Review Article

Psoriasis: Highlights on Pathogenesis, Adjuvant Therapy and Treatment of Resistant and Problematic Cases (Part I)

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Psoriasis is a common inflammatory disease of the skin and joints. Its etiology has been linked to complex interactions between predisposing genes and the environment. The pathophysiology of psoriasis is characterized by epidermal hyperproliferation, enhanced antigen presentation, T helper 1 cytokine production, T cell expansion, and angiogenesis. Tremendous advances in our understanding of this disorder have led to the development of novel therapeutics. In this review we focus on specific advances in our understanding of the pathogenesis and the unrecognized severe effects of psoriasis, and the systemic treatment of resistant and problematic cases which are of major clinical relevance to the clinician. *(J Egypt Women Dermatol Soc 2010; 7: 64 - 70)*

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Psoriasis is a chronic inflammatory skin condition that varies in severity, which has important implications in terms of medical costs and treatment strategies[1].

Pathogenesis

Psoriasis is characterized by hyperproliferation and abnormal differentiation of epidermal keratinocytes, lymphocyte infiltration consisting mostly of T lymphocytes and various endothelial vascular changes in the dermal layer, such as angiogenesis, dilatation and high endothelial venule (HEV) formation[2].

The current understanding of the molecular pathogenesis of psoriasis assigns central importance to an interaction between acquired and innate immunity. At the onset of the disease, special dendritic cells (DCs) in the epidermis and dermis are activated; among other effects, these cells produce the messenger substances tumor necrosis factor (TNF)-α and interleukin (IL)-23, which, in turn, promote the development of T helper (Th)1, and Th17 cells. These T cells secrete mediators that contribute to the vascular and epidermal changes of psoriasis[3].

T lymphocytes and the cytokines and chemokines release appear to be the principal driver of lesion development and persistence, although endothelial cells, neutrophils, and natural killer T cells may play an adjunctive role along with other cytokines and selectins such as intercellular adhesion molecule (ICAM)-1[2].

Role of T lymphocytes

The involvement of T lymphocytes in the pathogenesis of psoriasis can be described in terms of 3 events: the initial activation of T lymphocytes, the migration of T lymphocytes into the skin, and the various roles played by cytokines released from T lymphocytes and other cells[4].

T lymphocyte activation

This occurs in a series of steps, the first of which is incorporation of unidentified antigens by antigen-presenting cells (APCs) in the epidermis and dermis. This process involves binding of the antigens to the MHC on the APC surface[4], and the APC migrates to the lymph nodes. There, the APC binds reversibly and briefly with naïve or resting T cells through interactions between surface molecules located on both cells. Next, the MHC presents the antigen to a T lymphocyte receptor to begin activation of the T lymphocyte. The second signal for T lymphocyte activation is a non antigen/cell-cell interaction known as costimulation. If costimulation does not occur, the T lymphocyte will either undergo apoptosis or become unresponsive. Costimulation involves pairing of receptor with ligand on the T cell; these pairs include lymphocyte functional antigen (LFA)-3 interacting with CD2, B7 interacting with CD28, and ICAM-1 interacting with LFA-1[4].

Migration into the skin

The activated T lymphocytes expand, which results in proliferation of antigen-recognizing T lymphocytes, memory-effector cells. The T lymphocytes enter the circulatory system and, via cell-cell interactions with endothelial cells of the blood vessel, migrate to the inflamed skin[4].

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Role of cytokines

Interleukin-12 is a heterodimeric cytokine produced by DCs and macrophages. It induces differentiation of CD4 naïve T cells to Th1 cell and activates natural killer cells. These Th1 cells and activated natural killer cells produce interferon (IFN)-γ, and other type-1 cytokines, such as IL-2 and TNF-α[5].

Interleukin-23 is a more recently described cytokine that is closely related to IL-12 in structure. The dominant role of IL-23 involves the stimulation of a subset of CD4+ T cells (sometimes called IL-17 producing T cells) to produce IL-17 (Figure 1)[5]. IL-17 is a critical component in the establishment and perpetuation of autoimmune inflammation[1]. IL-17 induces the production of proinflammatory cytokines, predominately by endothelial cells and macrophages. It is believed that IL-17 and IFN-γ synergize to increase production of proinflammatory cytokines by keratinocytes, which is likely important for the development of inflammation in the skin seen in psoriasis[6].

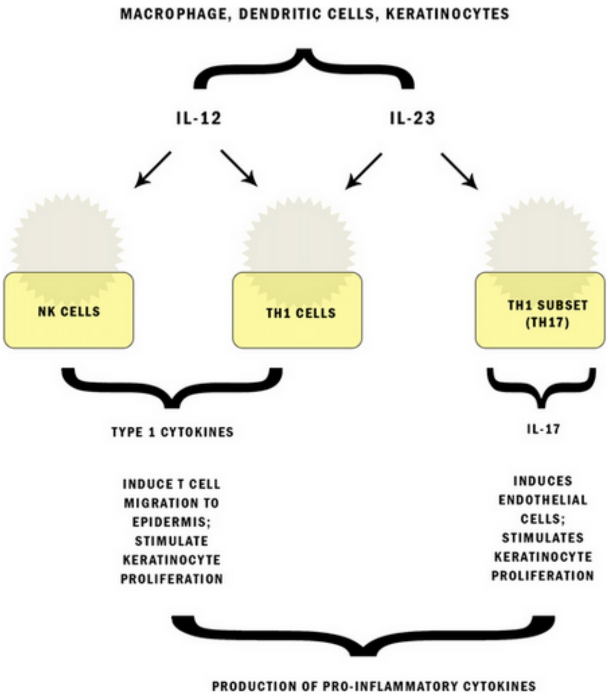

Figure 1. Pathways engaged by interleukin (IL)-12 and IL-23[5]. NK = Natural killer; Th1 = T helper 1.

Once at the inflamed skin site, the activated T lymphocytes encounter the initiating antigen, and release Th1 cytokines, which play a central role in the phenotypic expression of psoriasis[2]. Both CD4+ and CD8+ T lymphocytes produce Th1 cytokines. Key Th1-type cytokines involved in the pathogenesis of psoriasis are IFN-γ, IL-2, and TNF-α. IL-2 stimulates T lymphocyte growth[7]. IFN-γ may inhibit apoptosis of keratinocytes by stimulating expression of the anti-apoptotic protein Bcl-x in these cells. This probably contributes to the hyperproliferation of keratinocytes observed in psoriatic lesions[1]. TNF-α may promote psoriasis development in several ways, including increasing proliferation of keratinocytes and augmenting the production of proinflammatory cytokines from T lymphocytes and macrophages, of chemokines from macrophages, and of adhesion molecules from vascular endothelial cells[8]. In addition, Th1 cytokines cause the release of cytokines from other cells, producing a cascade of chemical messengers that largely affect the distinctive features of psoriatic lesions[2].

Defective T regulatory cell suppressor function

T regulatory (Treg) cell is a CD4+ T lymphocyte that constitutively expresses CD25 (the IL-2 receptor α-chain). This lymphocyte can suppress immune responses and prevent the development of autoimmune diseases in adoptive transfer animal model systems. These cells are anergic to TCR mediated stimulation but proliferate in response to exogenous IL-2, which is an important growth factor for this cell type. These Treg cells can suppress the activities of CD4+ and CD8+ T lymphocytes in a non antigen-specific manner, both in vitro and in vivo. This suppression of T lymphocyte responses is mediated by two non exclusive mechanisms: cell contact and suppressive cytokines such as IL-10 and transforming growth factor (TGF)-β. Other markers of Treg cells are expression of the transcription factor FoxP3, the costimulation receptor cytotoxic T lymphocyte antigen 4 (a signaling molecule that limits T lymphocyte proliferation), and neuropilin-1[9]. Sugiyama et al.[10] have demonstrated deficient Treg cell activity in the peripheral blood and in skin lesions of patients with psoriasis. Although the absolute number of circulating Treg cells in patients with psoriasis is normal compared with healthy controls, they were relatively deficient in their ability to suppress effector CD4+T lymphocyte proliferative responses. This explains the defective immunoregulatory activity in psoriasis that permits unrestrained T lymphocyte activation and cytokine production in skin lesions of psoriasis.

This finding of deficient Treg cell suppressor functional activity in psoriasis presents the opportunity for successful immunotherapy. Manipulation of Treg cell expansion or cytokine production in vitro or in vivo would potentially provide a novel therapeutic approach. Experimental approaches have involved the in vitro expansion of Treg cells with IL-2, which was successfully used in the treatment of autoimmune diabetes. Expansion of Treg cells with antigen-pulsed DCs and IL-2 is another approach that has been successfully used. In addition, mucosal administration of antigen leads to the development of another type of suppressor cell, Th3 regulatory T cells, which produce IL-10 or TGF-β[11].

Role of keratinocytes and other cells

Hyperplasia and altered differentiation of epidermal keratinocytes are classic features of psoriatic lesions. The proliferative cell population is approximately doubled in psoriasis, whereas the cell cycle is more than 8 times shorter (36 vs 311 hours) and daily production of keratinocytes in psoriatic lesions is approximately 28 times greater than that in normal epidermis. Keratinocyte hyperproliferation is stimulated by cytokines released from both T lymphocytes and keratinocytes. Keratinocytes produce IL-6, IL-8, TGF-α, TGF-β, and amphiregulin. TGF-α and amphiregulin both stimulate hyperproliferation of keratinocytes and are, along with TGF-β, ligands for IL-1 and epidermal growth factor receptor (EGF-R), the expression of which is increased in psoriasis[12]. IL-8 stimulates proliferation of keratinocytes and is also a chemoattractant for neutrophils. Intraepidermal accumulation of neutrophilic granulocytes is another characteristic feature of psoriatic lesions, and, although the role of neutrophils in the pathogenic process is incompletely understood, neutrophils may activate T lymphocytes and influence the growth and differentiation of keratinocytes[13].

Role of angiogenesis

Although angiogenesis may not be the primary event in the pathogenesis of psoriasis, understanding the pathways leading to angio-proliferation may help in finding novel antipsoriatic drugs. In fact, vitamin D analogues, retinoids, cyclosporine and sirolimus all possess anti-angiogenic activity as well as antiproliferative and anti-inflammatory effects[14].

Characteristic vascular changes also occur in the dermis of psoriatic lesions, including dilatation and tortuousity of capillaries, angiogenesis and HEV formulation[2]. This capillary dilation may help nourish the hyperproliferating skin. Angiogenesis and vascular hyperpermeability are the result of increased production of vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) by keratinocytes that have been stimulated by TGF-α produced by both T lymphocytes and keratinocytes. TNF-α is also a promoter of angiogenesis, whereas IFN-γ, TNF-α, and IL-1 up-regulate ICAM-1 expression in vascular endothelial cells. Endothelial ICAM-1 is important because its interaction with LFA-1 on T lymphocytes is a key step in the trafficking of T lymphocytes to affected skin[15].

Role of innate immunity

Toll like receptors (TLRs)

Toll like receptors belong to the so-called group of non clonal pattern recognition receptors, which recognize constitutive and conserved molecular patterns shared by many pathogens. TLRs are important in the early recognition of microbial structures. They signal via the transcription factor nuclear factor (NF)-κB, which is known to activate the promoter regions of numerous inflammatory genes. TLR1, TLR2 and TLR5 were shown to be expressed by keratinocytes in psoriasis. TLR1 and TLR2 were found to be highly expressed in the upper epidermis in lesional skin, while the expression of TLR5 in lesional epidermis was lower than that in the normal epidermis. These changes may be secondary to an altered keratinocyte differentiation pathway or result from the effects of proinflammatory cytokines such as TNF-α and IFN-γ present in the psoriatic lesion[16].

Antimicrobial peptides (AMPs)

Antimicrobial peptides are an important component of the innate immune system and play a major role in the homeostasis of surface organs such as the skin. Nearly all AMPs that have been identified to date are present in increased amounts in psoriasis lesions[17]. The overexpression of AMPs is characteristic of psoriasis and may be interpreted as a sign of activation of the innate immune system. In accordance with this hypothesis, bacterial infection of psoriatic lesions is not observed in clinical practice (in contrast to atopic dermatitis)[3].

Role of heredity

We could also accredit the impact of some environmental factors on the induction of psoriasis symptoms. Despite the clear familial aggregation of psoriasis, the precise inheritance model has been under debate. Currently, most investigators agree that psoriasis belongs to the group of complex diseases, the inheritance being multifactorial – genetic variants in multiple genes interact both with each other and the environment. Several disease susceptibility loci have been suggested as predisposing factors[18].

Other factors

- Triggering factors

One well-known trigger in psoriasis is physical damage to the papillary layer of the dermis, assumed to activate multiple inflammatory pathways (Koëbner's isomorphic phenomenon). Another cause for psoriasis exacerbations is streptococcal (throat) infection[19]. Other well-known triggers are stress and the use of beta blockers and lithium salts. Benzodiazepines, organic nitrates, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs have also been implicated[20].

- Diet and psoriasis

Energy intake

The prevalence and severity of psoriasis have been reported to be improved by low-calorie diets with decreased in the epidermal cell proliferation rate. The most important reason is probably the lack of arachidonic acid (AA) intake, resulting in lower leukotriene (LT) B4 production. During fasting, CD4+ T cell activation is reduced and anti-inflammatory cytokines such as IL-4 increase. Another reason may be a reduction of oxidative stress due to calorie restriction, because psoriasis appears to be associated with oxidative stress[21]. A vegetarian diet may be beneficial because it is associated with a reduced AA intake. As psoriasis is positively connected with body mass index (BMI)[22], weight reduction is recommended for obese patients.

Alcohol and Nicotine

As alcohol stimulates the release of histamine, skin lesions can aggravate as a consequence. Moreover, a high alcohol intake may be accompanied by an excessive intake of high-fat foods and saturated fats and a low intake of vegetables and fresh fruit. Therefore, alcohol intake should be restricted in psoriasis[23].

Nicotine alters a wide range of immunological functions, including innate and adaptive immune responses. Nicotine can modulate the functional capacity of DC and can increase the secretion of proinflammatory Th1 cytokines by DC. Additionally, nicotinic cholinergic receptors have been demonstrated on keratinocytes that stimulate calcium influx and accelerate cell differentiation; they can also control keratinocyte adhesion and upward migration in the epidermis. This suggests a biologic explanation for the association between smoking and psoriasis[24].

Polyunsaturated fatty acids

Two families of polyunsaturated fatty acids are distinguished depending on the location of the first double bond counted from the methyl end. The essential fatty acid linoleic acid (C18:2n-6) belongs to the n-6 family. It is found in seeds, e.g. sunflower seeds and can be converted to the more unsaturated derivative, AA (C20:4n-6). Food sources of AA are only animal-derived foods such as meat and egg yolk. The fatty acids α-linolenic acid (C18:3n-3), eicosapentaenoic acid (EPA; C20:5n-3) and docosahexaenoic acid (DHA; C22:6n-3) are the most abundant n-3 fatty acids in food. α-Linolenic acid is found in linseed and walnut oil, whereas EPA and DHA are typical fish oil fatty acids, which are contained in oily fishes such as mackerel and herring. AA can be converted to PGE2 and to LTB4, whereas eicosanoids derived from EPA are PGE3 and LTB5. The EPA-derived eicosanoids, PGE3 and LTB5, possess less inflammatory action than do PGE2 or LTB4, both formed from AA. This is why eicosanoids derived from AA can exacerbate inflammatory processes and those derived from EPA exhibit anti-inflammatory properties. Fatty acids can modulate proinflammatory cytokine production and actions. N-6 polyunsaturated fatty acids such as AA may enhance IL-1 production and tissue responsiveness to cytokines, whereas n-3 polyunsaturated fatty acids such as EPA or DHA have the opposite effect. Several trials have demonstrated the anti-inflammatory effects in psoriasis of fish oils which are rich in n-3 polyunsaturated fatty acids. Diets rich in n-3 fatty acids result in the substitution of AA by n-3 polyunsaturated fatty acids in membrane phospholipids. Low dietary AA intake which is typical for vegetarian diets can also reduce LTB4 synthesis and may additionally improve inflammation[25].

In contrast to the mostly negative results from oral supplementation studies with n-3 fatty acids, promising advances were made in parenteral application of n-3 fatty acids, indicating positive effects on acute inflammatory disorders[26].

Gluten

Patients with latent gluten sensitivity exhibited increased bowel permeability despite normal small intestinal histology. The increased intestinal permeability may allow the passage of small numbers of microbes which can act as superantigens and may induce the appearance or exacerbation of psoriasis in predisposed subjects which could be reversed by a gluten-free diet. Another explanation of the coincidence of celiac disease (CD) and psoriasis may be the profile of released cytokines. In psoriasis the predominating Th1 cells mainly produce IFN-γ and IL-2. T cells from patients with CD release a similar cytokine profile in response to a gluten challenge in vitro. Some case reports indicate that elevated serum levels of these cytokines may be sufficient to result in CD or psoriasis in predisposed individuals[27].

Oxidative stress and antioxidants

Oxidative stress and increased free radical generation have been linked to skin inflammation in psoriasis. Superoxide anion liberation was elevated in psoriatic dermal fibroblasts, which have been suggested to play a central role in the inflammatory mechanism of psoriasis. Patients with psoriasis exhibit several markers of oxidative stress and show impaired antioxidant status: increased concentrations of malondialdehyde (MDA), a marker of lipid peroxidation, in plasma and red blood cells and decreased plasma levels of β-carotene and α-tocopherol as well as decreased serum concentrations of selenium were found[21].

Fish oil supplementation not only altered the lipid pattern of erythrocyte membranes but also led to a reduction of MDA in patients with psoriasis and therefore may reduce oxidative stress. The consumption of vegetables and fruits may be beneficial in psoriasis due to their high content of various antioxidants such as carotenoids, flavonoids and vitamin C[22].

Vitamin D3 and analogues

Human cultured keratinocytes exposed to calcitriol showed marked inhibition of growth and accelerated maturation. The effects on cell proliferation and differentiation via the vitamin D receptor (VDR) led to the concept of using 1,25$(OH)_2$D3 in psoriasis. Calcitriol and its analogues exert antiproliferative and prodifferentiative as well as immunoregulatory activities. VDR ligands directly influence T cell activation and modulate the phenotype and function of APC and DC. Meanwhile, vitamin D analogues including calcipotriene, 1,24-dihydroxyvitamin D3 and 1,25$(OH)_2$D3 are considered the first line of treatment for psoriasis.

As insufficient vitamin D is a general problem, oral vitamin D supplementation may be considered in patients with psoriasis who do not use topical vitamin D analogues. In cases of topical treatment, such supplementation must be avoided because of the risk of hypercalcaemia[28].

Vitamin B12

Rich sources of cobalamin (vitamin B12) are animal organ meats (especially liver and kidney), fish, egg and milk products. Vitamin B12 may influence psoriasis due to its role in nucleic acid synthesis. In vitro studies also demonstrated immunomodulatory effects of vitamin B12 on T lymphocytes and cytokines[29].

Psoriasis and coronary atherosclerosis

The biologic mechanisms that putatively contribute to accelerated atherosclerosis and increased risk of cardiovascular events in psoriasis are largely unknown but are likely to be multifactorial. First, psoriasis and cardiovascular disease may share common risk factors, such as smoking and alcohol consumption. Second, patients with psoriasis may have a higher prevalence of conventional cardiovascular risk factors compared with those without psoriasis (eg, obesity, low physical activity). Third, medications commonly used to treat psoriasis may contribute to the increased risk. Indeed, methotrexate (MTX) use is associated with hyperhomocysteinemia, a risk factor for cardiovascular disease[30]. Cyclosporine use is associated with elevated blood pressure[31]. In addition, acitretin and cyclosporine use are associated with lipid abnormalities[32]. Fourth, inflammatory activity in psoriasis may act independently of conventional cardiovascular risk factors and medications to increase the risk through biological mechanisms, similar to those observed in other systemic inflammatory conditions. Another possible explanation is underdiagnosis and undertreatment of cardiovascular disease in patients with psoriasis compared with those without psoriasis, similar to other chronic diseases. Finally, shared genetic mechanisms may play a role. Overlapping of susceptibility loci has been demonstrated in psoriasis and diabetes. Namely the same functional polymorphisms in cytokine genes or genes that encode products that regulate immune system activation may increase susceptibility to both psoriasis and cardiovascular disease[33].

Inflammation has been implicated in the etiology of atherosclerosis, unstable coronary syndromes, and heart failure. Inflammatory immune activation may lead to increased blood levels of proinflammatory cytokines and acute phase reactants which are strongly associated with the risk and outcomes of coronary events[34].

Atherosclerosis shares many similarities with other immune-mediated diseases including psoriasis[34]. Inflammatory markers have been shown to be increased in both conditions, at local and systemic levels.[35] Histologically, both conditions involve monocytes, macrophages, mast cells, lymphocytes and connective tissue cells and the extracellular matrix. Activation of T cells, macrophages and mast cells releasing several cytokines, matrix-degrading proteases, and collagen-breaking enzyme, contributes to the evolution of psoriatic lesions and plays an important role in destabilization of atherosclerotic plaques[36].

The Th1/Th2 imbalance is involved in the pathogenesis of both atherosclerosis and psoriasis. Both the unstable atherosclerotic plaques and the psoriatic plaques have an increased percentage of activated T cells expressing the Th1 pattern of cytokines. Other similarities include the chemokines, local and systemic expression of adhesion molecules, endothelins, neoangiogenesis, and superantigens as possible triggers of T cell activation in both conditions[37]. Platelet activation and subsequent platelet-leukocyte interactions are common to pathogenesis of both inflammatory skin diseases and atherothrombosis[38].

Psoriasis and the metabolic syndrome

Psoriasis is associated with the complex disorder of metabolic syndrome, which incorporates hypertension, dyslipidemia, obesity, and impaired glucose tolerance, and that the association is stronger for severe psoriasis compared with mild psoriasis[39]. Similar to psoriasis, the metabolic syndrome is characterized by increases in the immunological activity of Th1, which suggests the hypothesis that psoriasis may be associated with the metabolic syndrome because of shared inflammatory pathways. Circulatory levels of TNF-α, soluble TNF-α receptors and in vitro TNF-α production have been shown to be elevated in patients with components of the metabolic syndrome, such as obesity and insulin resistance. Therefore, it is possible that the association of the diseases which characterize the metabolic syndrome and psoriasis is explained by dysregulation of Th1 pathways shared by these seemingly disparate diseases. Another explanation for the predisposition of psoriasis patients to develop metabolic syndrome may be that certain behaviors or the psychological impact of psoriasis itself (e.g., poor eating habits, alcohol consumption, stress and decreased exercise due to psoriasis symptoms or stigmatization) may lead to development of increased body weight and the metabolic syndrome. Lastly, the metabolic syndrome itself could predispose an individual to developing psoriasis[40].

Unrecognized severe effects of psoriasis:
Acute respiratory distress syndrome (ARDS)

Acute respiratory distress syndrome (capillary leak syndrome) is defined as the sudden onset of non cardiogenic pulmonary oedema with severe refractory hypoxaemia in the context of severe infection, aspiration pneumonia, trauma associated with shock and other causes. ARDS is caused by capillary hyperpermeability resulting in an accumulation of fluid and proteins in the interstitial space, with subsequent hypovolemic shock. Symptoms consist of fever, localized or diffuse skin edema, weight gain, renal failure and hypovolemic shock. Muscular edema may initiate myalgias and rhabdomyolysis and occasionally nerve compression. Other manifestations, such as pericardial effusion, cardiac tamponade and cardiogenic shock, may appear. Laboratory tests usually show leukocytosis, elevated hematocrit, neutrophilia, hypoproteinemia or hypoalbuminemia and IgG monoclonal gammopathy[41]. Three forms of capillary leak syndrome are recognized: (1) idiopathic[41]; (2) associated with cutaneous diseases, such as erythrodermic and pustular psoriasis[42] and (3) drug induced, such as the use of retinoids, docetaxel, gemcitabine, sirolimus, granulocyte colony-stimulating factor, IL-2 or anti-CD22 monoclonal antibodies[43]. Retinoic acid induced capillary leak syndrome has been described in the literature as retinoic acid syndrome and can appear in patients with psoriasis. Systemic corticosteroids are an effective treatment in retinoic acid syndrome. The pathogenesis of psoriasis- and retinoic acid induced capillary leak syndrome is yet unresolved. First, a role for an angiogenic peptide may be possible in the disease-induced capillary leak syndrome. It has been known for years that psoriasis is connected with a subclinical renal microvascular hyperpermeability (leading to albuminuria) and that the extent of albuminuria reflects the degree of psoriatic skin involvement[44]. Microalbuminuria in psoriasis may result from the activity of a circulating permeability factor produced by lesional tissue. Several angiogenic peptides have been found to be overexpressed in lesional psoriatic skin, and one of them is VEGF. The plasma concentration of VEGF is significantly elevated in psoriasis patients with extensive skin and joint involvement and acts on renal microvasculature to induced hyperpermeability[45].

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