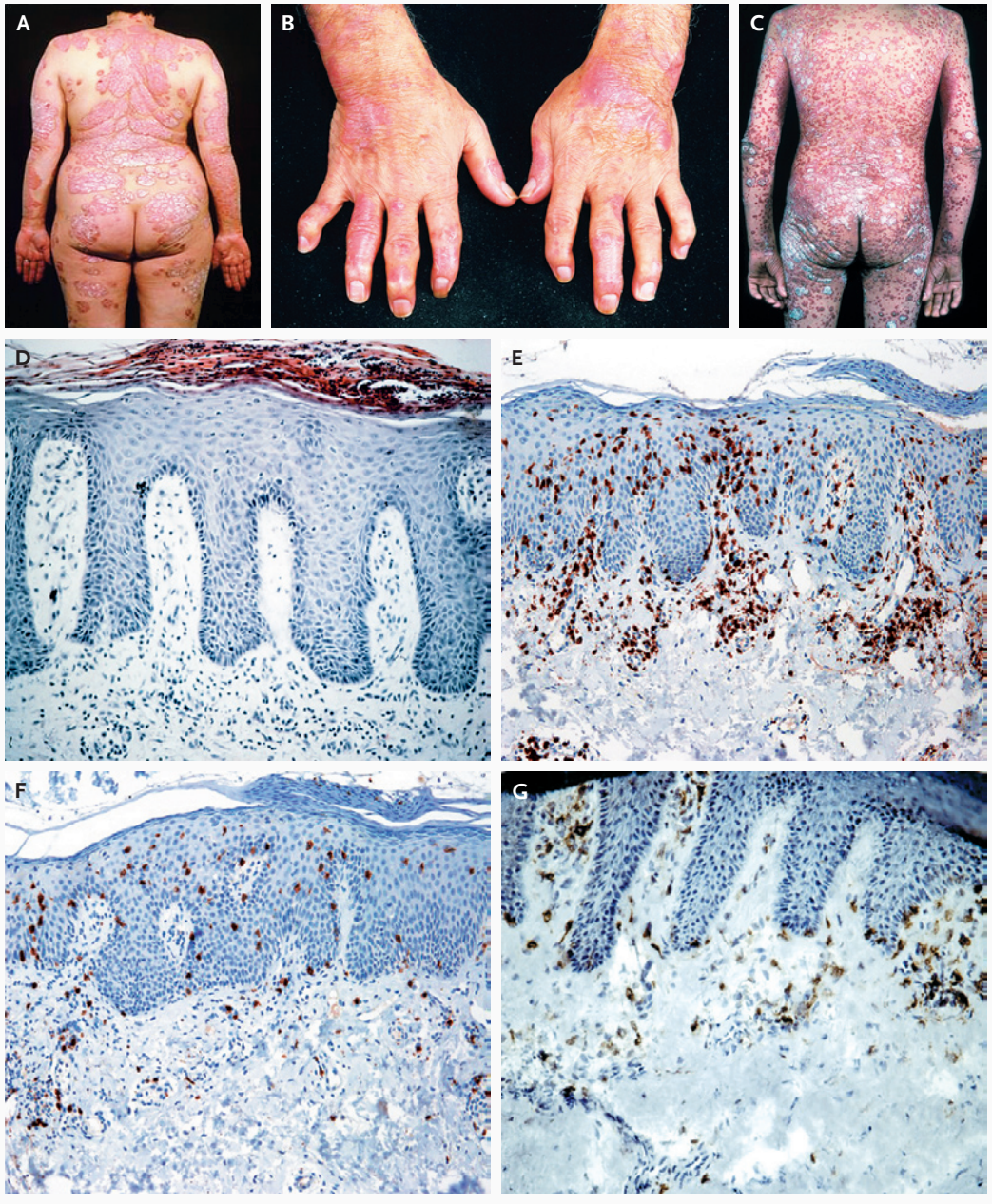


Figure 1. Clinical and Histologic Features of Psoriasis.

Erythematous, scaly, sharply demarcated plaques in different sizes and shapes are hallmarks of psoriasis. Although there are predilection sites such as the elbows, knees, and the sacral region, lesions may cover the entirety of the skin (Panels A and C). Concurrent psoriatic arthritis often affects multiple aspects of the interphalangeal joints of the hand (Panel B). The nails are frequently affected, with nail dystrophy and psoriatic lesions of the nail bed. The histopathological picture (Panel D, hematoxylin and eosin) is characterized by thickening of the epidermis, parakeratosis, elongated rete ridges, and a mixed cellular infiltrate. CD3+ T cells (Panel E, 3,3′-diaminobenzidine and hematoxylin) and CD8+ T cells (Panel F, 3,3′-diaminobenzidine and hematoxylin) are detected around capillaries of the dermis and in the epidermis. CD11c+ dendritic cells (Panel G, 3,3′-diaminobenzidine and hematoxylin) are detected mainly within the upper part of the dermis. (Clinical photographs courtesy of St. John's Institute of Dermatology.)

mitotic rate of the basal keratinocytes is increased as compared with that in normal skin. As a result, the epidermis is thickened (acanthosis), with elongated rete ridges; in combination with the dermal inflammatory infiltrate, this contributes to the overall thickness of lesions, which can vary between thick- and thin-plaque psoriasis and has been proposed as a distinctive trait.[6] The inflammatory infiltrate consists mainly of dendritic cells, macrophages, and T cells in the dermis and neutrophils, with some T cells in the epidermis. The redness of the lesions is due to increased numbers of tortuous capillaries that reach the skin surface through a markedly thinned epithelium.

GENETIC FACTORS

Population studies clearly indicate that the incidence of psoriasis is greater among first-degree and second-degree relatives of patients than among the general population.[7] That a genetic component may account for this finding is supported by studies of disease concordance among twins that show a risk of psoriasis that is two to three times as high among monozygotic twins as among dizygotic twins.[7]

The mode of inheritance of psoriasis is complex. Classic genomewide linkage analysis has identified at least nine chromosomal loci with statistically significant linkage to psoriasis; these loci are called psoriasis susceptibility 1 through 9 (*PSORS1* through *PSORS9*) (Table 1).[26] The major genetic determinant of psoriasis is *PSORS1*,[8] which probably accounts for 35 to 50% of the heritability of the disease, and the initial finding has been replicated in multiple genomewide studies. *PSORS1* is located within the major histocompatibility complex (MHC) on chromosome 6p, spanning an approximate 220-kb segment within the class I telomeric region of HLA-B.

Three genes within the region have been the major focus of investigation because of the strong association of polymorphic coding-sequence variants with psoriasis vulgaris.[27] *HLA-C* (associated variant, HLA-Cw6) encodes a class I MHC protein. *CCHCR1* (associated variant, WWCC) encodes the coiled-coil, x-helical rod protein 1, a ubiquitously expressed protein that is overexpressed in psoriatic epidermis.[28] Corneodesmosin (*CDSN*) (associated variant, allele 5) encodes corneodesmosin, a protein that is uniquely expressed in the granular and cornified layers of the epidermis and is up-regulated specifically in psoriasis.[29]

Absolute identification of the causative gene at this locus has been challenging because of the extensive linkage disequilibrium (i.e., genes on one chromosome are inherited together and are not easily separable by recombination events) observed within the MHC. Current data suggest that HLA-Cw6 is the susceptibility allele within *PSORS1*[9,30]; however, no disease-specific mutations have been identified, and variants in regulatory sequences potentially affecting several downstream genes cannot be ruled out. *HLA-C* is an interesting candidate gene, since it might be involved in immune responses at the levels of both antigen presentation and natural killer–cell regulation.

Studies have clearly shown that the clinical variants of psoriasis are genetically heterogeneous at least at the level of *PSORS1*. Thus, guttate psoriasis, an acute-onset form usually occurring in adolescents, is strongly associated with *PSORS1*,[31] whereas late-onset cases of psoriasis vulgaris (cases in persons over 50 years of age) and palmoplantar pustulosis are not associated with *PSORS1*.[32] The implications of genetic heterogeneity for disease management have yet to be determined, but such heterogeneity clearly points to potentially distinctive disease entities beyond the descriptive nomenclature of the current disease classification.

Genomewide association scans have identified variants in the gene encoding the interleukin-23 receptor (*IL23R*) and in the untranslated region of the interleukin-12B (*IL12B*) (*p40*) gene as being indicators of psoriasis risk.[12,13] *IL23R* variants are also associated with ankylosing spondylitis and psoriatic arthritis.[15,16] Another gene, *CDKAL1*, has been shown to be associated with psoriasis as well as Crohn's disease and type 2 diabetes mellitus.[19] Although the implications of this observation are unknown, it is intriguing, given the association of Crohn's disease and type 2 diabetes with moderate-to-severe psoriasis and the increased prevalence of cardiovascular disease among patients with psoriasis.

The results of several genomewide association scans of psoriasis have been reported.[9,12,13,18,33] The majority of hits and the strongest associations have been observed in the *PSORS1* region, and other associated genes have also been identified. In addition to the *IL23R* and *IL12B* vari-

Table 1. Major Psoriatic Gene Variants and Loci with Independent Replication.

Gene or Locus	Chromosomal Location	Odds Ratio for Disease	Comments	Other Disease Association	Reference
PSORS1	6p	6.4	Contains HLA-Cw6 (putative immune function) as major candidate gene and corneodesmosin	None	Trembath et al.,[8] Nair et al.,[9] Nair et al.[10]
PSORS2	17q	—	Putative role in immune synapse formation	None	Helms et al.[11]
IL12B	5q	1.4	T-cell differentiation	Crohn's disease	Cargill et al.,[12] Capon et al.,[13] Tsunemi et al.[14]
IL23R	1p	2.0	T-cell differentiation	Crohn's disease, ankylosing spondylitis, psoriatic arthritis	Nair et al.,[9] Cargill et al.,[12] Capon et al.,[13] Rahman et al.,[15] Rahman et al.,[16] Burton et al.[17]
ZNF313 (*RNF114*)	20q	1.25	Ubiquitin pathway	None	Nair et al.,[9] Capon et al.[18]
CDKAL1	6p	1.26	Unknown	Crohn's disease, type 2 diabetes mellitus	Wolf et al.,[19] Li et al.[20]
PTPN22	18p	1.3	T-cell signaling	Type 1 diabetes mellitus, juvenile idiopathic arthritis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroid disease	Li et al.,[20] Hüffmeier et al.,[21] Smith et al.[22]
Interleukin-4–interleukin-13 cytokine-gene cluster	5q	1.27	T-cell differentiation	Crohn's disease (distinct variant)	Nair et al.,[9] Chang et al.[23]
LCE3B/3C	1q	1.31	Epidermal differentiation		de Cid et al.,[24] Zhang et al.[25]

ants, these genes include zinc-finger protein 313 (*ZNF313*), which is also called ring-finger protein 114 (*RNF114*); this gene is abundantly expressed in skin. A recent comprehensive genomewide association study provides support for the association of psoriasis with the interleukin-23 pathway and provides additional evidence of susceptibility genes tumor necrosis factor α (TNF-α)–induced protein 3 (*TNFAIP3*) and TNFAIP3-interacting protein 1 (*TNIP1*) within the nuclear factor κB (NF-κB) pathway and of a genetic region that is potentially involved in the modulation of type 2 helper T cell (Th2) immune responses.[9,23] As in previous studies, no evidence of epistasis (the interaction between genes) has been shown. The relevance of structural genomic alterations to an understanding of psoriasis is underscored by the observation of DNA copy-number variation in the β-defensin gene cluster and a deletion in the late cornified envelope gene cluster associated with psoriasis.[24,25,34]

In addition to comprehensive analysis of gene variants, whole-genome analysis of the psoriasis-specific transcriptome has provided important insights into disease-relevant cells and pathways. Genomic signatures in psoriatic lesions point to dendritic cells and T cells as key cell types and type I interferons, interferon-γ, and TNF-α as key cytokines[35,36]; these findings reinforce the message from genetic association studies that cells and mediators of the immune system have key roles in susceptibility to and maintenance of psoriasis. An additional dimension for the regulation of gene-expression networks during inflammatory processes is potential control through microRNAs (miRNAs). Early studies suggest the possible involvement of miRNAs in psoriasis — for example, through interference with key inflammatory checkpoints.[37]

These recent studies have shown progress in obtaining a whole-genome perspective on psoriasis and have provided robust and reproducible data sets. These studies provide support for an important role of the immune system in the disease process.

IMMUNOPATHOLOGIC FEATURES OF PSORIASIS

Studies in the 1970s showed the presence of substantial numbers of immune cells in patients with psoriasis, suggesting a possible pathogenic role.[38] Compelling scientific evidence accumulated since then provides support for a functional role of a dysregulated immune system in psoriasis. This evidence includes the presence of increased numbers of immune cells (especially dendritic cells and T cells) in psoriatic lesions,[39,40] the appearance of clonal T cells in lesions over time,[41] the functional role of T cells and cytokines in human models of psoriasis,[42] the therapeutic activity of drugs targeting the immune system,[43,44] the findings that psoriasis may be cured in patients who have undergone bone marrow transplantation and that psoriasis can be transferred from transplant donor to recipient,[45,46] and the observation that top hits in whole-genome scans of genes and messenger RNA are immune-related. Thus, psoriatic lesions probably evolve as an interplay between cells and mediators of the immune system — specifically, its innate and adaptive function — and skin epithelium and connective tissue (Fig. 2 and 3).[47]

THE INNATE IMMUNE SYSTEM AND THE ROLE OF KERATINOCYTES

The innate immune system provides an early-response mechanism against harm to the host through recognition by preformed, nonspecific effectors. There is evidence of dysregulation of the innate immune system in psoriasis.[48] Clinical observations point to an important role of the innate cytokine interferon-α as an inducer of psoriasis.[49] The foremost producers of interferon-α, plasmacytoid dendritic cells, are increased and activated in early psoriatic lesions. The functional relevance of interferon-α and plasmacytoid dendritic cells has been demonstrated in relevant animal models of the disease,[50] and the type I interferon signature is prominent in psoriatic lesions.[35] Plasmacytoid dendritic cells are activated through complexes of the antimicrobial peptide LL-37 cathelicidin and DNA in a toll-like receptor (TLR) 9–dependent manner; this provides a potential explanation of the mechanism through which host DNA is turned into a proinflammatory stimulus that breaks immunologic tolerance in psoriasis.[51]

Psoriatic keratinocytes are a rich source of antimicrobial peptides, including LL-37, β-defensins, and S100A7 (psoriasin). In addition to their antimicrobial activity, antimicrobial peptides can also have a chemotactic function and shape immune-cell function, including that of dendritic

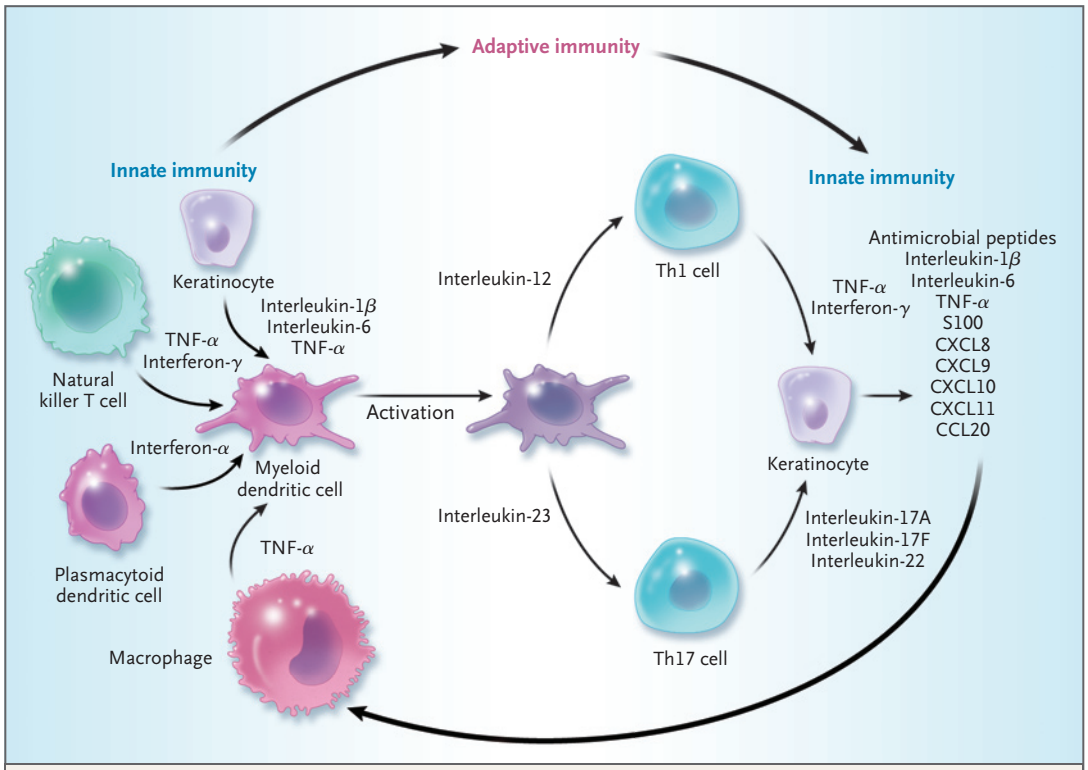


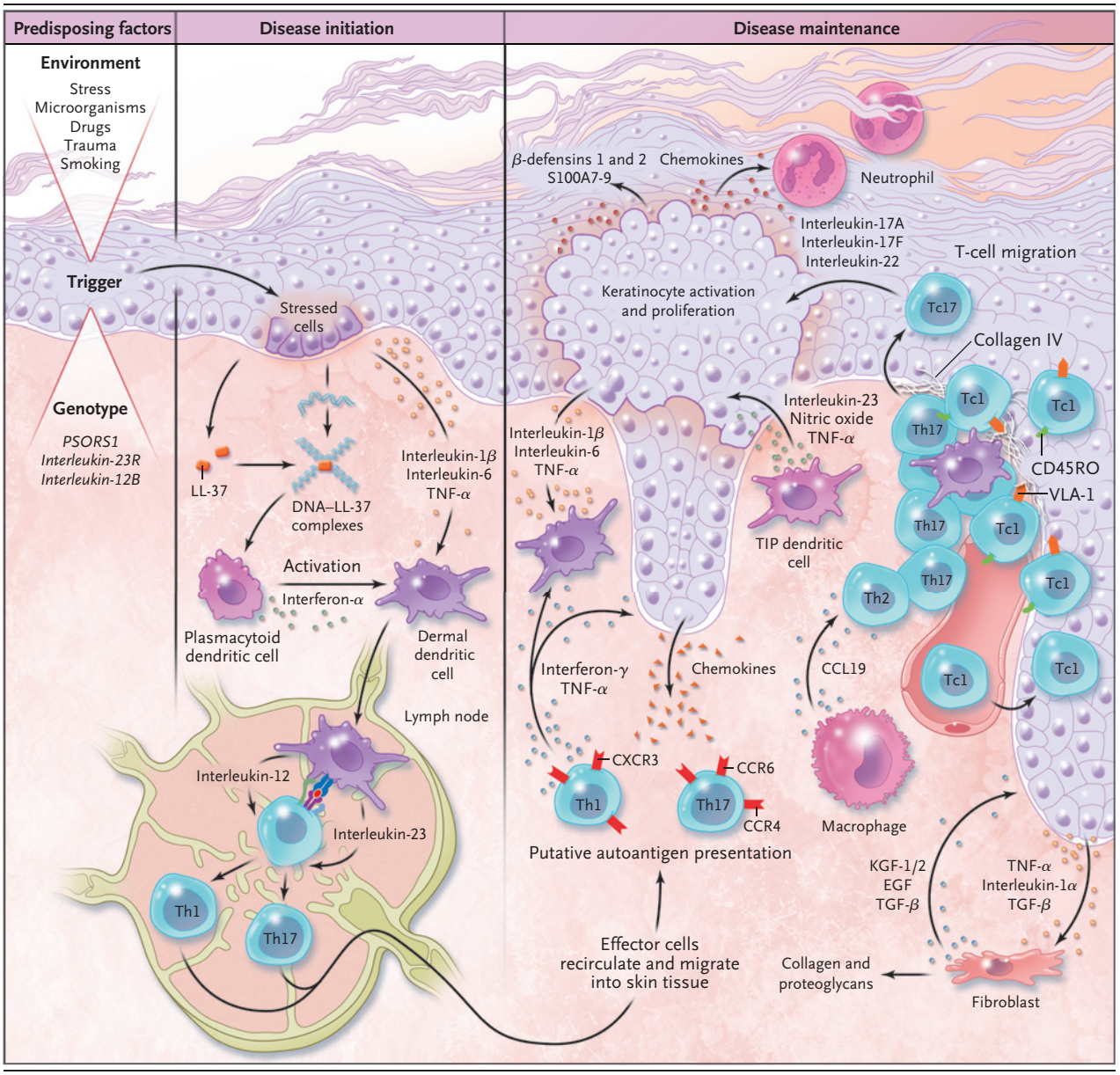
Figure 2. Key Cells and Mediators in the Transition from Innate to Adaptive Immunity in Psoriasis.

Innate immune cells produce key cytokines (tumor necrosis factor α [TNF-α], interferon-α, interferon-γ, interleukin-1β, and interleukin-6) that activate myeloid dendritic cells. Activated dendritic cells present antigens and secrete mediators such as interleukin-12 and interleukin-23, leading to the differentiation of type 17 and type 1 helper T cells (Th17 and Th1). T cells, in turn, secrete mediators (e.g., interleukin-17A, interleukin-17F, and interleukin-22) that activate keratinocytes and induce the production of antimicrobial peptides (e.g., LL-37 cathelicidin and β-defensins), proinflammatory cytokines (TNF-α, interleukin-1β, and interleukin-6), chemokines (CXCL8 through CXCL11 and CCL20), and S100 proteins. These soluble mediators feed back into the proinflammatory disease cycle and shape the inflammatory infiltrate.

cells and T cells.[52] Keratinocytes also have a potential accessory role in skin immune responses. They are responsive to key dendritic cell–derived and T-cell–derived cytokines, including interferons, TNF, interleukin-17, and the interleukin-20 family of cytokines, and in turn they will produce proinflammatory cytokines (e.g., interleukin-1, interleukin-6, and TNF-α) and chemokines (e.g., interleukin-8 [CXCL8], CXCL10, and CCL20) (Fig. 2). Thus, a rich interface between effectors of the innate and adaptive immune system shapes the psoriatic inflammatory process.

DENDRITIC CELLS

Dendritic cells are key sentinels of the immune system, bridging the gap between innate and adaptive immunity. Myeloid dermal dendritic cells are increased in psoriatic lesions and induce autoproliferation of T cells as well as production of type 1 helper T cell (Th1) cytokines.[53] They also have a proinflammatory capacity, and specialized subgroups (so-called TIP dendritic cells) produce TNF-α and inducible nitric oxide synthase.[54] Targeted immunotherapy and psoralen and ultraviolet A (PUVA) therapy reduce the numbers of dendritic cells in patients with psoriasis; this provides support for the key role of these cells in the pathogenesis of psoriasis.[55] A functional and potentially therapeutic role of plasmacytoid dendritic cells as potential drug targets has also been shown in models of psoriasis.[50] In addition, mouse models suggest a role of macrophages.[56,57] Thus, there is accumulating evidence that dendritic cells and possibly macrophages are key constituents of the psoriatic inflammatory process and potential future therapeutic targets.



T CELLS

A key question concerns the autoimmune nature of psoriasis and the contribution of autoreactive T cells to the disease process. Currently available data do not support the notion that psoriasis is a bona fide autoimmune disease. Psoriasis is probably best placed within a spectrum of autoimmune-related diseases characterized by chronic inflammation in the absence of known infectious agents or antigens.[58]

The transport of T cells from the dermis into the epidermis is a key event in psoriasis. It is controlled by the interaction of $\alpha_1\beta_1$ integrin (very late antigen 1 [VLA-1]) on T cells with collagen IV in the basement membrane of the psoriatic epidermis. Blocking of this interaction inhibits the development of psoriasis in clinically relevant models.[59] Psoriatic T cells predominantly secrete interferon-γ[60] and interleukin-17.[61,62] Recent interest has focused particularly on interleukin-17-A–producing type 17 helper T (Th17) cells. This cell type is specialized in immunosurveillance of epithelium, and it also secretes interleukin-22, a key cytokine linking adaptive immune effectors and epithelial dysregulation in psoriasis. Interleukin-22 induces proliferation of keratinocytes

Figure 3 (facing page). Proposed Schema of the Evolution of a Psoriatic Lesion from Initiation to Maintenance of Disease.

An interplay between environmental and genetic factors sets the scene for disease-initiating events. Initial triggers such as physical trauma or bacterial products start a cascade of events that include the formation of DNA–LL-37 complexes, activation of plasmacytoid dendritic cells, and secretion of interferon-α. Activated myeloid dendritic cells migrate into draining lymph nodes and induce the differentiation of naive T cells into effector cells such as type 17 helper T cells (Th17) or type 17 cytotoxic T cells (Tc17) and type 1 helper T cells (Th1) or type 1 cytotoxic T cells (Tc1). Effector cells recirculate and slow down in skin capillaries in the presence of selectin-guided and integrin-guided receptor–ligand interactions. Immune cells expressing the chemokine receptors CCR6, CCR4, and CXCR3 emigrate into skin tissue along chemokine gradients. Key processes during disease maintenance are the presentation of putative autoantigens to T cells and the release of interleukin-23 by dermal dendritic cells, the production of proinflammatory mediators such as tumor necrosis factor α (TNF-α) and nitric oxide by TNF-α and inducible nitric oxide synthase–producing (TIP) dendritic cells, and the production of interleukin-17A, interleukin-17F, and interleukin-22 by Th17 and Tc17 cells and interferon-γ and TNF-α by Th1 and Tc1 cells. These mediators act on keratinocytes, leading to the activation, proliferation, and production of antimicrobial peptides (e.g., LL-37 cathelicidin and β-defensins), chemokines (e.g., CXCL1, CXCL9 through CXCL11, and CCL20), and S100 proteins (e.g., S100A7-9) by keratinocytes. Dendritic cells and T cells form perivascular clusters and lymphoidlike structures around blood vessels in the presence of chemokines such as CCL19 produced by macrophages. A key checkpoint is the migration of T cells from the dermis into the epidermis; this migration is controlled through the interaction of $\alpha_1\beta_1$ integrin (very late antigen 1 [VLA-1]) on T cells and collagen IV at the basement membrane. Unconventional T cells, including natural killer T cells, contribute to the disease process. Feedback loops involving keratinocytes, fibroblasts, and endothelial cells contribute to tissue reorganization with endothelial-cell activation and proliferation and deposition of extracellular matrix. Neutrophils in the epidermis are attracted by chemokines, including interleukin-8 (CXCL8) and CXCL1. CD45RO denotes cluster designation 45RO, EGF epidermal growth factor, KGF-1/2 keratinocyte growth factor types 1 and 2, and TGF-β transforming growth factor β.

and production of antimicrobial peptides as well as chemokines.[63] A functional role of Th17 cells in psoriasis is suggested by their reduction during successful anti-TNF treatment.[64]

CYTOKINES

The hypothesis of a cytokine network in psoriasis proposed a central role of proinflammatory cytokines, including TNF-α.[65] In retrospect, this theory has been validated by the clinical success of anti-TNF therapy in the treatment of psoriasis.[66] On the basis of the analysis of gene signatures in this disease, three predominant cytokines seem to be at play: type I interferons, interferon-γ, and TNF-α.[35] Both TNF-α and interferon-γ also have antiinflammatory properties[67,68]; this might explain, in part, the counterintuitive clinical observation that anti-TNF therapy induces psoriasis in a minority of patients.[69] In addition, dendritic cell–derived interleukin-23 and downstream products of helper T cells, including interleukin-17A and interleukin-22, are of considerable importance.[70,71] Key cytokines in psoriasis act through a restricted set of signaling and transcriptional pathways: Janus kinases and signal transducers and activators of transcription (JAK-STATs) in the case of type I interferons, interferon-γ, interleukin-23, interleukin-12, interleukin-22, and NF-κB in the case of TNF-α. Thus, complex and in part redundant psoriasis-relevant cytokines converge on key well-known intracellular checkpoints that are common to many chronic inflammatory conditions.

COUNTERREGULATORY MECHANISMS

During tissue homeostasis, proinflammatory states are balanced through counterregulatory mechanisms. Although studies have indicated that the numbers of regulatory T (Treg) cells are not altered in lesional psoriatic skin, there seems to be a defect in their overall suppressive activity.[72] In CD18-knockout mice, a deficiency of Treg cells is associated with the development of psoriasiform features.[73] An important regulatory cytokine, interleukin-10, is decreased in psoriasis. Early clinical studies showed that interleukin-10 has moderate therapeutic effectiveness, an observation that has not been confirmed in larger, controlled trials.[74]

THE PSORIATIC MICROVASCULATURE

Evidence of a role of endothelial cells in psoriasis includes the increased expression of vascular endothelial growth factor (VEGF),[75] psoriasiform inflammation in mouse models with transgenic overexpression of VEGF in the epidermis, the association of psoriasis with VEGF gene variants,[76] and the efficacy of drugs targeting angiogenesis in animal models.[77] In contrast to the microvasculature of normal skin, the psoriatic microvas-

culature is characterized by tortuous and leaky blood vessels that facilitate leukocyte migration into inflamed skin. VEGF and angiopoietins are some of the factors believed to be responsible for these vascular changes in psoriasis.

MODELS OF PSORIASIS

With the exception of a few sporadic cases in primates, psoriasis is unique to humans. Thus, the available nonhuman models of psoriasis usually provide only an approximation of the disease. The three main types of in vivo animal models usually rely on mice as hosts and are based on the following experimental settings: spontaneous mutation, genetic engineering, and xenotransplantation. Spontaneous mutation in mouse models has resulted in inflammatory and scaly skin phenotypes, but these models usually represent only a limited set of psoriatic features.[78]

There are two broad categories of genetically engineered mice: mice in which a genetic element has been introduced (transgenic mice), and those in which a genetic element has been removed (knockout mice) or attenuated (hypomorphic mice). In most cases, genetic modification is targeted to the epidermis through specific promoters. These models test the hypothesis that overexpression of a given cytokine, growth factor, adhesion molecule, or signaling element contributes to an inflammatory skin disease.[79] The advantage of these models is that a given mediator or pathway can be studied in isolation and thus its role in skin inflammation in mice can be established.

Recently, an interesting new model induced psoriasiform skin inflammation in mice with the use of topical application of the TLR7/8 agonist imiquimod. This model recapitulated most of the known critical checkpoints in the pathogenesis of psoriasis, including activation of plasmacytoid dendritic cells and dependence on Th17 cells.[80] However, most mouse models do not reflect the complex pathogenic network in psoriasis, in part because of differences between human and mouse skin. These differences include the extent of interfollicular epidermis, the thickness of the epidermis, the density of hair follicles, the differentiation program of keratinocytes, and the presence of mouse versus human immune cells.[81]

In an attempt to overcome these problems and to develop humanized mouse models, the transplantation of skin from patients with psoriasis into immunosuppressed mice has been a promising area of investigation. Transplants can be obtained from either symptomless (nonlesional) or lesional skin of patients with psoriasis. Such xenotransplantation models allows studies of the development of psoriasis and of established psoriasis. Thus, these models can be used to address two seminal questions in psoriasis research (Fig. 3): What are disease-initiating events? What are disease-maintaining events? These insights ultimately have led to answers related to the prevention and treatment of psoriasis.[42] New discoveries based on such models include the necessity of an intrinsic skin factor for the development of psoriasis, the important role of immune cells in tissue, the key role of epidermal T cells, and the contribution of early innate trigger events.[82] Xenotransplantation models of psoriasis are also valuable tools in drug development.[42,83] They have been useful in reassessing the mechanisms of established psoriatic drugs in more detail, and they have also been helpful in validating potential new drug targets, including anti–interferon-α or anti–interleukin-22 therapy, which are currently in early clinical trials.

PSORIASIS AS A SYSTEMIC INFLAMMATORY DISEASE

There is increasing awareness that psoriasis as a disease is more than "skin deep" and that it has important systemic manifestations that are shared with other chronic inflammatory diseases, such as Crohn's disease and diabetes mellitus. The shared conditions include the metabolic syndrome, depression, and cancer.[3] It is unclear whether cancer, particularly lymphoma and skin cancer, is related to the disease or its treatment.[84] An associated arthropathy, psoriatic arthritis, has features in common with psoriasis but is considered to be a distinct disease entity with a distinct therapeutic spectrum.[85] Of emerging significance is the relationship between psoriasis and the risk of cardiovascular disease, including coronary-artery calcification.[86,87] Whereas there appears to be no excess risk among patients with mild psoriasis, moderate and severe disease is associated with an excess frequency of myocardial in-

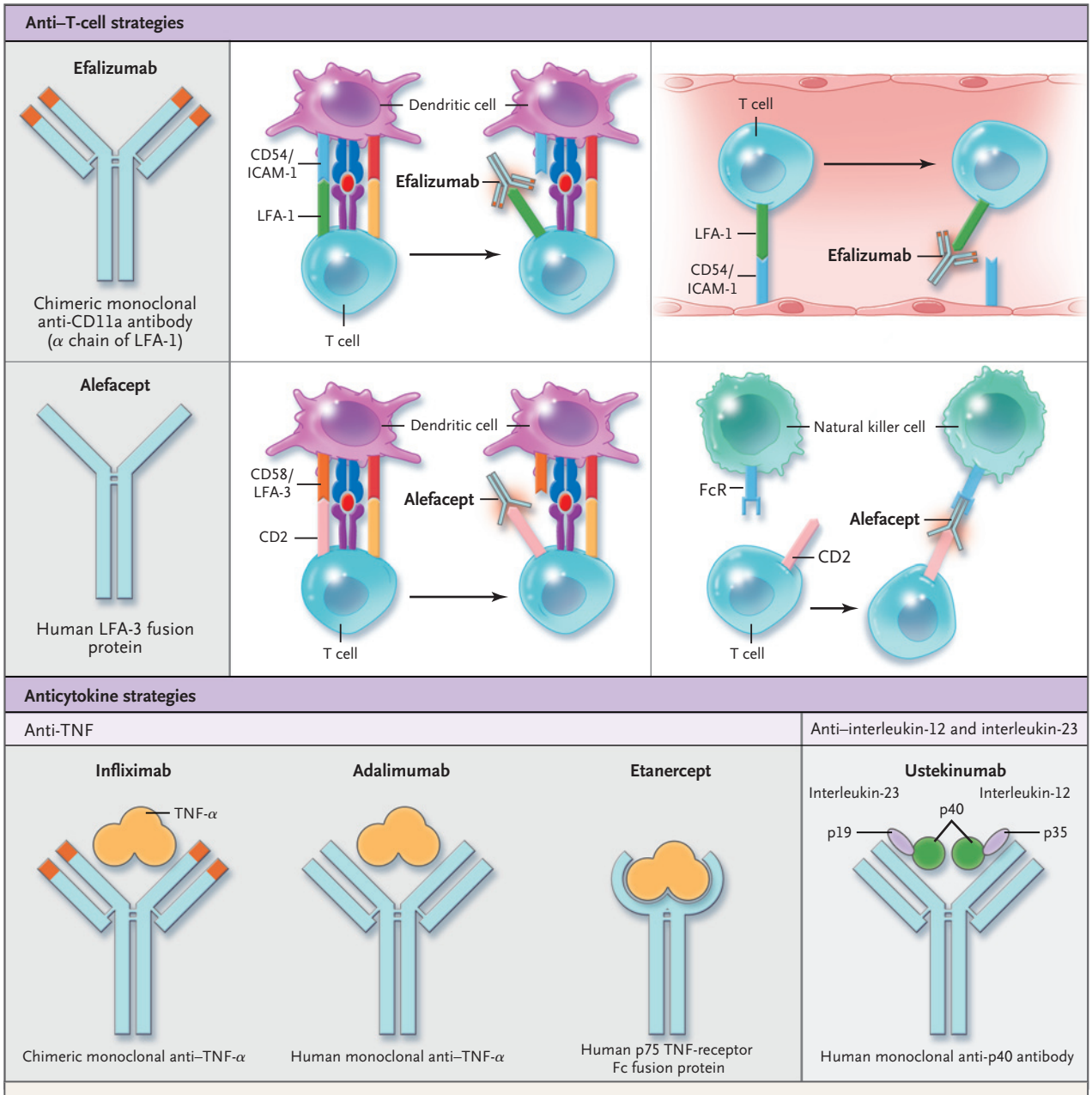


Figure 4. Pathogenesis-Based Targeted Therapy for Psoriasis.

Targeted biologic therapies that have been approved for marketing or for which phase 3 clinical data have been published are shown. The two major therapeutic classes are T-cell–targeted therapies (alefacept and efalizumab) and anticytokine therapies (anti–tumor necrosis factor [TNF] therapies): infliximab, adalimumab, etanercept, and a monoclonal antibody against interleukin-12 and interleukin-23 (ustekinumab). Efalizumab (which has been withdrawn from the market) is a chimeric monoclonal anti-CD11a antibody. It blocks the interaction of CD11a (lymphocyte-function–associated antigen [LFA] 1 [LFA-1]) with intercellular adhesion molecule 1 (ICAM-1), leading to a disruption of the interaction between dendritic cells and T cells at tissue sites and in lymph nodes as well as blocking of immune-cell binding to blood vessels. Alefacept is a human LFA 3 (LFA-3) Fc fusion protein that blocks the interaction between CD2 on T cells and LFA-3 on antigen-presenting cells. It also induces antibody-dependent cytotoxicity in T cells bound to alefacept. Anti-TNF strategies have three variants: a humanized chimeric anti–TNF-α monoclonal antibody, a fully human monocolonal anti–TNF-α antibody, and a human p75 TNF-receptor Fc fusion protein. Finally, blocking of interleukin-12 and interleukin-23 is achieved by means of antibodies targeting the common p40 chain of these cytokines. CD denotes cluster designation, and FcR Fc receptor.

farction and an increase in mortality, in large part because of cardiovascular events.[88] There is emerging evidence that systemic inflammation analogous to that observed in rheumatoid arthritis is involved in psoriasis.[89] Circulating factors that are indicative of systemic inflammation and endothelial activation have been detected. If confirmed, these findings would have major implications for future preventive and therapeutic strategies.

PATHOGENESIS-BASED APPROACHES TO THERAPY

Classic systemic treatments for psoriasis have not fully met the needs of patients.[90] Antibody-based or fusion protein–based selective targeting of key mediators of inflammation has been added to the treatment approaches for psoriasis.[81,91,92] The first biologic agent developed specifically for a dermatologic disease was alefacept, which was developed for the treatment of psoriasis.[93] Dermatologists have subsequently moved from serendipitous choices among the available therapeutic options to targeted intervention based on increased insights into the pathogenesis of psoriasis. The proof of principle of pathogenesis-based therapy in dermatology has created a multitude of opportunities for the development of new drugs that are currently moving through the phases of clinical development.

Biologic therapies in psoriasis are highly effective and can be classified according to their mechanism of action.[94] The two main classes are biologic agents targeted at T cells and biologic agents targeted at cytokines (Fig. 4). T-cell–targeted biologic agents such as alefacept and efalizumab (which has been withdrawn from the market) have validated the concept of a role of T cells in established disease. Anticytokine therapies have been developed through advances in anti-TNF therapy in chronic inflammatory diseases, including psoriasis. However, a multitude of issues, including long-term efficacy, relapse after drug withdrawal, safety, and costs, are driving the search for new and better therapies. The latest addition to the anticytokine drugs are antibodies targeted at the interleukin-12 and interleukin-23 family of heterodimeric cytokines that share a common p40 chain. Randomized, controlled studies have shown the efficacy and short-term safety of anti-p40 antibodies in psoriasis and psoriatic arthritis.[95-98] This therapeutic approach is conceptually new, since it targets mainly dendritic-cell–derived cytokines, in contrast to the broader targeting of anti-TNF therapies.

Current biologic therapies are well tolerated overall, and some are more effective than conventional systemic therapies.[99] However, the long-term safety of biologic agents is an unresolved issue and will be addressed in a satisfactory manner only if there is optimal use of and investment in postmarketing surveillance of these drugs, including the development of comprehensive registries of biologic drugs.[100]

CONCLUSIONS

The evolution of a psoriatic lesion is based on a complex interplay between environmental and genetic factors that sets the scene for disease-initiating events. A cascade of events leads to activation of dendritic cells and, in turn, the generation of effector T cells that emigrate to and reside in skin tissue. Cross-talk between epithelial cells and immune cells shapes and maintains the inflammatory milieu. Research in the past decade has identified many of the checkpoints governing these processes and has lead to the development of new, highly effective targeted therapies. Although this progress is remarkable, there are still many unknowns, especially in the area of disease prevention and the development of drugs with appropriate long-term risk–benefit and cost profiles. Future research will need to tackle these challenges in order to establish therapeutic and preventive approaches that ultimately lead to improved outcomes for patients.

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