Psoriasis: further evidence of a key role for leukocytes.

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Editorial

Psoriasis is a common inflammatory disease of the skin marked by excessive scaling associated with inflammation, affecting 1–2% of the American population (1). The severity of psoriasis runs the gamut from relatively minor disease consisting of 1 or 2 small plaques to life-threatening erythrodermic psoriasis covering the entire cutaneous surface. In addition, $\sim$ 5% of people with psoriasis will develop psoriatic arthritis. This is frequently mild but can be severe and mutilating. Furthermore, pustular variants exist and some can be life-threatening. The relationship of pustular psoriasis to common plaque-type psoriasis, known as psoriasis vulgaris, is complex and the subject of disagreements. Thus, this commentary will relate primarily to psoriasis vulgaris.

The pathogenesis of psoriasis has been obscure until only recently. Much discussion and debate has taken place over whether the primary cause of the disorder relates to abnormalities of epidermal keratinocytes (KC) or, rather, from a disorder of inflammatory cells. Of course, these two possibilities are not mutually exclusive. The dramatic increase in epidermal proliferation that occurs in psoriasis has led many investigators to focus on potential abnormalities in the KC. Defects in second messengers, polyamines, proteases, cytokines and arachidonic acid metabolism have been described. However, whether such abnormalities are primary or secondary has never been established.

Recently, several lines of evidence have suggested involvement of the immune system. Many agents effective in the therapy of psoriasis are immunosuppressive. Methotrexate, ultraviolet-B radiation, psoralen photochemotherapy, corticosteroids, cyclosporine and anthralin all inhibit aspects of an immune response. The finding of CD4+ and CD8+ lymphocytes at sites of psoriasis has led many authors to hypothesize that psoriasis is a T lymphocyte-mediated disease directed against unknown autoantigens. T cell clones have been isolated from psoriatic lesions (2–4) and supernatants conditioned by some of these clones stimulate KC proliferation (2, 3). Since psoriasis may be triggered or exacerbated by infection with group A β-hemolytic streptococci, a role for bacterial superantigens and/or cross-reactivity between bacterial antigen(s) and a KC protein, such as keratin, has been proposed (5). Indeed, it was reported that when clinically uninvolved skin from psoriasis patients was grafted onto severe combined immunodeficient (SCID) mice and injected with superantigen exfoliative toxin, some histologic and immunohistologic features of psoriasis were induced (6). The possibility that passenger leukocytes could be involved in this finding was not addressed. Furthermore, when patient's superantigen-stimulated peripheral blood mononuclear cells were administered intraperitoneally, homing of T cells to graft epidermis was observed (6). An intriguing observation is that individuals with HIV infection often have exacerbations of psoriasis or, sometimes, the new onset of psoriasis, although psoriasis in these individuals often has atypical features. This may not appear to fit well with the idea that psoriasis is an autoimmune disease. However, other autoimmune diseases, such as idiopathic thrombocytopenic purpura, occur in HIV infection and some aspects of immune responses appear exaggerated in the setting of HIV infection. Recently, a clinical study provided fairly direct evidence for an involvement of T cells in the pathogenesis of psoriasis (7). Administration of a fusion protein combining fragments of diptheria toxin and human interleukin-2 (IL-2) to psoriasis patients led to marked improvement in the majority of persons treated. Since this agent targets activated T cells expressing IL-2 receptors, this observation appears to directly demonstrate involvement of activated T cells in the pathogenesis of the disease. However, it does not eliminate the possibility that an abnormality of KC also plays a role in the development of psoriasis.

In this issue of *The Journal*, a report by Wrone-Smith and Nickoloff provides additional data implicating blood-borne cells in the pathogenesis of psoriasis (8). Uninvolved skin from patients with psoriasis or from healthy individuals with no skin disease was transplanted onto SCID mice. Then, autologous blood-derived cells obtained from heparinized blood by density centrifugation were injected intradermally into the xenograft. With skin from psoriasis patients the cells were preexposed to IL-2, staphylococcal enterotoxin B and staphylococcal enterotoxin C2 before injection, plaques developed that were characterized by flaking of the skin and histologic changes highly suggestive of psoriasis. Immunoperoxidase staining demonstrated that both epidermal and dermal compartments contained $CD3^+$, $CD4^+$ and $CD8^+$ T cells. The epidermis became diffusely positive for HLA-DR, (β1 integrin and keratin 16. These findings, as well as some others that were described, are similar to what is seen in psoriasis in situ. These changes were not observed in normal skin injected with activated cells; however, only two such specimens were evaluated. Although the data was not shown, it was stated that 1 of 4 normal skin grafts injected with allogeneic cells from a psoriatic patient also developed psoriasis. As a whole, these experiments strengthened the case for involvement of circulating leukocytes in psoriasis. The authors have used the term "immunocyte" to describe the cells they believe are responsible for this effect. Since these cells were isolated by Ficoll-Hypaque, the majority would be lymphocytes. However, presumably there would also be some other types of mononuclear cells present. Because of the histologic findings of $CD4^+$ and $CD8^+$ T cells in the grafts exhibiting psoriasis-like changes and the previous isolation of clonal populations of T cells from psoriatic lesions, the authors conclude that T cells are responsible for production of disease.

These findings demonstrate fairly directly that circulating elements are involved in the pathogenesis of psoriasis and, thus, complement and confirm earlier data as discussed above. The induction of psoriasis in a SCID mouse-human skin chimeric model is very elegant and will be helpful in further dissecting the mechanisms involved in the development of psoriasis. However, these results in themselves do not completely eliminate the possibility that a defect in KC also plays a role in the development of psoriasis nor do they conclusively establish that the process represents autoimmunity. Nonetheless, this

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paper is a welcome addition to the evidence implicating elements of the immune system in the development of psoriasis.

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