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Immunological mechanisms involved in psoriasis

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Introduction

Psoriasis is a common cutaneous disease affecting 2% of the population. However, there are global variations in incidence in that it is rare in Native Americans and commoner in Northern Europe. The disease is characterized by two main histological features namely epidermal hyperproliferation coupled with an inflammatory infiltrate. Until about 15 years ago experimental dermatologists researching the pathogenesis of psoriasis focused the majority of their attention on the hyperproliferative epidermal compartment and paid scant regard to the inflammatory infiltrate. Indeed, if one had questioned dermatologists in the 1970s as to whether immunological mechanisms played an integral role in the pathogenesis of psoriasis, it is probable that the overwhelming majority would have answered negatively. As a result of pioneering work performed in Europe and as a consequence of the proven efficacy of the selective T cell immunosuppressant, cyclosporine, it is now established that psoriasis is indeed immunologically mediated.

This article delineates the various immunological mechanisms believed to be involved in the psoriatic process, debates the relative impact of the contributions each pathway brings to the production of the psoriatic phenotype, and describes how newer immunoregulatory approaches to this disease have helped strengthen the immune-mediation hypothesis.

Genetics

The evidence that psoriasis is a genetically determined disease is considerable. Approximately one-third of affected individuals have at least one first-degree relative with psoriasis and epidemiological studies from Northern Europe have determined that relatives of psoriatics are three times more likely to suffer from

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the disease than are comparable members of the general population [53, 65]. A concordance rate of approximately 70% for monozygotic twins and 15%–30% for dizygotes seems to indicate an autosomal dominant inheritance [19, 33, 65, 101], although the comparatively low concordance rate in monozygotes implies that environmental factors play a key role in the expression of the psoriatic phenotype. Work by Hensler and Christophers [54] categorized psoriatics into two types dependent on age at onset of the disease. In the first type (type I), there is a strong association with the class I MHC antigen HLA-Cw6 which occurs in 85% of individuals in this group. In the second group (type II) characterized by late age of onset, (60 years old on average) there is a low association with HLA-Cw6. HLA-Cw6 is in linkage disequilibrium with HLA-B13, Bw17, and Bw37 and these three antigens are also more prevalent in psoriatics [89, 101, 103]. The association of psoriasis with HLA antigens provides incidental evidence for the importance of an autoimmune-based concept, particularly the high prevalence of HLA-DR7 and the strong correlation with HLA-B27 in those subjects who have psoriatic sacro-ileitis [3, 40, 106]. Ozawa et al. [83] was unable to find a strong relationship between HLA-Cw6 and psoriasis but did observe that in control, non-psoriatic subjects a restriction fragment length polymorphism (RFLP) in the 1-alpha-2 domain of Cw6 was lacking, thereby implying that its presence provided an increased suseptibility to psoriasis.

The increased incidence of the class I MHC molecule HLA-Cw6 or lack of an important RFLP for Cw6 in normal subjects would indicate an importance of $CD8^+$ T cells in psoriasis as these "suppressor" cells only bind and activate in the context of MHC class I. On these grounds it is possible that failure of CD8 suppression of CD4-driven activation may account for the persistence of psoriatic plaques [48]. Unfortunately, it is unlikely to be as simple as this postulation and most probably the role of class II MHC alleles, such as DR7, in recognition of specific antigens is as necessary as class I MHC restriction. Thus, inheritance is probably not one of a single "psoriasis gene" but likely is multifactorial with environmental factors such as infection holding a controlling interest in phenotypic expression of this genetic predisposition.

The role of T lymphocytes

Evidence exists for an impaired cell-mediated immunity in psoriasis [38]. Delayed hypersensitivity to standard prick-test antigens and streptococcal antigen is reduced in psoriatics, and intradermal antigen testing to purified protein derivative (PPD) is characterized by slow resolution of the reaction [30, 60, 70]. In vitro there is an inability of T cells from psoriatics to proliferate in response to concanavalin A [50]. Perhaps the most striking demonstration of an abnormality (perhaps genetic) in cellular T lymphocyte function in psoriatics are the reports of a cure of the disease following allogeneic bone marrow transplant [27]. This thesis is buttressed by the converse finding of transmission of psoriasis with allogeneic bone marrow transplant [36].

It was only with the advent of monoclonal antibodies that a rigorous investigation of the components of the dermal and epidermal inflammatory infiltrate in

psoriatic lesions could be performed. Until then it was known only that the T lymphocyte was a part of the infiltrate but subdivision into CD4, CD8, natural killer cells etc, could not be performed. In 1978 Bjerke et al. [15] demonstrated that the majority of the infiltrate was comprised of T cells of which $CD4^+$ cells formed the major part. Not until the work of Baker and colleagues [4, 100] was it apparent that the actual ratio of CD4:CD8 cells was important to both the genesis and resolution of a psoriatic plaque and that activation or HLA-DR expression of these subsets was also critical.

In normal skin there is a small yet significant epidermal traffic of T cells and these are mainly of the $CD4^+$ subset [18]. In active, evolving psoriasis of the guttate form there is an intraepidermal influx of activated DR^+ $CD4^+$ T cells, and the ratio of $CD4^+$:$CD8^+$ T cells is greater than that observed in peripheral blood of the same individuals [4, 100]. Indeed, the absolute numbers of total and $CD4^+$ T lymphocytes in the blood of psoriatics is lower than in normal subjects [5]. These numbers correlate with disease extent and may be a result of cutaneous sequestration. Spontaneous resolution of guttate psoriasis lesions is predated by an intraepidermal influx of DR^+ $CD8^+$ T cells coinciding with a decrease in DR^+ $CD4^+$ cells [4, 100]. The same phenomenon is observed during treatment of psoriatic plaques with psoralen ultraviolet A (PUVA) [10]. Indirect evidence for a role for activated $CD4^+$ T lymphocytes in psoriasis accrues from several sources. Psoriatic epidermal keratinocytes exhibit patchy expression of HLA-DR [4, 8], and although the extent of this keratinocyte HLA-DR expression is debatable, its presence probably indicates local production of gamma interferon (IFN-γ) [4, 8, 14, 41]. IFN-γ is produced solely by activated $CD4^+$ T cells and is the only cytokine capable of inducing the expression of HLA-DR [46, 78]. Other indirect evidence for the presence of activated $CD4^+$ T cells is detection of both IFN-γ mRNA and protein in psoriatic plaques [14] and keratinocyte expression of IFN-γ-inducible protein (IP-10) [42] and ICAM-1 [46]. Activation of $CD4^+$ T cells results in expression of the interleukin (IL)-2 receptor (IL-2R) and although there are no reports of IL-2 in psoriatic plaques there are increased levels of IL-2R in suction blister fluid [95].

Support for the importance of T lymphocytes in the induction and maintenance of psoriatic plaques comes from evidence derived from the efficacy in this disease of the relatively T cell-specific immunosuppressant cyclosporine. This evidence will be presented later in the chapter.

In the regrettable absence of a good animal model for psoriasis, researchers must utilize early stages of the disease itself for investigation. The Koebner phenomenon which is the ability of traumatized, uninvolved psoriatic skin to develop psoriasis is a useful model for the early events in the genesis of a psoriatic plaque. Koebnerization occurs in only 25% of psoriatics at any one time and is entirely dependent on disease activity [32]. In subjects who are Koebner positive there is evidence that the epidermal CD4:CD8 ratio in uninvolved skin is significantly higher than in those who are Koebner negative [7]. The increase in T cell subset ratio is mainly contributed to by a decrease in $CD8^+$ cells implying a removal of suppression and subsequent triggering of the response threshold.

Although difficult to place in the context of the pathogenesis of psoriasis, it is certain that humoral factors play a role. Stankler [92] made the salient observa-

tion that serum from patients recovering from active psoriasis had an inhibitory effect on the Koebner reaction and a healing action when injected into active lesions. This was contrasted to the non-inhibitory effect of serum from subjects with ongoing, active psoriasis.

The role of antigen-presenting cells

Psoriatic epidermis contains increased numbers of $CD1^-DR^+$ cells, whereas there is debate as to the number of $CD1^+DR^+$ Langerhans cells, with views varying from no difference from that found in normal or uninvolved psoriatic skin to increased or decreased numbers as compared to normal. The ability of psoriatic epidermal cell suspensions to stimulate autologous T cell activation and proliferation seems to be dependent on this $CD1^-DR^+$ subset [2]. Differing views exist as to the nature of these $CD1^-DR^+$ cells. They may be a heterogeneous group of macrophages and antigen-presenting cells [2] or, alternatively, immature Langerhans cells [6, 9]. Certainly the $CD1^-DR^+$ population is not specific for psoriasis but is found in other inflammatory dermatoses [9]. Alternatively, the CD1 surface antigen may be lost on activation of the Langerhans cell or in the presence of IFN-γ and the $CD1^-DR^+$ group may represent activation and heightened antigen-processing capacity of resident Langerhans cells.

The dermis, although admittedly a more difficult cutaneous compartment to study than epidermis, has received little attention as far as antigen-processing capabilities are concerned. Dermal Langerhans cells are increased in psoriatic relative to normal skin and are found clustered around the vessels of the dermal papillae [17]. This observation has been made in other inflammatory dermatoses such as allergic contact dermatitis and cutaneous T cell lymphoma [11, 68]. A recently described putative dermal antigen-presenting cell which resides in the upper papillary dermis and perivascular locale is the Factor XIIIA-positive dermal dendrocyte [52]. In psoriasis, the dermal dendrocytes are increased in number and appear to be activated by virtue of increased dendricity and DR positivity [20, 79]. These observations indicate a propensity for heightened dermal processing of antigen and possibly cytokine production in psoriasis.

The role of cytokines

Cytokines are small, cell-derived polypeptides which serve as intercellular chemical messengers. Initially believed to be secreted solely by lymphocytes and monocytes it is now recognized that virtually all cell types found within the skin are capable of producing these molecules. A most significant advance in our understanding of the cutaneous cytokine network came with the recognition that the keratinocyte is not merely an inactive, protective coating to the skin but is an active component of the skin immune system imbued with cytokine-secreting capacity [13]. The availability of sensitive assays, monoclonal antibodies and molecular techniques such as the polymerase chain reaction (PCR) have facilitated our ability to detect cytokines within the skin. Unfortunately, with the relentless

discovery of new cytokines comes the heightened complexity of understanding how they interact with one another to maintain a homeostatic cutaneous milieu or initiate and perpetuate a disease process such as psoriasis.

IL-1 with its ability to induce expression of endothelial adhesion molecules ICAM-1, ELAM-1, and VCAM-1 [47] and its capabilities of mononuclear cell chemotaxis and induction of keratinocyte proliferation would appear a good candidate for elevation in psoriasis [3]. Somewhat unexpectedly, activity of this interleukin in psoriasis is reduced as compared with normal or uninvolved psoriatic skin [23]. The observed reduction in IL-1 activity is a result of several compounding factors, namely reduced levels of IL-1α, the presence of a functionless form of IL-β (although protein levels are increased) and the appearance of an IL-1 inhibitor in psoriasis [23, 51]. The reduced levels of IL-1 activity in chronic plaque psoriasis may be attributable to consumption of IL-1 during evolution of the lesion and thus research directed at early, evolving psoriatic lesions could reveal increased IL-1 activity at this critical time.

IL-2 is produced by activated $CD4^+$ T cells and the presence of soluble IL-2R is indicative of activation. It is surprising that detection of this cytokine has not been reported in psoriatic skin. Suction blister assays and immunoperoxidase studies of cryostat sections have demonstrated increased levels of IL-2R in involved but not uninvolved psoriatic skin implying prior T cell activation [95]. Increased levels of soluble IL-2R have been detected in both atopic dermatitis and psoriasis [58, 59]. The report by Lee et al. [62] that intravenous IL-2 used for the treatment of carcinoma produced marked flaring of incidental psoriasis in two subjects indicates that IL-2 may be of prime importance in the initiation of a psoriatic response. As with IL-1 the absence of IL-2 in chronic, stable plaques of psoriasis may warrant investigation of the evolving lesion with its concomitant influx of activated $CD4^+$ T cells.

IL-6 is produced by fibroblasts, keratinocytes, T cells and macrophages and is known to be capable of stimulating keratinocyte proliferation [48]. Increased levels of IL-6 mRNA and protein have been found in both psoriatic plaques [48] and sera and levels of IL-6 protein are increased in psoriatic keratinocytes in vitro [76].

IL-8, previously known as neutrophil-activating peptide or neutrophil-activating factor, was first described as a chemotactic agent for neutrophils but is now recognized as a particularly potent T lymphocyte chemoattractant [61]. IL-8 is produced by keratinocytes, fibroblasts, and lymphocytes and is capable of inducing keratinocyte proliferation in vitro [88]. With this psorigenic capacity it is not surprising that IL-8 protein and mRNA have been observed in psoriatic plaques [21, 37, 81] and it is possible that this cytokine plays an important pathogenic role.

Tumor necrosis factor-alpha (TNF-α) has been demonstrated immunohistologically in the dermis of psoriatic plaques and is primarily localized to dermal dendrocytes with limited expression by Langerhans cells [81]. PCR of isolated psoriatic epidermis, however, did not demonstrate TNF-α mRNA [14], although TNF-α protein has been variously reported as being either elevated or decreased in psoriatic serum [39, 73]. Indirect evidence for the presence of TNF-α is the presence of TNF-α-inducible molecules such as transforming growth factor-α

(TGF-α) [28, 99] and IL-8 as well as endothelial expression of ICAM-1, VCAM-1 and ELAM-1 and keratinocyte expression of ICAM-1; TNF-α is the only cytokine known to induce this pattern of adhesion molecule expression [47]. Furthermore, angiogenesis which is an important component of psoriatic plaques, has been shown to be inducible by macrophage-derived TNF-α [63]. Epidermal changes are known to precede angiogenesis in advancing psoriatic plaques [84] and epidermal-derived angiogenic factors such as TNF-α may be responsible for this observation [67, 105]. Nickoloff [78] has proposed an elaborate thesis based upon the presence of TNF-α in psoriasis and has proposed this cytokine as the orchestrator of the disease process. However, systemically administered TNF-α is reported to clear psoriasis [24, 96] and injection of this cytokine into mouse tail inhibits keratinocyte proliferation [74]. It may be that supraphysiological levels of TNF-α overload and consequently down-regulate its receptors leading to a paradoxical inhibitory effect and consequent disease resolution.

Of all the cytokines measured so far in psoriasis, the candidate most likely to be central to the T cell-mediated paradigm for this disease is IFN-γ. IFN-γ is produced solely by activated $CD4^+$ T cells and indirect evidence for its existence in psoriatic plaques is keratinocyte expression of ICAM-1, HLA-DR, and IP-10 [41, 42, 44, 90]. PCR examination of epidermal sheets derived from psoriatic lesions reveals the presence of mRNA for IFN-γ, whereas this cytokine is absent in normal skin [14]. IFN-γ protein has been demonstrated in fluid from suction blisters raised on involved but not uninvolved psoriatic skin [16, 95] and is elevated in serum from psoriatic patients [39]. By comparison with normal keratinocytes, psoriatic keratinocytes are less sensitive to the growth inhibitory effects of IFN-γ in culture and are less disposed to expression of HLA-DR and ICAM-1 [8, 80]. These observations indicate that psoriatic keratinocytes are hyporesponsive to IFN-γ. During the course of treating psoriatic arthritis with subcutaneous injections of IFN-γ, it was observed in 10 of 42 patients that punctate, psoriatic foci were induced at the sites of injection of IFN-γ but not at the sites of vehicle injection [34]. Furthermore, injection of IFN-γ in normal subjects did not evoke this response. This observation is circumstantial evidence for an integral role for IFN-γ in psoriasis.

TGF-α is a potent inducer of keratinocyte hyperproliferation and is overexpressed in psoriatic plaques at both the mRNA and protein levels [28, 99]. The receptor for TGF-α (TGF-α – R/EGF-R) is increased in psoriatic epidermis [75]. Keratinocyte production of TGF-α can be induced by IFN-γ [80] and IL-6 in vitro. It appears that increases in TGF-α and subsequent epidermal hyperproliferation do not occur at the expense of a decrease in the growth-inhibiting cytokine TGF-β_1, as levels of this molecule appear to be the same in normal and psoriatic skin [28].

The role of an adhesion molecules

The discovery of adhesion molecules pertinent to cutaneous biology came with the observation that ICAM-1 expression could be induced on keratinocytes and

endothelial cells by TNF-α and IFN-γ [25]. Since then additional endothelial adhesion molecules have been described and there is little doubt that their interactions with mononuclear cells are pivotal to our understanding of cutaneous trafficking and inflammation. In normal, uninflamed skin, ICAM-1 is the sole adhesion molecule expressed and then only on endothelium [46, 90]. The expression of ICAM-1 by keratinocytes is indicative of the presence of TNF-α and/or IFN-γ, although protein kinase C agonists such as urushiol can directly induce keratincyte expression of ICAM-1 [44]. Endothelial expression of ICAM-1 can be up-regulated by TNF-α, IFN-γ, IL-1 and lipopolysaccharide. The two adhesion molecules peculiar to endothelium, ELAM-1 and VCAM-1, are only induced by IL-1 and TNF-α [78].

In psoriatic epidermis keratinocyte ICAM-1 is focally expressed, particularly in the region immediately overlying the dermal papillae and ICAM-1-expressing keratinocytes are observed closely juxtaposed to infiltrating LFA-1-expressing lymphocytes [46]. ICAM-1, ELAM-1, and VCAM-1 are all expressed by psoriatic endothelium, thereby implying the presence of IL-1 and/or TNF-α [49]. ELAM-1 binds neutrophils, monocytes and memory T cells. The receptor for ELAM-1 expressed by a distinct skin-homing subset of memory T cells is the cutaneous lymphocyte-associated antigen (CLA) [85]. This observation coupled with the finding that ELAM-1 is preferentially expressed in skin and synovium [82] may be of considerable importance to the pathogenesis of inflammatory skin disease, especially pertinent in the case of psoriasis with its associated arthritis.

New therapies as investigatory tools in psoriasis

The ability of selective immunosuppressive agents to suppress the cutaneous manifestations of psoriasis has been salutory in strengthening belief in the immune-mediated hypothesis of this disease. Perhaps the one drug which has done most to further this hypothesis has been cyclosporine. In 1979, Mueller and Hermann [72] made a salient serendipitous observation during a study of the use of oral cyclosporine for arthritis. In this study four subjects happened to have psoriatic arthritis and their concomitant cutaneous plaques resolved rapidly after initiation of therapy. Subsequently, open and double-blind studies of cyclosporine in psoriasis have confirmed this observation [30, 43, 45]. What then is the significance of these observations to our understanding of the pathogenesis of psoriasis?

Cyclosporine has a mechanism of action directed mainly at the $CD4^+$ T lymphocyte and is known to inhibit its production of IL-2 and IFN-γ [22, 29, 57]. Inhibition occurs as a result of cyclosporine complexing with its receptor, cyclophilin, which is a member of the peptidyl-prolyl cis-trans isomerase group of enzymes which are important in protein re-folding [94]. The cyclosporine/cyclophilin complex subsequently inhibits a calcium-activated protein, calcineurin phosphatase, and blocks translocation from the cytoplasm to the nucleus of a component of nuclear factor of activated T cells (NFAT) which ultimately leads to inhibition of T cell activation [22, 31, 64]. Cyclosporine has no direct antiproliferative effect on keratinocytes except under non-physiological, low

calcium, serum-free conditions where the concentration of cyclosporine exceeds that measured in skin during systemic treatment of psoriasis [35]. Lamellar ichthyosis is an autosomal recessive disease chracterized by epidermal hyperproliferation which occurs in the absence of any appreciable lymphocytic infiltrate. Treatment of this condition with cyclosporine has been unsuccessful [55], an observation which provides strong but circumstantial evidence that the hyperproliferative keratinocyte is not cyclosporine's primary target.

When psoriasis is treated with systemically administered cyclosporine a large reduction in $CD4^+$ and $CD8^+$ T cells occurs within the plaques but only a small decrease in the DR^+CD4^+ T cell subset [6]. This observation implies that, although activated DR^+CD4^+ cells are still present, they are in effect paralyzed and unable to produce cytokines capable of perpetuating the psoriatic process. The failure of topically applied cyclosporine in the treatment of psoriasis [43] necessitated intralesional studies of this drug in chronic plaque psoriasis, an approach which produces resolution of the injected plaques over a period of 4 weeks. Sequential biopsies taken during those studies led to seminal observations concerning the role of $CD4^+$ T cells. Prior to any clinical improvement, a reduction occurs in numbers of intraepidermal DR^+CD4^+ T cells, however, immediate to this event there is a 67% reduction in keratinocyte ICAM-1 expression implying inhibition of DR^+CD4^+ T cell-derived IFN-γ [43, 56]. It is postulated that a reduction in keratinocyte ICAM-1 expression would free LFA-1-expressing T cells from their apposition to keratinocytes and allow their return to the dermis and hence to recirculation. Other cytokines (such as IL-6) derived from T cells could also be inhibited by cyclosporine ultimately leading to resolution. FK506 is a macrolide antibiotic, structurally unrelated to cyclosporine but with an extremely similar mechanism of action and binding protein [98], which has been reported successful in the treatment of psoriasis [1]. The efficacy of this macrolide antibiotic further emphasizes the T cell-mediated nature of psoriasis particularly, as FK506 also has no direct effect on keratinocytes [91].

Newer, more specific therapies targeted at the T cell and the T cell receptor are being introduced into the treatment of autoimmune disease and both by design and by chance these have been used in psoriasis. Monoclonal antibodies targeted at the T cell, e. g., anti-CD3, are being used for the treatment of multiple sclerosis. One such patient also suffering from psoriasis was treated with anti-CD3 and a marked improvement in psoriasis was noted [102]. More specific antibodies directed against CD4, are also in use. To date, there are three reports totalling five patients which indicate that systemically administered anti-CD4 monoclonal antibodies will clear or markedly improve psoriasis [77, 86, 87]. As with all therapies for psoriasis, the disease relapses after cessation of treatment.

Many all-encompassing theories have been proposed for the immunopathogenesis of psoriasis and only time will dictate their accuracy [3, 12, 78]. For any theory to be viable, it should take into account the following points: inheritance, Koebner phenomenon, epidermal hyperproliferation, inflammation and angiogenesis.

Antigen presentation to cutaneous T cells by Langerhans cells, dermal dendrocytes, and possibly keratinocytes most likely motivates the psoriatic process in genetically predisposed individuals. The most attractive candidates (on current

knowledge) for putative initiating antigens are members of the β-hemolytic streptococcal family [97]. The propensity of streptococcal infection (particularly of the β-hemolytic sub-type) to exacerbate chronic plaque psoriasis and initiate guttate psoriasis has been widely reported [97, 104]. Additionally, systemic antibiotics, e. g., penicillin, are known to prevent recurrence of the disease process. McFadden [69] has hypothesized that the observed reduction in delayed-type hypersensitivity to streptococcal antigen in psoriatics may serve as a protective mechanism against scarlet fever. The M protein of streptococci has the ability to behave as a superantigen, thereby activating T cells without class II MHC restriction. Molecular mimickry and cross reactivity between streptococcal protein and keratins may also account for perpetuation [71, 93]. Viral particles are also implicable as has been learnt from the exacerbation of psoriasis by AIDS most probably as a result of presentation of HIV antigens by Langerhans cells and dermal dendrocytes to T lymphocytes within the skin [26, 66]. Thus, in AIDS patients with psoriasis there is a somewhat paradoxical vigorous immune response taking place within the skin occurring in the face of systemic immunosuppression.

Activation of Langerhans cells and dermal dendrocytes would initiate production of IL-1 and TNF-α both of which are capable of inducing ELAM-1, ICAM-1, and VCAM-1 on dermal capillary endothelium. TNF-α can further induce TNF-α production by keratinocytes in both autocrine and paracrine fashions and stimulate IL-8 production by keratinocytes. In addition, TNF-α and other epidermal-derived cytokines would stimulate angiogenesis. Endothelial adhesion molecule expression, particularly ELAM-1, would allow binding of circulating T cells most probably of the memory, CLA-expressing subset. IL-8 and IL-1 derived both from keratinocytes and dermal dendrocytes may attract these adherent T cells away from the vascular wall and towards dermal antigen-presenting cells. Subsequent to this migration and antigen-processing, the T cells are activated. In all likelihood T cells could be activated at sites distal to the skin, such as lymph nodes and tonsils and then migrate to the skin in a fully primed state, thus obviating the need for cutaneous antigen presentation. Activation releases a cascade of cytokines including IFN-γ which in turn up-regulates ICAM-1 on keratinocytes allowing close T cell/keratinocyte binding and subsequent interactions. Once the amplification process has begun, further production of cytokines such as IL-6, IL-8, and TGF-α will promulgate epidermal hyperproliferation and overwhelming of the negative feedback imposed by $CD8^+$ T cells.

The Koebner phenomenon may be explicable by direct epidermal injury (which is necessary for this process) releasing keratinocyte-derived cytokines, such as IL-1 and TNF-α, capable of up-regulation of endothelial and keratinocyte adhesion molecules and initiation of T cell trafficking without recourse to antigen presentation.

The defect in psoriasis, which most likely is multifactorial, may reside in the keratinocyte, Langerhans cell or T cell. However, to explain the decreased sensitivity of psoriatic keratinocytes to IFN-γ, the enhanced antigen-presenting capacity of psoriatic Langerhans cells, the defects in cellular immunity and the "cure" of psoriasis by allogeneic bone marrow transplant, it is possible that the genetic defects are expressed in multiple cell types and that no abnormality in a single cell type can account for all the features of psoriasis.

Conclusions

The past decade has borne witness to tremendous advances in our knowledge of the pathogenesis of psoriasis and the weight of evidence is now on the side of the T cell as being an integral mediator of this process. Advances in molecular technology have enabled direct in vivo measurement of cytokines and, although no animal model exists for the study of psoriasis, the use of cyclosporine has served as an excellent investigatory tool. The utilization of therapeutics to study psoriatic mechanisms is an unusual approach in that one must derive conclusions from disappearance of measurable factors such as cytokines and assume that these same factors are vital to the initiation and maintenance of a psoriatic plaque. Studying disease evolution using the Koebner phenomenon or relapse following treatment would supply a more accurate picture of initiating events. Based on the immune hypothesis, therapeutic modalities which are now entering the arena include T cell vaccination, particularly if psoriasis-specific T cell receptor V_β-restricted clones can be isolated from psoriatic plaques.

There is little doubt that by the end of this century, cutaneous biologists will have built substantially on the immunological foundation laid by the early work outlined here. Most likely the genetic contribution(s) to the manifestations of psoriasis will be more fully elucidated and that gene therapy will carry more than a futuristic promise. At least for the present we believe that such significant advances have been made that the majority of dermatologists if questioned nowadays as to whether psoriasis is an immunologically-mediated disease would answer in the affirmative.

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