Psoriasis Research - Mega Techno Speak

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Hello-

This is a repost of a paper I did for an autoimmune disease class I just completed recently. Although it's pretty scientific, there's a lot of good general information as well. Hope this helps some, folks!
Peace-
-Emery

PSORIASIS

Psoriasis is a chronic remitting and relapsing scaly and inflammatory skin disorder. Sufferers of the most common form of psoriasis - plaque psoriasis - exhibit scaly lesions on the skin which can range from mild cases, in which less than ten percent of the skin is involved, to severe cases in which almost the entire skin, including the scalp, is affected. Established lesions show increased epidermal thickness, abnormal keratinization, absence of granular layer, and deposition of antibodies and complement components in the stratum corneum. Most notable is the hyperproliferation of keratinocytes in the epidermis. These keratinocytes exhibit an increased mitotic rate and have ten times the turnover rate of normal keratinocytes. There is also an infiltration of CD4+ T lymphocytes, monocytes and neutrophils into the epidermis. Recently there has been much debate over whether psoriasis is mediated by an autoimmune process.

The disease affects roughly two percent of the population in the United States. It has the greatest prevalence among Scandinavians and Northern Europeans, where it affects three percent of the population, and the least prevalence among North American Indians, with just half a percent being affected. Psoriasis seems to affect both males and females equally. There are two types of the disease. Type I generally occurs during adolescence, with an average age of onset of sixteen years for females and twenty-two years for males. Type II affects people over sixty years of age.

There are several immunological abnormalities associated with psoriasis. Early psoriatic changes occur in advancing lesions before the accumulation of inflammatory cells. These changes are mediated by activated CD4+ T lymphocytes and can be detected before visible pathology to the skin occurs. Activated T lymphocytes exhibiting an increase in HLA-DR and IL-2R can be seen in close proximity to Langerhans cells in the dermis before lesion formation. Since Langerhans cells are antigen presenting cells, activation of the T cells may occur by the recognition of an as-yet unidentified antigen in the context of MHC class II. These activated T lymphocytes then migrate to the epidermis and activate epidermal keratinocytes.

At this point, a cascade of events occurs and appears to become cyclic after up-regulation of certain cytokines. This cyclic tendency is probably responsible for the static nature of many psoriatic plaques. An increase in ICAM-1 and ELAM-1 (endothelial leukocyte adhesion molecule) in the vascular endothelium underlying the plaque recruits inflammatory cells

to the site of the lesion. Activated T cells produce increased IFN-gamma, which in turn induces HLA-DR and ICAM-1 expression in keratinocytes. This increase in ICAM-1 production causes increased retention of activated T-lymphocytes in the epidermis, localizing them to the site of the lesion. The IFN-gamma released by activated T-lymphocytes also causes an up-regulation of keratinocytic cytokines, specifically IL-1, IL-6, IL-8 and TGF-alpha. TGF-alpha, IL-6, and IL-8 are all keratinocyte mitogens, so their release stimulates the activation of surrounding keratinocytes, inducing more ICAM-1 expression and causing increased retention of activated T lymphocytes at the site of the lesion. IL-1 also serves to increase ICAM-1 expression in keratinocytes. IL-8 (neutrophil activating factor) mediates migration of monocytes, neutrophils, and CD4+ T-cells from the vascular endothelium to the epidermis.

There are several indirect lines of evidence that implicate an autoimmune role in the onset of psoriasis. There is an increased prevalence of certain HLA haplotypes which have been associated with the disease. The major haplotype which exhibits this correlation is HLA-Cw6. Cw6 gives a relative risk of twenty for developing psoriasis, and eighty-five percent of Type I sufferers are positive for this HLA haplotype. The correlation isn't as great for Type II sufferers - fifteen percent - but is still significant. There is a lesser association with other HLA haplotypes as well, notably A1, B13, B17, B27, B37, DR7, but some of these may be due to linkage disequilibrium with Cw6. One study showed that transgenic rats expressing haplotype B27 develop psoriasis-like plaques on their tails, strengthening the argument for HLA correlation. Furthermore, the most common cutaneous manifestation associated with HLA-B27 is Reiter's syndrome (keratoderma blenorrhagica), which shares clinical and histophysiological features with psoriasis.

There is other evidence for a genetic link, as well. Thirty percent of psoriasis patients have a first degree afflicted relative. Among sufferers of Type I psoriasis, fifty percent have an afflicted parent (the same study showed that no Type II patients had an afflicted parent). There is a seventy-two percent concordance between monozygotic twins, which fits the pattern of an autoimmune disease, since they are usually multifactorial. Recently, a study linked some cases of psoriasis to a gene on the distal end of the long arm of chromosome seventeen. These cases were not Cw6 associated, indicating that psoriasis susceptability may be correlated with genetic variation at a genetic locus other than the HLA locus. A gene involved in the activation of T cells - ILF (interleukin enhancer binding factor) - was shown (by others) to lie within this region of chromosome seventeen. ILF binds to purine-rich regions of the IL-2 promoter (along with NFAT), so alterations in this gene could possibly cause an up-regulation of expression of IL-2, resulting in the inflammatory cascade and hyperproliferation characteristic of lesional skin.

A study of a murine autoimmune disease involving the skin may give clues to the possible autoimmune component involved in psoriasis. A murine epidermal antigen, Skn, is a target for adoptively transferred autoimmune disease affecting the skin. Murine recipients injected with anti-Skn splenocytes exhibited histopathologic alterations with psoriasiform features in their skin lesions, including hyperkeratosis and dermal infiltration of mononuclear cells and neutrophils.

Another intriguing factor is the efficacy of immunosuppressive treatments when used for psoriasis. Cyclosporin A (CSA) has been shown to be very effective in treating psoriasis, but is rarely used due to its nephrotoxic and hypertensive properties. CSA blocks the formation of a calcineurin dependent factor (NFAT) essential for transcription of IL-2 in

T cells, and thus can interfere in T cell activation. CSA can also abrogate Langerhans cell function and is cytostatic for keratinocytes. Recent work with anti-CD4 antibodies has shown them to be effective as well. A chimeric human/mouse anti-CD4 monoclonal antibody treatment was used to treat a sixty-three year old man with severe generalized pustular psoriasis. The pustular psoriasis dried and disappeared, and the man's plaque psoriasis, present since age nineteen, also disappeared. The plaque psoriasis returned after treatment was stopped, but responded well to conventional phototherapy.

A high association between Streptococcal infection and psoriasis has been known for almost fifty years, especially in the case of guttate psoriasis (a juvenile form), where up to eighty percent of sufferers have evidence of recent Streptococcal infection. Studies have shown binding of monoclonal antibodies raised to Streptococcal antigen to products of keratinocytes. Cytokeratins are quite immunogenic, and if this binding is due to shared antigens it raises the possibility that memory T cells specific for Streptococal antigen may activate by recognizing antigens on keratinocytes.

There exist a variety of treatments for psoriasis, but no cure. The most popular treatment is a combination of a topical agent and phototherapy involving UV light. Coal tar is a major topical agent prescribed for psoriasis. Many times the tincture includes corticosteroids, and other times topical corticosteroids are prescribed alone. Coal tar is usually used in conjunction with UVB phototherapy. Emollients are also used, such as soft yellow paraffin or aqueous cream (aquaphor), and these may be effective due to a reversal of the inflammatory consequences of damage to the stratum corneum. Another treatment involoves keratolytic agents, such as salicylic acid, which soften the scaly layers of plaques and ease their removal. These agents also enhance the efficacy of topical corticosteroids and coal tar by increasing their absorption.

Phototherapy involves the use of either UVA or UVB light exposure to affected skin. UVB light inhibits Langerhans cell function and is cytotoxic for keratinocytes. If the Langerhans cells are indeed causing the activation of CD4+ T lymphocytes, it makes sense that this type of therapy would have a beneficial effect. UVA therapy is usually done in conjunction with methoxalen, a photosensitizing drug. A proposed theory for the efficacy of this treatment states that there is an intercalation of methoxalen into DNA forming cross-links between strands that interfere with DNA synthesis and block cell proliferation. This form of therapy is also known to have a suppressive effect on cell-mediated immune responses in the skin, which is an important point because a recent study has shown that CD8+ lymphocytes also play an important role in the pathogenesis of this disease.

Several orally administered drugs are also used in the treatment of psoriasis. Methotrexate, a folic acid antagonist, has been shown to be effective. It had been proposed that methotrexate may work by causing a blockage of DNA synthesis, but recent evidence has demonstrated that it may affect mononuclear cells in skin, blood, and lymphatic tissue, leading to an immunosuppressive effect. The downside of this treatment is liver and kidney damage. Etretinate, a retinoic acid derivative, is used in conjunction with UVA treatments to lower the effective dose of both. Systemic corticosteroids are also quite effective in treatment of psoriasis, but many physicians do not prescribe them since the psoriatic condition may worsen after usage is discontinued. Other, more recent agents include Cyclosporin A, FK506, anti-CD4 mAb, calcipotriol, acetazolamide, and tin-protoporphyrin (with UVA).

Psoriasis appears to fit the pattern of an autoimmune disease, or at least Type I psoriasis fits the pattern. It has its onset around adolescence, and the onset is gradual rather than sudden. The lesions can remit and relapse, and the trigger appears to be multifactorial, as can be demonstrated by the seventy-two percent concordance between identical twins. The disease remains for the lifetime of the affected person, as well. The murine experiments identifying the Skn antigen as an autoimmune target may be a clue indicating that a similar antigen exists in humans, although this antigen is yet to be identified. The CD4+ T cells are somehow getting activated and starting the cascade of events which leads to lesion formation. If this activation is occuring due to a shared antigen between keratinocytes and Streptococcus, then psoriasis would fit the definition of an autoimmune disease triggered by molecular mimicry. However, this correlation is not demonstrated in all sufferers. The high correlation between HLA-Cw6 and psoriasis also indicates an autoimmune role in the disease, as does the effectiveness of immunosuppressive treatments. A recent article speculated that psoriasis may be mediated by a genetic defect affecting keratinocytes. Langerhans cells are under the influence of cytokines released by keratinocytes. The Langerhans cells in the dermis and epidermis are able to process protein antigens with great efficiency, but are only able to present the antigens to high affinity memory T cells. Langerhans cells found in nodal regions do not have this high efficiency of protein processing, but have the ability to activate both naive and memory T cells. The intraepidermal Langerhans cells in psoriasis patients look more like intranodal cells than normal intraepidermal Langerhans cells, giving them the ability to activate naive T cells. If challenged cutaneously, perhaps these cells can non-specifically activate naive T cells, leading to the cascade of events that generates the pathology associated with a psoriatic lesion. Indeed, psoriatic lesions can occur at the site of local trauma many times (Koebner's phenomenon). However, if this genetic defect was the definitive cause of the disease, then everybody afflicted with this defect would acquire the psoriatic phenotype. This does not occur - the onset appears to be multi-factorial. I believe that Type I psoriasis is an autoimmune disease, but the process mediating its onset is yet to be elucidated. I supect that there may be a self -antigen present in the epidermis which is causing an autoimmune reaction. This antigen may be only expressed during adolescence, hence the onset of disease during this time. It could be that these sufferers have lost tolerance to this self antigen and have initiated an autoimmune response to the new challenge. There may be other genetic defects which can lead to the psoriatic phenotype, but these are probably distinct from Type I psoriasis, which I believe to be a true autoimmune disease.

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