Psoriasis takes center stage in immune-mediated diseases

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Psoriasis has long been considered a banal disease confined to the skin. Early researchers focused on the impressive epidermal proliferation seen in this disease, believing that the root cause was a defect in the epidermis. However, in the past 20 years, the focus has shifted dramatically away from the epidermal surface toward the immune system’s role in psoriasis. This change was sparked by the 1979 discovery that cyclosporine, a drug that inhibits T-cell activation and cytokine release, cleared concurrent psoriasis in a patient with rheumatoid arthritis (1).

Additional strong evidence linking the immune system to psoriasis comes from the fact that psoriasis is associated with the inheritance of certain major histocompatibility complex (MHC) antigens. Furthermore, immunohistochemical analysis of psoriatic lesions has isolated activated T cells within the lesions. This evidence has led current investigators to believe that immune abnormalities are at the heart of this disease and to aim toward defining them. Psoriasis is now considered to be a systemic disease of immune dysfunction that just happens to be visible on the skin, much like the immune abnormalities of rheumatoid arthritis (RA) that show up in joints, and those of Crohn’s disease, in the bowel. Evidence supports the central role that psoriasis plays in diseases of the immune system and that drugs currently used for psoriasis and those under development may have a role in the treatment of other immune-mediated diseases, including cancers and graft-versus-host disease (GVHD) after bone marrow transplantation.

EPIDEMIOLOGIC AND CLINICAL FINDINGS

Psoriasis is a common disease that affects up to 2% of the population in Western countries (2). Based on epidemiologic and clinical studies, the peak onset of psoriasis is between 20 and 35 years of age, and 70% to 90% of patients manifest the disease before reaching 40 years of age. However, <10% of patients present with lesions during childhood. Psoriasis has been divided into 2 subtypes, much like diabetes mellitus, based on the age of onset: type I psoriasis, which typically presents prior to age 40, and type II psoriasis, which occurs after age 50. Immunogenetic distinctions between the 2 types will be discussed later.

The 3 cardinal features of psoriasis are scaling, erythema, and induration. The characteristic silvery scale reflects the increased proliferation and turnover of keratinocytes and is the pathogenic process that differentiates psoriasis from other common inflammatory skin diseases such as eczema. Erythema and induration reflect the inflammatory infiltrate of T lymphocytes, monocytes, and neutrophils in psoriatic lesions (3). A classic feature of psoriasis is demonstrated by scratching the lesion surface lightly with a fingernail or tongue depressor to elicit fine pinpoint bleeding within seconds. This is the Auspitz sign, which is due to enlarged and tortuous capillaries close to the skin surface. These capillaries not only reflect the inflammation going on within the plaque, but also impart the characteristic red hue to the lesions.
Although these features comprise the cutaneous manifestations of psoriasis, the disease can present in a number of phenotypically distinct ways (4, 5). Morphological variants include discoid plaque psoriasis, elephantine psoriasis, erythrodermic psoriasis, flexural psoriasis, guttate psoriasis, palmar-plantar psoriasis, and pustular psoriasis. Chronic plaque psoriasis accounts for 90% of the cases and consists of localized disk-shaped plaques, usually on the elbows, knees, and scalp, that remain stable throughout the history of the disease (Figure 1). Other classic areas of involvement include the face, genital regions, and intertriginous folds. In most cases, the distribution of lesions is highly symmetrical, although trauma or scratching can modify the symmetry. Flexural psoriasis is characterized by plaques in body folds, including the buttocks, axillae, groin, breasts, ears, and glans penis. It is seen most in the skin folds of obese patients, frequently in association with candidiasis. Elephantine psoriasis describes the variant of large, thick plaques >15 cm in diameter that may be found on the lumbosacral regions and legs of patients with long-standing disease. Guttate psoriasis is characterized by guttate lesions, or papules, between 0.1 cm and 1.0 cm in diameter, commonly seen after streptococcal infections in young patients. In palmar-plantar psoriasis, the palms and soles may be involved as part of a generalized eruption, or they may be the only manifestation of the disease (Figure 2). Generalized pustular psoriasis is a rare but serious and sometimes fatal disease. Numerous tiny, sterile pustules evolve from an erythematous base and coalesce into lakes of pus. Erythrodermic psoriasis is a severe and highly unstable disease (Figure 3) that usually covers the entire body surface and is triggered by infections, inappropriate systemic glucocorticoid use, burns incurred during phototherapy, or by abrupt discontinuation of methotrexate therapy. Psoriasis also manifests itself in the nails and in the joints (Figure 4). Pitting is the best known and probably most frequent nail abnormality. Others include separation of the nail from the nail bed (onycholysis), subungual crusting from hyperkeratosis, and nail fragmentation and crumbling. Psoriatic arthritis is a distinct form of arthritis that is rheumatoid factor negative. It affects 5% to 8% of psoriatics. The prevalence is higher among patients with more severe cutaneous disease.

Psoriasis is a disease of wide clinical variability. With the new understanding that it is a systemic, immune-mediated disease, psoriasis needs to be recognized as a spectrum of diseases, in the same light as lupus erythematosus (LE), another immune-mediated disease. Lupus erythematosus can range from mild-to-moderate disease confined to the skin, to a devastating systemic disease involving the heart, kidneys, and central nervous system. Similarly, psoriasis can range from well-controlled, stable plaques involving <10% of the body surface, to erythrodermic and pustular forms with joint and nail deformities that can cause significant morbidity and even death.

IMMUNOPATHOLOGY

Systemic immunological abnormalities

Early clues that psoriasis is a disease of the immune system came from the observance of systemic alterations. Raised serum levels of immunoglobulin A, E, and G have been demonstrated, as well as circulating immune complexes (6). Psoriasis patients have variations in suppressor-helper T-cell ratios and in granulocyte and monocyte function (7). Elevated circulating soluble interleukin (IL)-2 receptor, neopterin, and soluble adhesion molecules (intercellular adhesion molecule [ICAM-1], vascular cell adhesion molecule [VCAM-1], and E-selectin) also have been observed (8) (Groves RW, Barker JN, Haskard...
DO, Bird C, MacDonald DM: Circulating cytokines and soluble adhesion molecules in widespread inflammatory skin disease. *Brit J Derm* 1992;127:428 [abstract]). Whether these abnormalities are secondary to the process occurring within psoriatic plaques or are more central to the pathogenic process is unknown.

**Local immunological abnormalities**

Current theory on the immunopathogenesis of psoriasis has at its center an interaction between antigen-presenting cells (APCs) and T lymphocytes (9). Lesional APCs process an antigen and present it on their surface through MHC class I or II molecules. This antigen causes the T cell to interact with the APC, and the interaction triggers an immune response through the activation of T cells and subsequent release of lymphokines. This immunologic activation injures the epidermis, leading to hyperproliferation and disordered differentiation. It also activates the keratinocytes themselves, causing them to release cytokines that perpetuate the inflammation and the cell-mediated immune response. Thus, the current model no longer considers the epidermal changes themselves to be primary causative factors of psoriasis, but instead to be a response to underlying immunologic injury.

Although the antigen triggering the APC–T cell interaction in psoriasis has not been identified, there are several current theories. One thought is that streptococcal proteins or toxins may be the trigger, because a sizable fraction of adolescent patients with acute guttate psoriasis have as a precipitating factor an antecedent streptococcal infection (10). Cross-reactivity exists between streptococcal antigens and antigens present in the skin (11), and monoclonal antibodies raised to group A streptococci cross-react with various keratinocyte proteins (12). This leads to the “molecular mimicry” theory of autoimmunity in psoriasis, where T lymphocytes responding to a peptide fragment of an infectious agent in the skin see a host protein as homologous and react to self as well as to the infectious agent. The fact that most patients have no preceding streptococcal infection lends more weight to the theory that autoantigens alone are triggering the APC–T cell interaction in genetically susceptible patients. Another theory is that in patients with explosive acute guttate psoriasis, streptococcal superantigens stimulate a polyclonal T-cell response (13). Superantigens stimulate T cells by binding to distinct V? regions of the T-cell receptor. However, another study found that single T-cell receptor sequences from lesional skin accounted for up to 56% of a T-cell receptor family, and these were absent in V? T-cell receptors amplified from normal skin (14). These results are evidence against a superantigen-driven T-cell stimulation and suggest instead an antigen-specific immune response.

Although the antigen triggering the immune response in psoriasis is unclear, there are data to support the APC–T cell interaction as instigating the immune response in psoriatic lesions. In normal human skin, APCs are represented by Langerhans’ cells that are MHC II positive (HLA-DR+). Baadsgaard et al have shown that the activated APCs driving T cells are actually non-Langerhans’ CD1a+ DR+ macrophage-like cells (15). The APCs have been shown to induce T lymphocytes to produce a range of cytokines that may modulate the psoriatic process (7). Morganroth et al have shown that a second type of APC is present within the lesional dermis (16). These activated APCs, termed dermal dendrocytes, are located high in the papillary dermis around blood vessels and are factor XIIIa positive. These 2 types of activated APCs are responsible for the heightened APC activity found in the lesions and support the role of the APC presenting lesional T cells with an antigen to cause T-cell activation.
Further data support the role of T cells in psoriasis. Histologic studies of skin biopsies of early psoriatic skin lesions demonstrate CD4$^+$ and CD8$^+$ T lymphocytes in both the dermis and the epidermis (17). Their influx precedes that of neutrophils and precedes the epidermal hyperproliferation characteristic of psoriasis (18). Interleukin-2 receptor positivity on lesional T cells is evidence that these T cells are activated and proliferating and thus have the potential to cause disease (9). Lesional T cells also have been shown to produce the lymphokines of activated T-1 cells: IL-2 and interferon (IFN-)\(\gamma\) (19). The injection of IL-2 or IFN-\(\gamma\) into psoriasis patients has resulted in disease flares in significant numbers of patients (20). In addition, lymphokine-containing supernatants prepared from T cells cloned from psoriatic lesions caused the proliferation of uninvolved psoriatic keratinocytes when they were added to the keratinocytes in vitro. This keratinocyte growth was inhibited by adding antibodies to IFN-\(\gamma\) to the supernatants prior to adding to the keratinocyte cultures (21). These data implicate IFN-\(\gamma\) release from T-1 type T cells within the lesions as a critical factor in the disease pathogenesis. They also link immune system activation to the epidermal hyperproliferation seen in psoriasis. Current research aims to more precisely define the role of CD4$^+$ and CD8$^+$ T lymphocytes. Other goals include finding therapies targeted at inhibiting cytokine release and reducing the activity of the infiltrating lymphocytic cells.

**IMMUNOTHERAPY**

Since the serendipitous finding of Mueller and Hermann that cyclosporine cleared psoriasis (1), immunosuppressive drugs have been studied for, and used to treat, psoriasis. Based on the above discussion of the activated APC–T cell complex in psoriatic lesions, drugs that suppress any part of this complex and its subsequent release of lymphokines should clear psoriatic lesions. Cyclosporine impairs the signal transduction mechanism within T cells and thereby blocks T-cell growth and IFN-\(\gamma\) release. Ellis et al have shown that cyclosporine produces rapid resolution of psoriatic lesions when given systemically (22). It is also effective intralesionally, but not topically, most likely because of lack of penetration through epidermal structures (23). Tacrolimus, ascomycin, and rapamycin have the same mechanism of action as cyclosporine and also have shown to be beneficial in psoriasis. Methotrexate currently is the “gold standard” systemic therapy for psoriasis, having been used for over 30 years. It was originally thought to work in psoriasis through inhibiting DNA synthesis in the rapidly dividing cells of the hyperproliferating epidermis. Now that immunologic activation is believed to cause psoriasis, methotrexate is thought to clear the lesions through its immunosuppressive effects. Methotrexate promotes the accumulation of extracellular adenosine, which, via A2 receptors, causes immunosuppression (24). Sulfasalazine appears to act via a similar mechanism (25). Other agents commonly used to treat psoriasis, such as steroids, retinoids, and vitamin D$_3$ derivatives, block T-cell transcription of lymphokine genes (26, 27). Ultraviolet radiation works by inducing the formation of IL-10 which is believed to be a natural suppressant of the cutaneous inflammatory response (28).

Current research in psoriasis immunotherapy is testing antibodies to various lymphokines and CD4$^+$ cell receptors, as well as peptide vaccines. Multiple clinical studies using immune-modulating drugs, including CTLA4IG, fusion protein LFA-3/IgG$_1$, anti–IL-8, and IL-10, are currently under way at the Baylor Psoriasis Research Unit. The common mechanism to all these therapeutic approaches is immunosuppression, which may have important applications for other immune-mediated diseases. Because psoriasis manifests so
visibly on the skin, the therapeutic response can be monitored easily. In addition, as most psoriasis subjects are relatively healthy, they represent a good model in which to study the effects of immunosuppressive therapy.

OTHER IMMUNE-MEDIATED DISEASES WITH CUTANEOUS MANIFESTATIONS

Lupus erythematosus

Psoriasis is one of several immune-mediated diseases that affect the skin (29, 30). Lupus erythematosus is a systemic disease that, like psoriasis, has a spectrum of disease manifestations. Discoid LE consists primarily of lesions localized to the skin, with systemic involvement in only 5% to 10% of patients. The lesions are most often on the face, scalp, or external ears and consist of erythematous papules or plaques with a thick adherent scale that occludes hair follicles. Long-standing lesions develop atrophy, scarring, and hypopigmentation with erythematous raised borders at the periphery. Subacute cutaneous LE is a more serious form of cutaneous LE, characterized by a widespread photosensitive nonscarring eruption. It is often papulosquamous and closely resembles psoriasis (Figure 5). About half of these patients have systemic LE, but severe renal or central nervous system involvement is uncommon. Acute cutaneous LE often occurs with multisystem disease and is characterized by erythema of the nose and malar prominences and a “butterfly” distribution. It can also show widespread indurated erythema, especially on the extensor surfaces of the extremities and upper chest.

The tissue damage of LE is caused by production of numerous diverse autoantibodies to nuclear and cytoplasmic cell components and by immune complexes. Immunofluorescent microscopy of the skin lesions shows deposition of immunoglobulin and complement along the dermal-epidermal junction. In subacute cutaneous LE, antibodies to Ro/SSA antigens have been found. There is thought to be a clonal selection of B cells secreting antibodies to autoantigens. In most murine lupus models, T-cell help is critical to the development of full-blown disease. CD4+, CD8+, and CD4+CD8+ T cells all help autoantibody production in murine and human LE.

Rheumatoid arthritis

Rheumatoid arthritis is characterized by a persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The synovial inflammation causes cartilage destruction and bone erosions with subsequent changes in joint integrity. Rheumatoid factor is positive in 90% of cases. Rheumatoid arthritis is identical to 1 of the 5 forms of psoriatic arthritis, except for rheumatoid factor being negative in psoriatic joint disease. Proximal interphalangeal and metacarpophalangeal joints of the hands, wrists, ankles, and knees are commonly involved in a symmetric fashion in RA. The distal interphalangeal joints are rarely involved. Joints are red, swollen, tender, and limited in motion. Characteristic deformities of the hands include ulnar deviation of the digits and swan-neck and boutonniere deformities. Extra-articular manifestations include rheumatoid nodules, weakness and atrophy of skeletal muscle, pleuropulmonary manifestations, splenomegaly, neutropenia, osteoporosis, and rheumatoid vasculitis. When rheumatoid vasculitis affects the skin, it presents as crops of small brown spots in the nail beds, nail folds, and digital pulp. Larger ischemic skin ulcers also may develop, especially in the
lower extremities.

Rheumatoid arthritis is an immune disease of both activated T cells and B cells. The earliest event in the synovitis appears to be a nonspecific inflammatory response initiated by an unknown stimulus. Subsequently, a response of CD4+ T cells is induced that amplifies and perpetuates the inflammation. The presence of activated T cells is thought to induce polyclonal B-cell stimulation and the local production of rheumatoid factor. The activity of cytokines produced from active lymphocytes, macrophages, and fibroblasts causes synovial tissue inflammation, synovial fluid inflammation, synovial proliferation, cartilage and bone damage, and even the systemic manifestations of RA. Thus, the inflammatory cascade in RA is similar to that of psoriasis, with the synovium “substituted” for the skin. As tissue damage in RA occurs, additional autoantigens are revealed, and further clones of CD4+ T cells are recruited to the inflammatory site. As a result of persistent exposure to the inflammatory milieu, the function of synovial fibroblasts is altered so that they acquire destructive potential that no longer requires stimulation from T cells or macrophages, and damage progresses without control. Drugs used in therapy for RA, as well as for LE, include steroids, azathioprine, sulfasalazine, and cyclosporine. These are often first-line drugs for patients with psoriasis.

**Graft-versus-host disease**

In GVHD, the histoincompatible, immunocompetent donor bone marrow cells attack the tissues of the host. Even when the donor and host are completely matched at the HLA loci, there are differences at minor histocompatibility loci. Donor CD4+ and CD8+ and natural killer cells participate in the immune response against host antigens. The activated T cells and natural killer cells produce IFN-γ and tumor necrosis factor (TNF)-α, which are thought to mediate the tissue destruction in acute GVHD that occurs within 3 months of transplantation. Interleukin-4 from activated T cells has been suggested as the primary mediator of chronic GVHD, which can evolve from acute GVHD or can arise de novo. Graft-versus-host disease is characterized by acute cutaneous changes ranging from maculopapular eruption to toxic epidermal necrolysis. Diarrhea and liver dysfunction also occur acutely. Chronic skin changes include lichenoid eruptions and changes identical to scleroderma. Psoralen plus ultraviolet A therapy, commonly used to treat psoriasis, frequently is of great value in treating patients with GVHD.

**Cutaneous T-cell lymphoma**

As the name implies, cutaneous T-cell lymphoma (CTCL) is a malignancy of helper T cells (CD4+) that first manifests in the skin. However, because the neoplastic process involves the entire lymphoreticular system, the lymph nodes and internal organs become involved in the course of the disease. Skin findings in mycosis fungoides, the primary form of CTCL, progress through various stages. Initially, lesions can vary from a nonspecific pruritic eruption or pruritus alone, to eczematous patches, psoriasis-like plaques, and “cigarette-paper” atrophic skin lesions with telangiectasia and mottled pigmentation (Figure 6). A number of patients have been referred to the Psoriasis Treatment Center at Baylor with a working diagnosis of psoriasis and have been shown on further evaluation to have CTCL. The disease then progresses through a patch stage, a plaque stage, and finally a tumor stage. In the early stages, the disease remains confined to the skin. Superficial lymphadenopathy may be detected in the plaque stage, and deep lymphadenopathy with visceral metastases to
the spleen, lungs, or gastrointestinal tract may occur during the tumor stage.

Cutaneous T-cell lymphoma is a malignancy of a single clone of CD4+ T cells that may originate from stimulation by an antigen, possibly from a mutation or a virus. The malignant cells express mature, activated T-helper cell markers: CD2, CD3, CD4, CD5, CD7, IL-2 receptor, and transferrin receptor. Initially, Langerhans’ cells carry antigens from the skin to peripheral lymph nodes. There they present the antigens to CD4+ T cells and convert them to cutaneous T cell lymphoma cells. These cells acquire cutaneous lymphoid antigen on their surface, which acts as a homing receptor directing them to the skin. The cellular growth environment of the epidermis is conducive to the malignant cells’ proliferation.

Agents currently used to treat CTCL include systemic retinoids and psoralen plus ultraviolet A therapy, which are both used as well for psoriasis patients.

**Acquired immunodeficiency syndrome**

Psoriasis can be the initial sign or one of the first signs of acquired immunodeficiency syndrome (AIDS). An explosive onset of psoriasis with erythroderma or pustular lesions should lead to the suspicion of AIDS. This association with the human immunodeficiency virus (HIV), one that dysregulates and destroys the human immune system, supports the hypothesis that psoriasis is an immune-mediated disease. Duvic suggests several hypotheses regarding HIV-associated psoriasis (31). One is that the immunodysregulation resulting from HIV infection may trigger psoriasis, especially if psoriasis is an autoimmune disease. Another is that the decreased cellular immunity may allow the emergence of opportunistic infectious organisms that could act as the antigens triggering psoriasis or could activate a latent retrovirus. Because HIV has been shown to infect the cutaneous Langerhans’ cells, Duvic also proposes that HIV may have a more direct causative role in psoriasis. The fact that zidovudine, a drug that reduces viral replication, is associated with a dramatic remission when given to patients with HIV-associated psoriasis supports the role of the virus in causing psoriasis (32). Acquired immunodeficiency syndrome provides an interesting model in which to study the role of the immune system and specific gene products in the pathogenesis of psoriasis and other immune diseases.

**IMMUNOGENETICS**

There is overwhelming evidence that psoriasis is a genetic disease. Family studies have shown that up to 30% of patients have an affected first-degree relative, and monozygotic twins show a 72% concordance rate (33). Disease association studies link psoriasis to a number of HLA antigens, which not only suggests immune system involvement in the pathogenesis, but makes a case for autoimmunity. The strongest association appears to be with HLA-Cw6. Patients with type I psoriasis are much more likely to possess the Cw6 antigen and have a first-degree relative with the disease than are patients with type II. The 70% concordance rate for monozygotic twins is evidence that environmental factors also play a role in triggering the disease.

A consensus on the genetic locus for psoriasis susceptibility has yet to be determined. The National Psoriasis Gene Tissue Bank (NPGTB) at Baylor was created to help find the genes involved in psoriasis. It provides a tissue bank resource of immortalized cells derived from hundreds of members of psoriatic families for gene study by all interested geneticists. Initial families enrolled in the NPGTB were required to have had at least 3 generations of living
family members with psoriasis, of which at least a pair of siblings was affected and at least 2 living members were unaffected. Current studies are enrolling 250 sibling pairs with psoriasis and 1 living parent.

Using genetic linkage analysis strategy in conjunction with The University of Texas Southwestern Medical School, analysis of 8 of our original families in the NPGTB revealed the first published psoriasis locus, at the distal end of chromosome 17q (34). Evaluation of 7 Irish families revealed another genetic linkage was found at 4q (35). Subsequently, another study failed to find association between the disease and chromosomes 17q or 4q (36). Most recently, family studies have produced evidence for linkage to 2 new foci, 16q and 20p, as well as confirmed the previous findings of 17q and HLAB and C linkages (37). The newly discovered gene locus associated with Crohn’s disease, a disease also thought to have an immune basis, is on 16q, very close to the one for psoriasis, thus implying that the immune abnormalities in these 2 diseases may have a common genetic basis.

The ultimate treatment for psoriasis and other autoimmune and inflammatory diseases is gene-based therapy. Treatment of RA using local gene transfer to joints is being studied. Systemic delivery of proteins therapeutic for RA, such as inhibitors of TNF-α and IL-1, also are being considered using genetically modified cells. As vectors to transfer the genes improve and identification of appropriate therapeutic proteins progresses, the prospects for gene therapy for psoriasis become more promising, making a “gene patch” for psoriasis a fascinating therapeutic possibility.

SUMMARY

Now considered to be a systemic, immune-mediated condition, psoriasis represents a spectrum of diseases that have their primary manifestations on the skin. Systemic immunological abnormalities in psoriasis are important clues, but studies of the local inflammatory milieu provide ample evidence to support the APC–T cell interaction as the backbone of the immune response. Activated APCs have been characterized in the lesions, as have activated CD4+ and CD8+ lymphocytes. The antigen triggering the immune response remains unclear, but cross-reactivity between streptococcal antigens and skin antigens may play a role, or streptococcal antigens may be acting as superantigens to trigger the response.

The mainstay of psoriasis treatment is immunosuppressive therapy. Current research in psoriasis immunotherapy involves testing the efficacy of antibodies to lymphokines and T-lymphocyte receptors, as well as peptide vaccines. Because psoriasis has visible manifestations of disease, it provides an excellent model in which to study various advances in immunotherapy. Interaction with our colleagues at BUMC in gastroenterology, rheumatology, transplantation, oncology, and the newly established Baylor Institute for Immunology Research will enable us to further define new immunotherapeutic agents of potential benefit not only to psoriasis, but to other disorders of the immune system, such as LE, RA, GVHD, CTCL, and cancer.

Finally, the results of our NPGTB endeavors continue to further establish the genetic loci involved in psoriasis. Ultimately, this may lead to gene therapy, not only for psoriasis, but also for other diseases associated with dysfunction of the immune system.
References

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Figure 4

Figure 5

Figure 6