

# Update on the Pathophysiology of Psoriasis

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## PRACTICE POINTS

- Psoriasis is a systemic inflammatory disease.
- We now have an increased understanding of the specific cytokines involved in the disease.
- Therapies have been developed to target these cytokines.

Psoriasis is a genetically programmed pathologic interaction among skin cells, immunocytes, and numerous biologic signaling molecules that is triggered by environmental stimuli. The immune response is a cellular one; type 1 (T<sub>H</sub>1) and type 17 (T<sub>H</sub>17) T cells are activated by IL-12 and IL-23 secreted by antigen-presenting cells (APCs) in the skin. Through various cytokines, such as tumor necrosis factor (TNF)  $\alpha$ , these cells cause a chronic inflammatory state and alter epidermal hyperproliferation, differentiation, apoptosis, and neoangiogenesis that produce the cutaneous findings seen in this disease. The newer biologic therapies target the immunologic signaling pathways and cytokines identified in the pathogenesis of psoriasis and provide notable clinical improvement. Further study in the pathogenesis of psoriasis can help identify targets for future therapies.

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Increased understanding of the pathophysiology of psoriasis has been one of the driving forces in the development of new therapies. An understanding of the processes involved is important in the optimal management of the disease. The last 30 years of research and clinical practice have revolutionized our understanding of the pathogenesis of psoriasis as the dysregulation of immunity triggered by environmental and genetic stimuli. Psoriasis was originally regarded as a primary disorder

of epidermal hyperproliferation. However, experimental models and clinical results from immunomodulating therapies have refined this perspective in conceptualizing psoriasis as a genetically programmed pathologic interaction among resident skin cells; infiltrating immunocytes; and a host of proinflammatory cytokines, chemokines, and growth factors produced by these immunocytes. Two populations of immunocytes and their respective signaling molecules collaborate in the pathogenesis: (1) innate immunocytes, mediated by antigen-presenting cells (APCs) (including natural killer [NK] T lymphocytes, Langerhans cells, and neutrophils), and (2) acquired or adaptive immunocytes, mediated by mature CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes in the skin. Such dysregulation of immunity and subsequent inflammation is responsible for the development and perpetuation of the clinical plaques and histological inflammatory infiltrate characteristic of psoriasis.

Although psoriasis is considered to be an immune-mediated disease in which intralesional T lymphocytes and their proinflammatory signals trigger primed basal layer keratinocytes to rapidly proliferate, debate and research focus on the stimulus that incites this inflammatory process. Our current understanding considers psoriasis to be triggered by exogenous or endogenous environmental stimuli in genetically susceptible individuals. Such stimuli include group A streptococcal pharyngitis, viremia, allergic drug reactions, antimalarial drugs, lithium, beta-blockers, IFN- $\alpha$ , withdrawal of systemic corticosteroids, local trauma (Köbner phenomenon), and emotional stress. These stimuli correlate with the onset or flares of psoriatic lesions. Psoriasis genetics centers on susceptibility loci and corresponding candidate genes, particularly the psoriasis susceptibility (PSORS) 1 locus on the major histocompatibility complex (MHC) class I

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region. Current research on the pathogenesis of psoriasis examines the complex interactions among immunologic mechanisms, environmental stimuli, and genetic susceptibility. After discussing the clinical presentation and histopathologic features of psoriasis, we will review the pathophysiology of psoriasis through noteworthy developments, including serendipitous observations, reactions to therapies, clinical trials, and animal model systems that have shaped our view of the disease process. In addition to the classic skin lesions, approximately 23% of psoriasis patients develop psoriatic arthritis, with a 10-year latency after diagnosis of psoriasis.<sup>1</sup>

### Principles of Immunity

The immune system, intended to protect its host from foreign invaders and unregulated cell growth, employs 2 main effector pathways—the innate and the acquired (or adaptive) immune responses—both of which contribute to the pathophysiology of psoriasis.<sup>2</sup> Innate immunity responses occur within minutes to hours of antigen exposure but fail to develop memory for when the antigen is encountered again. However, adaptive immunity responses take days to weeks to respond after challenged with an antigen. The adaptive immune cells have the capacity to respond to a greater range of antigens and develop immunologic memory via rearrangement of antigen receptors on B and T cells. These specialized B and T cells can then be promptly mobilized and differentiated into mature effector cells that protect the host from a foreign pathogen.

Innate and adaptive immune responses are highly intertwined; they can initiate, perpetuate, and terminate the immune mechanisms responsible for inflammation. They can modify the nature of the immune response by altering the relative proportions of type 1 ( $T_H1$ ), type 2 ( $T_H2$ ), and the more recently discovered type 17 ( $T_H17$ ) subset of helper T cells and their respective signaling molecules. A  $T_H1$  response is essential for a cellular immunologic reaction to intracellular bacteria and viruses or cellular immunity. A  $T_H2$  response promotes IgE synthesis, eosinophilia, and mast cell maturation for extracellular parasites and helminthes as well as humoral immunity, while a  $T_H17$  response is important for cell-mediated immunity to extracellular bacteria and plays a role in autoimmunity.<sup>3</sup> The innate and adaptive immune responses employ common effector molecules such as chemokines and cytokines, which are essential in mediating an immune response.

### Implicating Dysregulation of Immunity

Our present appreciation of the pathogenesis of psoriasis is based on the history of trial-and-error therapies; serendipitous discoveries; and the current immune targeting drugs used in a variety of chronic inflammatory conditions, including rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease. Before the mid-1980s, research focused on the hyperproliferative

epidermal cells as the primary pathology because a markedly thickened epidermis was indeed demonstrated on histologic specimens. Altered cell-cycle kinetics were thought to be the culprit behind the hyperkeratotic plaques. Thus, initial treatments centered on oncologic and antimetabolic therapies used to arrest keratinocyte proliferation with agents such as arsenic, ammoniated mercury, and methotrexate.<sup>4</sup>

However, a paradigm shift from targeting epidermal keratinocytes to immunocyte populations was recognized when a patient receiving cyclosporine to prevent transplant rejection noted clearing of psoriatic lesions in the 1980s.<sup>5</sup> Cyclosporine was observed to inhibit messenger RNA transcription of T-cell cytokines, thereby implicating immunologic dysregulation, specifically T-cell hyperactivity, in the pathogenesis of psoriasis.<sup>6</sup> However, the concentrations of oral cyclosporine reached in the epidermis exerted direct effects on keratinocyte proliferation and lymphocyte function in these patients.<sup>7</sup> Thus, the question was raised as to whether the keratinocytes or the lymphocytes drove the psoriatic plaques. The use of an IL-2 diphtheria toxin-fusion protein, denileukin diftitox, specific for activated T cells with high-affinity IL-2 receptors and nonreactive with keratinocytes, distinguished which cell type was responsible. This targeted T-cell toxin provided clinical and histological clearing of psoriatic plaques. Thus, T lymphocytes rather than keratinocytes were recognized as the definitive driver behind the psoriatic plaques.<sup>8</sup>

Additional studies have demonstrated that treatments that induce prolonged clearing of psoriatic lesions without continuous therapy, such as psoralen plus UVA irradiation, decreased the numbers of T cells in plaques by at least 90%.<sup>9</sup> However, treatments that require continual therapy for satisfactory clinical results, such as cyclosporine and etretinate, simply suppress T-cell activity and proliferation.<sup>10,11</sup>

Further evidence has linked cellular immunity with the pathogenesis of psoriasis, defining it as a  $T_H1$ -type disease. Natural killer T cells were shown to be involved through the use of a severe combined immunodeficient mouse model. They were injected into prepsoriatic skin grafted on immunodeficient mice, creating a psoriatic plaque with an immune response showing cytokines from  $T_H1$  cells rather than  $T_H2$  cells.<sup>12</sup> When psoriatic plaques were treated topically with the toll-like receptor 7 agonist imiquimod, aggravation and spreading of the plaques were noted. The exacerbation of psoriasis was accompanied by an induction of lesional  $T_H1$ -type interferon produced by plasmacytoid dendritic cell (DC) precursors. Plasmacytoid DCs were observed to compose up to 16% of the total dermal infiltrate in psoriatic skin lesions based on their coexpression of BDCA2 and CD123.<sup>13</sup> Additionally, cancer patients being treated with interferon alfa experienced induction of psoriasis.<sup>14</sup> Moreover, patients being treated for warts with intralesional interferon alfa developed psoriatic plaques in neighboring prior asymptomatic skin.<sup>15</sup>

Patients with psoriasis who were treated with interferon gamma, a  $T_H1$  cytokine type, also developed new plaques correlating with the sites of injection.<sup>16</sup>

### Intralesional T Lymphocytes

Psoriatic lesions contain a host of innate immunocytes, such as APCs, NK cells, and neutrophils, as well as adaptive T cells and an inflammatory infiltrate. These cells include CD4 and CD8 subtypes in which the CD8<sup>+</sup> cells predominate in the epidermis, while CD4<sup>+</sup> cells show preference for the dermis.<sup>17</sup> There are 2 groups of CD8<sup>+</sup> cells: one group migrates to the epidermis, expressing the integrin CD103, while the other group is found in the dermis but may be headed to or from the epidermis. The CD8<sup>+</sup> cells residing in the epidermis that express the integrin CD103 are capable of interacting with E-cadherin, which enables these cells to travel to the epidermis and bind resident cells. Immunophenotyping reveals that these mature T cells represent chiefly activated memory cells, including CD2<sup>+</sup>, CD3<sup>+</sup>, CD5<sup>+</sup>, CLA, CD28, and CD45RO<sup>+</sup>.<sup>18</sup> Many of these cells express activation markers such as HLA-DR, CD25, and CD27, in addition to the T-cell receptor (TCR).

### T-Lymphocyte Stimulation

Both mature CD4<sup>+</sup> and CD8<sup>+</sup> T cells can respond to the peptides presented by APCs. Although the specific antigen that these T cells are reacting to has not yet been elucidated, several antigenic stimuli have been proposed, including self-proteins, microbial pathogens, and microbial superantigens. The premise that self-reactive T lymphocytes may contribute to the disease process is derived from the molecular mimicry theory in which an exuberant immune response to a pathogen produces cross-reactivity with self-antigens.<sup>19</sup> Considering that infections have been associated with the onset of psoriasis, this theory merits consideration. However, it also has been observed that T cells can be activated without antigens or superantigens but rather with direct contact with accessory cells.<sup>20</sup> No single theory has clearly emerged. Researchers continue to search for the inciting stimulus that triggers the T lymphocyte and attempt to determine whether T cells are reacting to a self-derived or non-self-derived antigen.

### T-Lymphocyte Signaling

T-cell signaling is a highly coordinated process in which T lymphocytes recognize antigens via presentation by mature APCs in the skin rather than the lymphoid tissues. Such APCs expose antigenic peptides via class I or II MHC molecules for which receptors are present on the T-cell surface. The antigen recognition complex at the T-cell and APC interface, in concert with a host of antigen-independent co-stimulatory signals, regulates T-cell signaling and is referred to as the immunologic synapse. The antigen presentation and network of co-stimulatory and adhesion molecules optimize T-cell activation, and dermal DCs release IL-12 and IL-23 to

promote a  $T_H1$  and  $T_H17$  response, respectively. The growth factors released by these helper T cells sustain neoangiogenesis, stimulate epidermal hyperproliferation, alter epidermal differentiation, and decrease susceptibility to apoptosis that characterizes the erythematous hypertrophic scaling lesions of psoriasis.<sup>21</sup> Furthermore, the cytokines produced from the immunologic response, such as tumor necrosis factor (TNF)  $\alpha$ , IFN- $\gamma$ , and IL-2, correspond to cytokines that are upregulated in psoriatic plaques.<sup>22</sup>

Integral components of the immunologic synapse complex include co-stimulatory signals such as CD28, CD40, CD80, and CD86, as well as adhesion molecules such as cytotoxic T-lymphocyte antigen 4 and lymphocyte function-associated antigen (LFA) 1, which possess corresponding receptors on the T cell. These molecules play a key role in T-cell signaling, as their disruption has been shown to decrease T-cell responsiveness and associated inflammation. The B7 family of molecules routinely interacts with CD28 T cells to co-stimulate T-cell activation. Cytotoxic T-lymphocyte antigen 4 immunoglobulin, an antibody on the T-cell surface, targets B7 and interferes with signaling between B7 and CD28. In psoriatic patients, this blockade was demonstrated to attenuate the T-cell response and correlated with a clinical and histological decrease in psoriasiform hyperplasia.<sup>23</sup> Biologic therapies that disrupt the LFA-1 component of the immunologic synapse also have demonstrated efficacy in the treatment of psoriasis. Alefacept is a human LFA-3 fusion protein that binds CD2 on T cells and blocks the interaction between LFA-3 on APCs and CD2 on memory CD45RO<sup>+</sup> T cells and induces apoptosis of such T cells. Efalizumab is a human monoclonal antibody to the CD11 chain of LFA-1 that blocks the interaction between LFA-1 on the T cell and intercellular adhesion molecule 1 on an APC or endothelial cell. Both alefacept and efalizumab, 2 formerly marketed biologic therapies, demonstrated remarkable clinical reduction of psoriatic lesions, and alefacept has been shown to produce disease remission for up to 18 months after discontinuation of therapy.<sup>24-26</sup>

### NK T Cells

Natural killer T cells represent a subset of CD3<sup>+</sup> T cells present in psoriatic plaques. Although NK T cells possess a TCR, they differ from T cells by displaying NK receptors comprised of lectin and immunoglobulin families. These cells exhibit remarkable specificity and are activated upon recognition of glycolipids presented by CD1d molecules. This process occurs in contrast to CD4<sup>+</sup> and CD8<sup>+</sup> T cells, which, due to their TCR diversity, respond to peptides processed by APCs and displayed on MHC molecules. Natural killer T cells can be classified into 2 subsets: (1) one group that expresses CD4 and preferentially produces  $T_H1$ - versus  $T_H2$ -type cytokines, and (2) another group that lacks CD4 and CD8 that only produces  $T_H1$ -type cytokines. The innate immune system employs NK T cells early in the immune response because of their

direct cytotoxicity and rapid production of cytokines such as IFN- $\gamma$ , which promotes a T<sub>H</sub>1 inflammatory response, and IL-4, which promotes the development of T<sub>H</sub>2 cells. Excessive or dysfunctional NK T cells have been associated with autoimmune diseases such as multiple sclerosis and inflammatory bowel disease as well as allergic contact dermatitis.<sup>27-29</sup>

In psoriasis, NK T cells are located in the epidermis, closely situated to epidermal keratinocytes, which suggests a role for direct antigen presentation. Furthermore, CD1d is overexpressed throughout the epidermis of psoriatic plaques, whereas normally CD1d expression is confined to terminally differentiated keratinocytes. An *in vitro* study examining cytokine-based inflammation demonstrative of psoriasis treated cultured CD1d-positive keratinocytes with interferon gamma in the presence of alpha-galactosylceramide of the lectin family.<sup>30</sup> Interferon gamma was observed to enhance keratinocyte CD1d expression, and subsequently, CD1d-positive keratinocytes were found to activate NK T cells to produce high levels of IFN- $\gamma$ , while levels of IL-4 remained undetectable. The preferential production of IFN- $\gamma$  supports a T<sub>H</sub>1-mediated mechanism regulated by NK T cells in the immunopathogenesis of psoriasis.

### Dendritic Cells

Dendritic cells are APCs that process antigens in the tissues in which they reside, after which they migrate to local lymph nodes where they present their native antigens to T cells. This process allows the T-cell response to be tailored to the appropriate antigens in the corresponding tissues. Immature DCs that capture antigens mature by migrating to the T-cell center of the lymph node where they present their antigens to either MHC molecules or the CD1 family. This presentation results in T-cell proliferation and differentiation that correlates with the required type of T-cell response. Multiple subsets of APCs, including myeloid and plasmacytoid DCs, are highly represented in the epidermis and dermis of psoriatic plaques as compared with normal skin.<sup>31</sup> Dermal DCs are thought to be responsible for activating both the T<sub>H</sub>1 and T<sub>H</sub>17 infiltrate by secreting IL-12 and IL-23, respectively. This mixed cellular response secretes cytokines and leads to a cascade of events involving keratinocytes, fibroblasts, endothelial cells, and neutrophils that create the cutaneous lesions seen in psoriasis.<sup>3</sup>

Although DCs play a pivotal role in eliciting an immune response against a foreign invader, they also contribute to the establishment of tolerance. Throughout their maturation, DCs are continuously sensing their environment, which shapes their production of T<sub>H</sub>1-versus T<sub>H</sub>2-type cytokines and subsequently the nature of the T-cell response. When challenged with a virus, bacteria, or unchecked cell growth, DCs mature into APCs. However, in the absence of a strong stimulus, DCs fail to mature into APCs and present self-peptides with MHC molecules, thereby creating regulatory T cells involved in peripheral tolerance.<sup>32</sup> If this balance between

immunogenic APCs and housekeeping T cells is upset, inflammatory conditions such as psoriasis can result.

### Cytokines

Cytokines are low-molecular-weight glycoproteins that function as signals to produce inflammation, defense, tissue repair and remodeling, fibrosis, angiogenesis, and restriction of neoplastic growth.<sup>33</sup> Cytokines are produced by immunocytes such as lymphocytes and macrophages as well as nonimmunocytes such as endothelial cells and keratinocytes. Proinflammatory cytokines include IL-1, IL-2, the IL-17 family, IFN- $\gamma$ , and TNF- $\alpha$ , while anti-inflammatory cytokines include IL-4 and IL-10. A relative preponderance of T<sub>H</sub>1 proinflammatory cytokines or an insufficiency of T<sub>H</sub>2 anti-inflammatory cytokines induces local inflammation and recruitment of additional immunocyte populations, which produce added cytokines.<sup>34</sup> A vicious cycle of inflammation occurs that results in cutaneous manifestations such as a plaque. Psoriatic lesions are characterized by a relative increase of T<sub>H</sub>1-type (eg, IL-2, IFN- $\gamma$ , TNF- $\alpha$ , TNF- $\beta$ ) to T<sub>H</sub>2-type (eg, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13) cytokines and an increase in T<sub>H</sub>17-type cytokines. Natural killer T cells stimulated by CD1d-overexpressing keratinocytes increase production of proinflammatory IFN- $\gamma$  without effect on the anti-inflammatory IL-4. In addition to the cytokines produced by T cells, APCs produce IL-18, IL-23, and TNF- $\alpha$  found in the inflammatory infiltrate of psoriatic plaques. Both IL-18 and IL-23 stimulate T<sub>H</sub>1 cells to produce IFN- $\gamma$ , and IL-23 stimulates T<sub>H</sub>17 cells. Clearly, a T<sub>H</sub>1- and T<sub>H</sub>17-type pattern governs the immune effector cells and their respective cytokines present in psoriatic skin.

### Tumor Necrosis Factor $\alpha$

Although a network of cytokines is responsible for the inflammation of psoriasis, TNF- $\alpha$  has been implicated as a master proinflammatory cytokine of the innate immune response due to its widespread targets and sources. Tumor necrosis factor  $\alpha$  is produced by activated T cells, keratinocytes, NK cells, macrophages, monocytes, Langerhans APCs, and endothelial cells. Psoriatic lesions demonstrate high concentrations of TNF- $\alpha$ , while the synovial fluid of psoriatic arthritis patients demonstrates elevated concentrations of TNF- $\alpha$ , IL-1, IL-6, and IL-8.<sup>34</sup> In psoriasis, TNF- $\alpha$  supports the expression of adhesion molecules (intercellular adhesion molecule 1 and P- and E-selectin), angiogenesis via vascular endothelial growth factor, the synthesis of proinflammatory molecules (IL-1, IL-6, IL-8, and nuclear factor  $\kappa\beta$ ), and keratinocyte hyperproliferation via vasoactive intestinal peptide.<sup>35</sup>

A role for TNF- $\alpha$  in psoriasis treatment was serendipitously discovered in a trial for Crohn disease in which infliximab, a mouse-human IgG1 anti-TNF- $\alpha$  monoclonal antibody, was observed to clear psoriatic plaques in a patient with both Crohn disease and psoriasis.<sup>36</sup> Immunotherapies that target TNF- $\alpha$ , including infliximab, etanercept, and adalimumab, demonstrate notable



efficacy in the treatment of psoriasis.<sup>37-39</sup> Tumor necrosis factor  $\alpha$  is regarded as the driver of the inflammatory cycle of psoriasis due to its numerous modes of production, capability to amplify other proinflammatory signals, and the efficacy and rapidity with which it produces clinical improvements in psoriasis.

### IL-23/T<sub>H</sub>17 Axis

A new distinct population of helper T cells has been shown to play an important role in psoriasis. These cells develop with the help of IL-23 (secreted by dermal DCs) and subsequently secrete cytokines such as IL-17; they are, therefore, named T<sub>H</sub>17 cells. CD161 is considered a surface marker for these cells.<sup>40</sup> Strong evidence for this IL-23/T<sub>H</sub>17 axis has been shown in mouse and human models as well as in genetic studies.

IL-23 is a cytokine that shares the p40 subunit with IL-12 and has been linked to autoimmune diseases in both mice and humans.<sup>3</sup> It is required for optimal development of T<sub>H</sub>17 cells<sup>41</sup> from a committed CD4<sup>+</sup> T-cell population after exposure to transforming growth factor  $\beta$ 1 in combination with other proinflammatory cytokines.<sup>42,43</sup> IL-23 messenger RNA is produced at higher levels in inflammatory psoriatic skin lesions versus uninvolved skin,<sup>44</sup> and intradermal IL-23 injections in mice produced lesions resembling psoriasis macroscopically and microscopically.<sup>45</sup> Furthermore, several systemic therapies have been shown to modulate IL-23 levels and correlate with clinical benefit.<sup>3</sup> Alterations in the gene for the IL-23 receptor have been shown to be protective for psoriasis,<sup>46-48</sup> and the gene coding for the p40 subunit is associated with psoriasis.<sup>46,47</sup>

Type 17 helper T cells produce a number of cytokines, such as IL-22, IL-17A, IL-17F, and IL-26; the latter 3 are considered to be specific to this lineage.<sup>42</sup> IL-22 acts on outer body barrier tissues, such as the skin, and has antimicrobial activity. Blocking the activity of IL-22 in mice prevented the development of skin lesions,<sup>49</sup> and psoriasis patients have elevated levels of IL-22 in the skin and blood.<sup>50,51</sup> The IL-17 cytokines induce the expression of proinflammatory cytokines, colony-stimulating factors, and chemokines, and they recruit, mobilize, and activate neutrophils.<sup>52</sup> IL-17 messenger RNA was found in lesional psoriatic skin but not unaffected skin,<sup>53</sup> and cells isolated from the dermis of psoriatic skin have been shown to produce IL-17.<sup>54</sup> IL-17A is not elevated in the serum of psoriatic patients (unlike other autoimmune diseases),<sup>55</sup> and it is, therefore, thought that T<sub>H</sub>17 cells and IL-17A production are localized to the affected psoriatic skin. Consistent with this concept is the finding that treatments such as cyclosporin A and anti-TNF agents decrease proinflammatory cytokines in lesional skin but not in the periphery.<sup>56-58</sup> These cytokines released by T<sub>H</sub>17 cells in addition to those released by T<sub>H</sub>1 cells act on keratinocytes and produce epidermal hyperproliferation, acanthosis, and hyperparakeratosis characteristic of psoriasis.<sup>3</sup>

New therapies have been developed to target the IL-23/T<sub>H</sub>17 axis. Ustekinumab is approved for moderate to severe plaque psoriasis. This treatment's effect may be sustained for up to 3 years, it is generally well tolerated, and it may be useful for patients refractory to anti-TNF therapy such as etanercept.<sup>59</sup> Briakinumab, another blocker of IL-12 and IL-23, was studied in phase 3 clinical trials, but its development was discontinued due to safety concerns.<sup>60</sup> Newer drugs targeting the IL-23/T<sub>H</sub>17 axis include secukinumab, ixekizumab, brodalumab, guselkumab, and tildrakizumab.

### Genetic Basis of Psoriasis

Psoriasis is a disease of overactive immunity in genetically susceptible individuals. Because patients exhibit varying skin phenotypes, extracutaneous manifestations, and disease courses, multiple genes resulting from linkage disequilibrium are believed to be involved in the pathogenesis of psoriasis. A decade of genome-wide linkage scans have established that PSORS1 is the strongest susceptibility locus demonstrable through family linkage studies; PSORS1 is responsible for up to 50% of the genetic component of psoriasis.<sup>61</sup> More recently, HLA-Cw6 has received the most attention as a candidate gene of the PSORS1 susceptibility locus on the MHC class I region on chromosome 6p21.3.<sup>62</sup> This gene may function in antigen presentation via MHC class I, which aids in the activation of the overactive T cells characteristic of psoriatic inflammation.

Studies involving the IL-23/T<sub>H</sub>17 axis have shown genetics to play a role. Individuals may be protected from psoriasis with a nonsynonymous nucleotide substitution in the IL23R gene,<sup>47-49</sup> and certain haplotypes of the IL23R gene are associated with the disease<sup>47,49</sup> in addition to other autoimmune conditions.

Genomic scans have shown additional susceptibility loci for psoriasis on chromosomes 1q21, 3q21, 4q32-35, 16q12, and 17q25. Two regions on chromosome 17q were recently localized via mapping, which demonstrated a 6 megabase pairs separation, thereby indicating independent linkage factors. Genes *SLC9A3R1* and *NAT9* are present in the first region, while *RAPTOR* is demonstrated in the second region.<sup>63</sup> *SLC9A3R1* and *NAT9* are players that regulate signal transduction, the immunologic synapse, and T-cell growth. *RAPTOR* is involved in T-cell function and growth pathways. Using these genes as an example, we can predict that the alterations of regulatory genes, even those yet undetermined, can enhance T-cell proliferation and inflammation manifested in psoriasis.

### Conclusion

Psoriasis is a complex disease whereby multiple exogenous and endogenous stimuli incite already heightened innate immune responses in genetically predetermined individuals. The disease process is a result of a network of cell types, including T cells, DCs, and keratinocytes that, with the

production of cytokines, generate a chronic inflammatory state. Our understanding of these cellular interactions and cytokines originates from developments, some meticulously planned, others serendipitous, in the fields of immunology, cell and molecular biology, and genetics. Such progress has fostered the creation of targeted immune therapy that has demonstrated remarkable efficacy in psoriasis treatment. Further study of the underlying pathophysiology of psoriasis may provide additional targets for therapy.

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