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Review Article

'PSORIASIS' - AN IMMUNE DISEASE IN THE RESEARCH PIPELINE

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ABSTRACT

The current review article focuses on "Psoriasis", a form of over-active wound healing response, relatively common, chronic, inflammatory and hypersensitive disease of unsolved pathogenesis affecting skin and joints in 2-3% of the general population. Psoriasis is a skin disease driven by immune system which starts below the skin's surface and cause severe pain and adverse mental health effects. Genetic susceptibility as well as environmental factors plays an important role in determining the development and prognosis of psoriasis.

Natural Killer (NK) cells are lymphocytes that are best known for killing virally infected and cancer cells. However, evidence is emerging to support a role for NK cells in psoriasis. NK cells are found in the inflammatory infiltrate in psoriatic skin lesions. They can produce a range of inflammatory cytokines, many of which are important in the pathogenesis of psoriasis. Elucidation of the Immunopathogenesis of psoriasis has led to the discovery of novel biologic agents for the treatment of moderate to-severe plaque psoriasis. There are countless therapies currently in the research pipeline, with mechanisms ranging from receptor antagonism to signal transduction pathway inhibition.

Keywords: Pathogenicity, Immune perspectives, Differential Diagnosis, Therapy

INTRODUCTION

Psoriasis is chronic inflammatory condition of the skin with significant morbidity, affecting approximately 2% of the Caucasian population.[1] Psoriasis comprises red, scaly patches of skin, which usually have very well defined edges, appear covered by silvery flaky surface.[2] The redness is explained by impressive growth and dilation of superficial blood vessels.[3] They most often occur on the elbows, knees, other parts of legs, scalp, lower back, face, palms, and soles of the feet, but they can occur on skin anywhere on the body.[4] The disease may also affect the fingernails, the toenails, and the soft tissues of the genitals and inside the mouth.[5]

Recent scientific advances have highlighted the role of the immune system in psoriasis.[6, 7] Activation of memory T-cells is important for immune system to generate. Activated T-cells release cytokines, which signal accelerated epidermal cell turnover and the keratinocytes and vascular changes seen in psoriasis.[8]

Psoriasis is sometime associated with arthritis, myopathy, enteropathy, spondylitic heart disease or the AIDS.[9] Psoriasis is a lifelong immune-mediated disease affecting approximately 1.5% of the world's population and is characterized by periods of exacerbations and remission. Of the 3 to 5 million people in the United States who are affected by psoriasis, approximately 20% to 25% have extensive disease requiring aggressive therapy.[10, 11, 12] The impact of psoriasis on physical and emotional functioning is as great as that of many other serious medical conditions, such as canceu`r, heart disease, and Crohn's disease.[13] As many as 25% of patients with psoriasis have suicidal death because of their disease.[14]

About one quarter of patients with Psoriasis (Pso) also develop psoriatic arthritis (PsA).[15] Nail involvement is common in patients with Pso and more so with PsA.[16] This may explain why the severity and progression of skin, joint, and nail symptoms are frequently asynchronous, [17] with joint disease in most of the patients developing up to 10 years after the initial skin presentation. Psoriasis does not affect skin and joints only. It is a multisystem disease associated with a multitude of comorbidities and thus psoriasis has become increasingly important for all medical fields, beyond just dermatology and rheumatology. Psoriasis patients show an increased risk for cardiovascular events.[18, 19] The prevalence of metabolic syndrome – a combination of obesity, dyslipidemia, impaired glucose regulation, and hypertension – is elevated in psoriasis patients.[20] The prevalence of depression is increased, and psoriasis can have a substantial psycho-logical impact on patients.[21, 22]

ROLE OF NATURAL KILLER (NK) CELLS IN PSORIASIS

In addition to cell surface receptors, various molecules are important in NK cell functions. The given figure below **(Fig 1)** shows that NK cells can interact with keratinocytes through a range of cell surface receptors. NK cells express cell surface receptors that regulate their interactions with other cell types including keratinocytes. Among these receptors is the NKG2A/CD94 inhibitory receptor that recognises and binds to HLA-E on target cells. NK cells also express a number of activating receptors including NKG2D which recognises MICA/B stress antigen and the Fas receptor which can activate cytokine secretion by NK cells. The activating KIR receptor 2DS1 (and its inhibitory counterpart, 2DL1) binds the HLA-Cw6 molecule and HLA-Cw6 is the strongest genetic association known in psoriasis. There is evidence in the literature to suggest that these receptors play a role in psoriasis. Activated NK cells are triggered to release their cytotoxic granule contents which contain perforin and granzymes.[23]

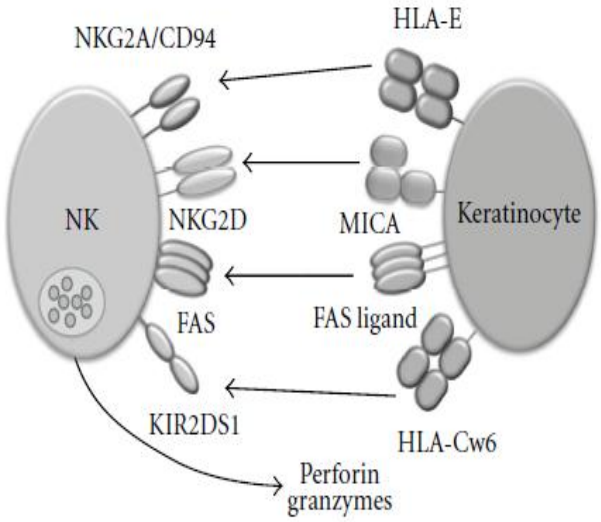

FIGURE.1 Interaction of NK cells with Keratinocytes through range of cell surface receptors (Courtesy: Sinead and Clair [23])

In one study, perforin, a pore-forming protein found in the cytotoxic granules of NK cells and a key mediator of cytotoxicity, was expressed at higher levels in the lesional psoriatic skin relative to uninvolved psoriatic or healthy control skin.[24] Psoriasis patients also had higher levels of perforin in their peripheral blood lymphocytes compared to healthy controls. However, the source of this perforin does not seem to be circulating NK cells, as no difference between the number of CD56+Perforin+ or CD16+Perforin+ cells was observed in psoriasis patients compared to controls [25]; it seems likely that CTL*s* are responsible for the elevated perforin levels. Another study[26] has given evidence for a role of NK cell-produced perforin in psoriasis, with a significantly higher percentage of CD56+Perforin+ found in the peripheral blood of patients with severe disease versus those with mild psoriasis, but interestingly this difference was not observed comparing individuals with severe psoriasis to healthy controls. It was also noted that the vast majority of blood cells expressing CD16 were also positive for perforin in those with severe disease while a significantly lower frequency of CD16 positive cells co-expressing perforin was found in patients with mild psoriasis. Cells expressing granzyme B, a serine protease that is released from NK cell granules and that triggers DNA degradation in target cells, have also been found in significantly higher numbers in involved psoriatic skin compared to uninvolved psoriatic and healthy skin.[24]

TYPES AND PATHOGENICITY OF PSORIASIS

There are several specific subtypes of psoriasis. The most common type of psoriasis, affecting more than 90% of patients, is chronic plaque psoriasis or psoriasis vulgaris.[11] Other types of psoriasis include guttate, erythrodermic, and pustular psoriasis.[10,11] Psoriatic arthritis is seen in approximately 30% of patients with psoriasis and, if left untreated, can cause significant joint damage.[11,22]

Psoriasis guttate occurs in about 10% of patients[8] and displays small, scattered plaques.[27,28] This form may develop into psoriasis vulgaris.[28] Pustular psoriasis is an uncommon form of the disease consisting of raised pus-filled bumps and large areas of reddened skin.[28] A proportion of psoriasis patients will develop psoriatic arthritis (PsA), a debilitating joint disease.[8,27,28]

The cause of psoriasis is still unknown although it is clear that there is a strong genetic component to the disease. Several immune genes have been associated with psoriasis with the major histocompatibility complex on chromosome 6 being strongly implicated.[29, 30] Outbreaks of psoriasis can occur at sites of physical trauma and streptococcal infections have been particularly linked to psoriasis guttate, perhaps indicating a role for molecular mimicry.[28] There is some evidence that psoriasis may be an autoimmune disease; it shares many characteristics with multiple sclerosis and diabetes mellitus type 1,[31, 32] but as yet no autoantigens or self-reactive T-cells have been identified.[30,33]

Biological evidence also supports a physiological differentiation. For example, selected key immune mediators of disease in the skin and joints differ. Pathologic events in the skin are mediated by autoreactive T cells,[1] whereas cells in the affected synovium of PsA patients do not exhibit the same type of autoreactivity.[34] Skin and joint symptoms frequently do not respond equally or in parallel to systemic or biologic therapeutic agents.[35]

Psoriasis vulgaris, the common form of psoriasis, is characterized by red, scaly, raised plaques. Although psoriasis vulgaris can occur in children, it often begins in late adolescence or early adulthood and then usually persists for life. Classic psoriasis vulgaris has a predilection for certain areas such as elbows, knees and the scalp. It may remain localized or become generalized over time. There are clinical variants of psoriasis, defined as subsets, with identical histopathological changes in the skin. Guttate psoriasis is characterized by small, scattered papules and is potentially linked to preceding streptococcal infections.[36] other recently described variants of psoriasis vulgaris include thick versus thin plaque disease, [37] and small versus large plaque disease.[38] A notable subset of patients with psoriasis develops psoriatic arthritis, a potentially debilitating illness.[8]

Psoriasis is essentially a disease of Caucasians, in whom its frequency is 1–2%. It is less common in Asians (about 0.1%) and is rarely seen in Africans.[30] That psoriasis has a genetic basis has been accepted for many years[30] and it is commonly thought of as a complex trait. So far, between 10 and 20 chromosome regions have been proposed to harbour psoriasis genes but less than a handful of genes have been identified.[29, 30] One locus consistently identified in studies of psoriasis is the class I region of the major histocompatibility locus antigen cluster (MHC).[30] However, its low penetrance — about 10% — indicates that other genetic and environmental factors are also involved.[39] The identity of psoriasis susceptibility 1 (*PSORS1*) remains controversial. Although its association with human leukocyte antigen (HLA) Cw6 and psoriasis was reported more than 25 years ago, [40] the extensive linkage disequilibrium across the class I region and its complex evolutionary history has made identification of the susceptibility variant(s) very difficult.

Some genetic variants such as those from the epidermal differentiation complex (EDC) might directly affect keratinocyte proliferation or differentiation.[30] How subtle alterations in keratinocytes differentiation interact with alterations in the immune system to lead to the development of an inflammatory skin disease will be an important area of research as genetics progresses to global association scans, attempting to identify most of the common alleles.

It is important to understand that human skin does a complex organ comprise many distinct tissues, and that its structure is significantly different from the skin of lower species. Compared with fur-bearing animals, human skin has broad areas of epidermis situated between hair follicles, known as interfollicular epidermis. There are many different skin diseases that involve altered growth of epidermal keratinocytes and inflammation in the interfollicular epidermis, and psoriasis and atopic eczema are common examples. These disorders do not appreciably alter the growth of keratinocytes in the follicular epithelium or the growth of hair. Other diseases can alter the growth of follicular epithelium, sebaceous glands or hair (the pilosebaceous unit), and many such conditions are associated with immune infiltrates in or around follicular structures. Psoriasis does not exist as a spontaneous disease in the skin of lower animals[41] but some features of psoriasis have been induced in murine skin by genetic or immune manipulations. Even so, the structure of murine skin imposes serious limitations on resultant cellular alterations and, so far, psoriasis has not been faithfully reproduced by manipulation of native skin in any

lower species. The relationship between psoriasis and HIV-1 is also interesting because of the clinical observation that HIV-1 infection can exacerbate existing psoriasis or trigger new-onset psoriasis.[42] As HIV-1 infection progresses and CD4+ T cell counts decrease, psoriasis can worsen.[43, 44] This has puzzled dermatologists and infectious disease clinicians because it has been convincingly established that psoriasis is an immune disorder that is mediated through activation of T cells. Several explanations for this "psoriasis HIV-1 paradox" have been proposed, including sHIV- 1 induced destruction of regulatory CD4+ T cells,[45] an increase in number of memory CD8+ T cells late in disease,[46] HIV 1 proteins acting as super antigens,[47] or co-stimulation through traditional antigenic presentation.[45]

THE IMMUNE PERSPECTIVE

There is a plethora of studies supporting the view that dysregulation of the immune system is central in psoriasis pathogenesis, particularly through T-cell-dependent mechanisms. Therapeutic efficacy of pharmaceuticals like cyclosporine, which inhibit the production of cytokines involved in T-cell activation, demonstrated the importance of immunity in psoriasis pathogenesis.[48] More recently, antibodies against specific T-cell-bound activating molecules like CD2 and CD11a indicated a more specific role for T-cells.[49] Moreover, healthy individuals transplanted with bone marrow from donors with psoriasis can develop the disease, while psoriasis patients receiving bone marrow from a healthy donor can clinically improve.[50, 51] Immunocytes present in human psoriasis skin engrafted on to different immunodeficient mice induce signs of disease.

Distinctive patterns of cell infiltration occur in lesional psoriasis skin; CD8+ T cells as well as neutrophils target the epidermis, the latter forming microabscesses that contain large amounts of cellular debris. Dendritic (DC) and CD4+ T-cells tend to accumulate in the interpapillary dermis. Large immune cell conglomerates can be found in deeper dermal locations, reminiscent of lymphoid tissues elsewhere.[52] The majority of T-cells in psoriasis lesions are activated memory cells expressing co-stimulatory molecules and the cutaneous lymphocyte-associated antigen, CLA. The mode of cooperation between different cell types in psoriasis is under exploration, but it is clear that T-cell and DC interaction is necessary for disease to occur. Several DC types are found in psoriatic skin besides resident Langerhan's cells, such as immature dermal DCs and plasmacytoid DCs. Of these, plasmacytoid DCs may be of particular significance in psoriasis pathogenesis due to their ability to produce large amounts of IFN-α.[53] Psoriasis is considered a Th1-driven disease as opposed to atopic dermatitis which is regarded as Th2-regulated based on the cytokine patterns produced in the respective lesions.[54]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of psoriasis is vast and depends on the clinical subtype. Chronic plaque psoriasis must be distinguished from the mycosis fungoides variant of cutaneous T-cell lymphoma (CTCL). The latter often exhibits signs of epidermal atrophy or poikiloderma which allow its differentiation from plaque psoriasis; however, occasionally, a skin biopsy is the only way to distinguish between the two. Pityriasis rubra pilaris (PRP) is clinically distinguished from plaque psoriasis by the presence of red-orange palmoplantar keratoderma, keratotic follicular papules, and the classic islands of sparing on the trunk. Histopathologically, the alternating vertical and horizontal ortho- and parakeratosis as well as follicular plugging help distinguish PRP from psoriasis. Nummular dermatitis and Bowen's disease are also in the differential diagnosis of plaque psoriasis. Nummular dermatitis is more pruritic than psoriasis and is often associated with a history of atopy. Histopathological examination is the most reliable way to differentiate between a plaque of psoriasis and Bowen's disease.

When psoriasis involves the shins, a diagnosis of hypertrophic lichen planus may be entertained, but typical lichen planus lesions elsewhere on the body as well as mucosal involvement may help to differentiate between the two. Guttate psoriasis is often straightforward to diagnose; however, the clinical differential diagnosis includes small plaque parapsoriasis, pityriasis rosea, pityriasis lichenoides chronica (PLC), and secondary syphilis. These entities can be distinguished on the basis of key historical, clinical, pathologic, and laboratory findings. Small plaque parapsoriasis usually presents with variably erythematous plaques which are covered with fine scale. Occasionally, it may present with elongated, finger-like patches symmetrically distributed on the flanks, also known as "digitate dermatosis." Pityriasis rosea is distinguished from psoriasis by the presence of a herald patch and resolution of the lesions within a few months. Secondary syphilis may be clinically distinguished on the basis of palmoplantar involvement, which does not happen in guttate psoriasis, as well as on the basis of histopathologic and serologic findings. PLC is clinically characterized by recurrent crops of spontaneously regressing, scaly red-brown papules.

Histologically, there is an interface dermatitis composed predominantly of monoclonal T-lymphocytes and necrotic keratinocytes. Pustular psoriasis may resemble a pustular drug reaction, such as acute generalized exanthematous pustulosis (AGEP), Sneddon–Wilkinson disease, or IgA pemphigus. The presence of peripheral eosinophilia and tissue eosinophils on the skin biopsy, as well as a history of a preceding culprit medication favors AGEP. Sneddon–Wilkinson disease can be distinguished clinically by its annular or polycyclic plaques with a predilection for flexural surfaces. The diagnosis of IgA pemphigus is made via positive direct immunofluorescence, which is absent in both psoriasis and Sneddon–Wilkinson disease. The annular form of pustular psoriasis may also mimic Sneddon–Wilkinson disease. The principal differential diagnostic considerations of flexural psoriasis include intertrigo and Langerhans cell histiocytosis in infants.

Patients with Langerhans cell histiocytosis may have scaling and crusting of the scalp, as well as internal organ involvement (eg, hepatomegaly, lytic bone lesions). A skin biopsy is diagnostic. The differential diagnoses for palmoplantar psoriasis include dyshidrotic dermatitis and tinea manuum/pedum. Yellow-brown macules intermixed with sterile pustules favor a diagnosis of palmoplantar psoriasis. KOH examination of the associated scale can help diagnose a dermatophyte infection. Nail psoriasis may mimic alopecia areata, lichen planus, or trachyonychia. Nail pitting is a feature of both psoriasis and alopecia areata; however, pits are large, deep and irregularly distributed in psoriasis in contrast to alopecia areata, where they are small, superficial, and regularly distributed. Oil drops, distal onycholysis, and splinter hemorrhages may also serve to distinguish between the two entities.

Lateral nail thinning, longitudinal ridging, fissuring, and dorsal pterygium are features which favor lichen planus. Trachyonychia, or twenty-nail dystrophy, may be due to alopecia areata, lichen planus, or psoriasis. In the absence of cutaneous findings, a nail unit biopsy may help establish the underlying cause. Scalp psoriasis may resemble tinea capitis or seborrheic dermatitis. While psoriasis can often be clinically differentiated from tinea capitis, laboratory testing is sometimes necessary to establish the diagnosis of a dermatophyte infection. This includes a KOH preparation, a fungal culture, or microscopic examination of a skin biopsy specimen. Seborrheic dermatitis and psoriasis may present clinically very similarly and often respond to the same topical treatment. The presence of psoriatic plaques on the trunk as well as a positive family history may favor psoriasis.

Histopathological examination remains the standard of differentiating between the two. Finally, erythrodermic psoriasis has a vast differential, as there are many other causes of erythroderma including seborrheic dermatitis, atopic dermatitis, Sezary syndrome, PRP, drug reactions, and graft-versus-host disease. A skin biopsy may or may not establish the underlying cause. Often, psoriatic erythroderma is preceded by classic psoriatic plaques; however, typical features of psoriasis are lost after generalization of the erythema. Nail changes, such as nail pitting, oil drops, or onycholysis may still be visible and provide a clue to the diagnosis of psoriatic erythroderma.[55]

CONVENTIONAL THERAPY

Approximately 80% of the psoriatic population has mild-to-moderate disease (localized cutaneous manifestations; body surface area # 10%) of which the majority can be successfully managed with topical agents such as corticosteroids, vitamin D3 analogs, vitamin A derivatives, emollients, keratolytics, and/or coal tar.[56, 57] Moderate-to-severe disease with more widespread cutaneous manifestations (body surface area. 10%) and/or nail or joint disease may require phototherapy (ultraviolet B or ultra violet a radiation) with psoralen, known as photochemotherapy, or systemic agents.[58] Conventional systemic therapies such as MTX, CSA and acitretin can be used in the long term, but often have limitations due to more severe side effects (organ toxicity, skin cancer), lack of sustainable efficacy, and inconvenient administration schedules.[59, 60]

TRADITIONAL THERAPY

Even without modern knowledge of psoriasis pathogenesis, patients have benefited from the constant improvement of conventional therapies. Most of the currently accepted systemic treatments for psoriasis were developed empirically or were found by pure chance. However, modern knowledge has shed light on the mode of action of some of these classic treatments. Fumaric acid and cyclosporine are mainly immunosuppressive, retinoids target keratinocytes, and methotrexate affects both keratinocytes and immune cells.[48, 61, 62, 63] Even though these therapies continue to play an important role in psoriasis treatment, they have not fully met the needs of patients.[64]

TARGETED BIOLOGIC THERAPY

Elucidation of the immunologic circuits in the pathogenesis of psoriasis has encouraged the development of novel targeted systemic treatment options known as "biologics". By targeting specific pathways in the immunopathogenesis of psoriasis, progression of the disease can be interrupted, resulting in both cutaneous and systemic disease clearance. In some instances, disease clearance may be complete (eg, PASI 100) and long-standing. There are currently five biologic agents approved by the US Food and Drug Administration for psoriasis, alefacept (Amevive®, Biogen Inc, Cambridge, MA), etanercept (Enbrel®, Amgen, Seattle, WA), infliximab (Remicade®, Janssen Biotech Inc, Horsham, PA), adalimumab (Humira®, Abbott Laboratories, North Chicago, IL), and ustekinumab (Stelara®, Janssen Biotech Inc). Newer more targeted agents are in development and in clinical trials. Another immunosuppressant inhibiting lymphocyte activation and cell migration out of blood vessels into tissues, efalizumab (Raptiva®, Genentech, South San Francisco, CA), was taken off the market in 2009 when four cases of progressive multifocal leukoencephalopathy (John Cunningham virus brain infection) were reported in plaque psoriasis patients.[65]

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