Review paper

Cytokine network in psoriasis. Cross-talk between keratinocytes and cells of the skin immune system

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Abstract

Psoriasis is a common autoimmune skin disease characterized by T cell-mediated hyperproliferation of keratinocytes. The cutaneous and systemic overexpression of a variety of proinflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8, IL-15, IL-18, IL-19, IL-20, IL-22, IL-23 and IFN-gamma, has been demonstrated. The cellular composition of the inflammatory infiltrate within the psoriatic plaques, as well as the keratinocytes hyperproliferation, appear to be directed by these cytokines. Here we briefly review the role of cytokines in the pathogenesis of psoriasis. We present evidence that cytokines of type-1 are responsible for the development, maintenance and resolution of psoriatic lesions. In particular, we have focused our attention on recently discovered cytokines. IL-23, but not IL-12, is considered to be a major factor that drives pathogenic Th1 lymphocytes. On the other hand, IL-19, IL-20 and IL-22, cytokines structurally related to IL-10, affect differentiation and migration of human keratinocytes. Importantly, in contrast to IL-10, they show proinflammatory activities and are involved in the pathogenesis of psoriasis. Finally, we discuss the effectiveness of cytokine therapies in psoriasis, in particular anti-TNF therapy.

Key words: *psoriasis, keratinocytes, Th1 lymphocytes, inflammation, proinflammatory cytokines.*

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Introduction

Etiology and pathogenesis of psoriasis. Genetic basis

Psoriasis is a common chronic inflammatory skin disease characterized by localized hyperproliferation of keratinocytes. The disease has certain distinct but overlapping clinical phenotypes including chronic plaque lesions (psoriasis vulgaris), acute and usually self-limiting guttate type eruptions, seborrhoeic psoriasis, pustular lesions, and at least 10% of these patients develop arthritis [1]. Although the etiology of psoriasis remains unknown, it is generally assumed that it is a T-cell mediated autoimmune disease.

In recent years, genetic analyses of multiply affected families have identified some susceptibility variants for psoriasis. One of the most compelling susceptibility factors for psoriasis is the presence of HLA-Cw*0602 allele, which was found in about 50% of psoriasis patients [2]. Psoriasis is not genetically homogenous diseases, but interestingly, it is the only chronic inflammatory disease that has a strong association with HLA-C. Interestingly, in recent years, genetic connections between psoriasis and other chronic inflammatory diseases such as atopic dermatitis, rheumatoid arthritis and Crohn's disease have been demonstrated [3]. Type I psoriasis, defined by the onset of psoriasis before age of 40 years, had a stronger genetic basis as a greater proportion of patients had a family history of psoriasis, stronger HLA associations (HLA-Cw*0602) and more severe symptoms. Patients with type II psoriasis were characterized by a later age of onset, after 40 years of age, and were found to have lower familial tendency [4, 5].

Triggering factors, both external (which directly interact with the skin) and systemic, can elicit psoriasis in genetically predisposed individuals. Psoriatic lesions can be induced by

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various forms of cutaneous injury (trauma, sunburn), drug eruptions or viral exanthems. For example, in 90% of psoriatic skin samples, polymerase chain reaction has revealed DNA of human papillomaviruses (mainly EV HPV5) [6]. In addition to that, considerable clinical evidence exists for the role of stress in onset and exacerbation of psoriasis [7].

Several drugs have been incriminated as inducers of psoriasis (lithium, β-blockers, interferons, angiotensin--converting enzyme inhibitors) as well as increased alcohol consumption and increased incidence of smoking [8, 9]. Although all these factors have been implicated, infection with β-hemolytic streptococci is the only well defined external trigger that has convincingly been associated with induction and/or aggravation of psoriasis [1]. It has been reported that patients with chronic plaque psoriasis can experience an exacerbation after streptococcal throat infection [10]. It is assumed that streptococcal toxins can act as superantigens, resulting in a complex cascade of T-cell, Langerhans cell and keratinocyte activation and interactions [11]. Moreover, it has been postulated that psoriasis is mediated by T cells that cross-react with epitopes which are common to streptococcal M proteins and type I keratins that are up-regulated in psoriatic lesions [12].

Histology of psoriatic lesions

Psoriasis is a papulosquamous disease with variable morphology, distribution, severity and course. The morphology of psoriatic lesion can range from small tear shaped papules (guttate psoriasis) to pustules (pustular psoriasis) and generalized erythema and scale (erythrodermic psoriasis). These different forms of psoriasis may be localized or widespread and disabling [13, 14]. Chronic plaque psoriasis, the most common variant of psoriasis vulgaris, is characterized by sharply demarcated and erythematous papulosquamous lesions. The classic findings of erythema, thickening and scaling are reflections of elongated dilated vertical dermal capillaries that are close to the skin surface, epidermal acanthosis plus cellular infiltrates, and abnormal keratinization. Increased keratinocyte proliferation observed in psoriasis is a consequence of an increase in the proliferating cell compartment in the basal and suprabasal levels of the epidermis; the number of cycling cells is increased approximately sevenfold. Multiple growth factors, in particular transforming growth factor-α (TGF-α), epidermal growth factor (EGF), keratinocyte growth factor (KGF), insulin-like growth factor I (IGF-I) appear to be an important autocrine mediators of these events. Increased level of these factors and increased expression of their receptors were found in psoriatic lesions and cultured psoriatic keratinocytes [15-17].

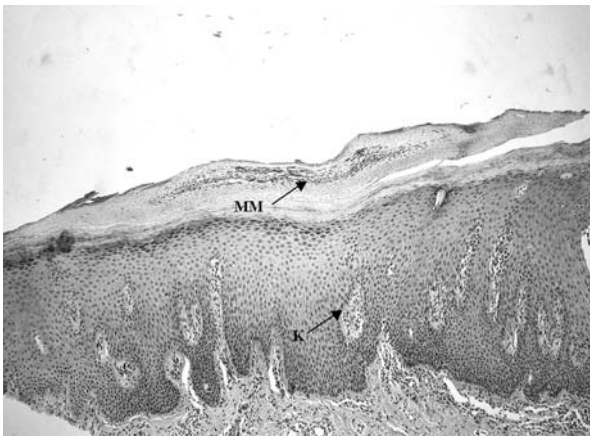

Fig. 1. Histology of psoriatic skin (Psoriasis pustulosa) showing major landmarks. A superficial perivascular infiltrate of leukocytes with papillary edema and dilatation of capillaries in the dermis. The acanthotic epidermis with focal accumulations of neutrophils and lymphocytes ("spongiform pustule of Kogoj") (**K**). Above these foci, stratum granulosum partially broken. Munro microabscesses present within parakeratotic areas of stratum corneum (**MM**) (H-E stain; 20x)

The histopathological findings in an active lesion are diagnostic for psoriasis. In the dermis the capillaries are increased in number and length. Marked edema is seen especially at the tops of the papillae, in these place there is a mixed perivascular infiltrate of lymphocytes, macrophages and neutrophils. The epidermis is acanthotic with focal accumulations of neutrophils and lymphocytes which have migrated from the underlaying dermis. Above these foci, the granular layer is absent and the stratum corneum contains flattened nuclei. Accumulations of neutrophils in the stratum corneum (microabscess of Munro) and in the epidermis (spongiform pustule of Kogoj) are pathognomonic for psoriasis. Therefore psoriatic keratinocytes proliferate and mature rapidly so that terminal differentiation, normally occurring in granular keratinocytes, is incomplete. Hence, squamous keratinocytes aberrantly contain intact nuclei (so-called parakeratosis) (figure 1).

Cytokine network: Cross-talk between keratinocytes and the immune cells in psoriasis

The pathogenesis of psoriasis remains primarily unclear. Nevertheless, the presence of T-lymphocyte subsets in an early phase of the disease and the response to T-cell targeting therapies strongly suggest that these cells are the driving force in the pathogenesis of psoriasis [18, 19]. The clinical features of psoriasis, such as the hyperproliferation of keratinocytes, inflammation and increased neovascularization, reflect the pathological interplay between keratinocytes and immune cells [20]. Psoriasis is considered to be a primary chronic inflammatory disorder mediated by type-1 T memory cells [3]. Although CD4+ T cells seem to be essential for initiating psoriatic lesions, CD8+ T cells may also play an important role in the pathogenesis of psoriasis as dermal T lymphocytes are a mixture of CD4+ and CD8+ T cells. Increased numbers of T cells are a highly consistent finding, while neutrophils are quite variably expressed in psoriatic lesions from different patients [21, 22]. Apart from T cells, dendritic cells (DC)

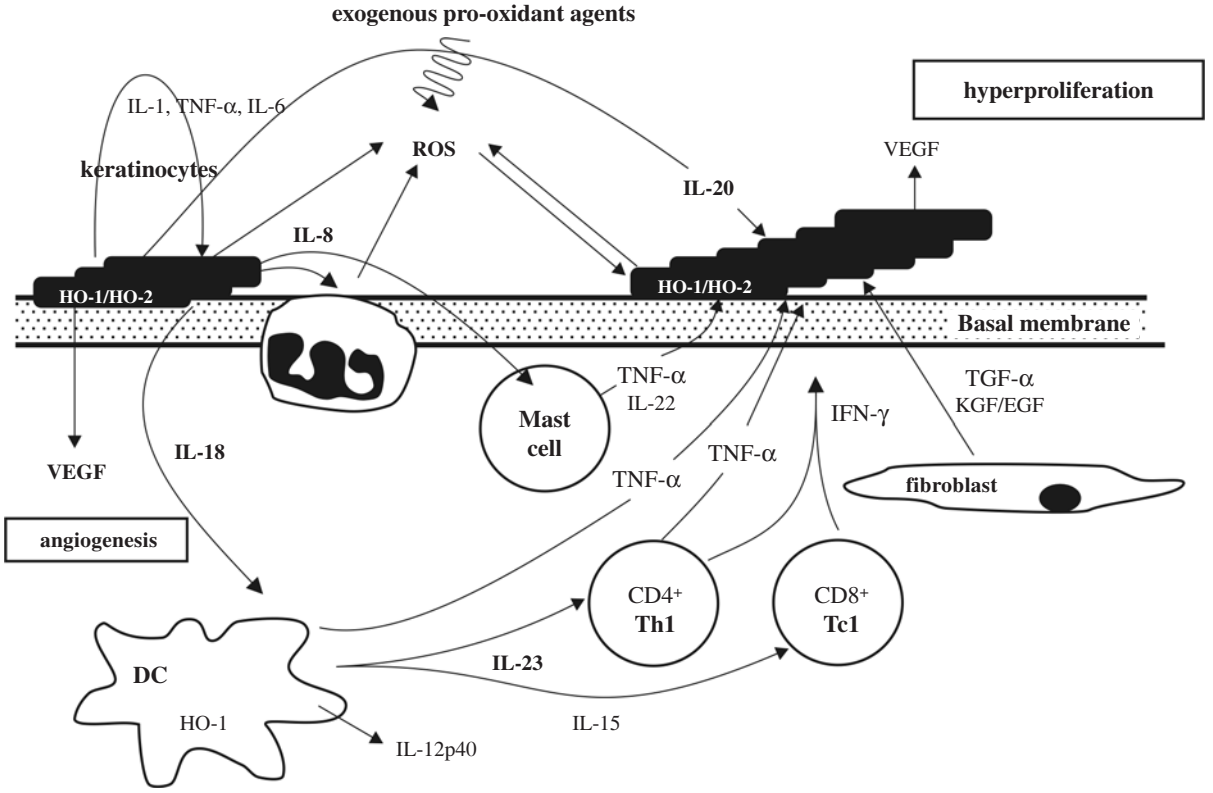

Fig. 2. Cytokine network in psoriasis. Cross-talk between keratinocytes and the cells of skin immune system. Th1 cytokines such as IL-18, IL-23, IFN-γ and TNF-α prevail in the cytokine network in psoriasis. Keratinocytes, dermal DCs, CD4+ Th1 and CD8+ Tc1 lymphocytes are major producers of cytokines in the psoriatic lesions. Pro-inflammatory cytokines are responsible for production of ROS by activated keratinocytes and neutrophils. In addition, cytokines are involved in the proliferation of keratinocytes. Keratinocytes as well as DCs respond to oxidative stress by an increased expression of cytoprotective, anti-oxidant and anti-inflammatory heme oxygenase system (HO-1/HO-2)

Table 1. The array of immune cells that appear in psoriatic lesions. In normal skin dermal DC are represented by Langerhans cells – resident immature dendritic cells. The major immune cells that are abundant in psoriatic skin lesions are: IDEC – inflammatory epidermal dendritic cells; CD4+ and CD8+ T cells (Th1 and Tc1, respectively); neutrophils and mastocytes [2]

Cells	Normal skin	Psoriatic lesions
Dermal dendritic cells:		
Langerhans cells	+	+
IDEC (CD 83$^+$, DC-LAMP$^+$)	–	+ + +
CD4$^+$ Th	(few)	+ + +
CD8$^+$ Tc	(few)	+ +
Neutrophils	–	+ + +
Mast cells	+	+ +
NKT	–	+

form another major class of leukocytes that are found in increased numbers in psoriatic skin lesions along with mastocytes and natural killer cells (NK-T cells) [23]. Skin DCs, such as Langerhans cells (resident immature dendritic cells) and IDEC – inflammatory epidermal dendritic cells (CD83+, DC-LAMP+) play a crucial role in the development of optimal cutaneous immune responses and are known as strong polarisers of T cell responses (table 1) [3, 24].

In the pathogenic models of psoriasis all these immune cells along with keratinocytes contribute to the development of chronic skin inflammation through the production of cytokines [20]. They produce a number of effector and regulatory cytokines, predominantly of Th1-type, creating very complex cytokine network (figure 2). Psoriatic keratinocytes continuously produce enormously wide spectrum of cytokines showing distinct biological functions (TNF-α, IL-1, IL-6, IL-7, IL-8, IL-15, IL-18, IL-19, IL-20, IL-23) [1].

TNF-α, IL-1, IL-6, the major proinflammatory cytokines, activate keratinocytes in an autocrine manner for the production of other inflammatory mediators, such as

ROS, NO and various cytokines [25-27]. Some of these cytokines are responsible for accumulation of inflammatory immune cells in psoriatic plaques. For example, IL-8 plays a role in the migration of neutrophils and mast cells to lesion sites, while IL-7 and IL-15 activate CD8+ T cells [28, 29]. The exact role of TNF-α in pathogenesis of psoriatic lesions is still unclear, however, anti-TNF-α therapy demonstrated significant antipsoriatic effects indicating that this cytokine plays a crucial role in this disease [25, 26].

It is well documented that Th1 cytokines, such as IL-23, IFN-γ and TNF-α predominate in psoriatic lesions [1, 30]. IFN-γ is produced by both CD4+ Th1 and CD8+ Tc1 cells, and may be a central effector cytokine in psoriasis. However, this is IL-23, the cytokine produced by keratinocytes and/or skin DC activated with IL-18, that plays a principal role in activating T cells in psoriasis [31, 32]. IL-23 is a heterodimer, sharing a p40 subunit with IL-12 but having a distinct p19 subunit. IL-23 stimulates T cells for IFN-γ production polarizing the immune response into type-1. It has been recently postulated that IL-23, but not IL-12, plays a major role in the perpetuation of the inflammation process in psoriasis [33, 34].

Other cytokines contribute to hyperplasia of keratinocytes, the major hallmark of psoriatic lesions. IL-19, IL-20 and IL-22, play a special role in psoriasis; they all belong to a family of cytokines structurally related to IL-10, but in contrast to IL-10, they have proinflammatory activities [35, 36]. The increased IL-19, IL-20, IL-22 mRNA expression and detection of their receptors in lesional psoriatic skin suggests that these cytokines are involved in the pathogenesis of psoriasis [37, 38]. A number of separate studies confirmed recently this hypothesis. It has been shown that IL-19 stimulates dermal macrophages for production of IL-6 and TNF-α [39]. In addition, it has been demonstrated that IL-19, as well as IL-20, stimulates CD8+ T cells to produce KGF (keratinocyte growth factor), which contributes to sustaining the hyperproliferative status of keratinocytes [37, 40]. On the other hand IL-22 inhibits epidermal differentiation and induces proinflammatory gene expression and migration of keratinocytes [41].

The pattern of cytokines involved in pathogenesis of psoriasis may be defined as proinflammatory and type-1 (Th1 inducers), and is characteristic for many inflammatory autoimmune diseases. However, unique for psoriasis is the effect of cross–talk between hyperproliferating keratinocytes and immune cells. At inflammatory psoriatic lesions both keratinocytes and inflammatory cells produce high amounts of ROS and NO which leads to the expression of heme oxygenase-1 (HO-1), a stress inducible enzyme with anti-oxidant, cytoprotective and anti-inflammatory properties (figure 2) [42].

In recent years our knowledge about the role of cytokines in pathogensis of psoriasis has improved dramatically. The question is how to use this knowledge to treat this disease.

Major strategies of psoriasis treatment. Cytokine therapies

The traditional strategy of treatment of psoriasis is to minimize the severity of psoriatic lesions. First–line therapy of psoriasis includes topical application of agents which affect keratinocyte proliferation and production of inflammatory mediators involved in pathogenesis of psoriatic skin inflammation [43]. However, the role of topical therapeutic agents in improving the balance between oxidants and antioxidants is unclear and not consistent with the suggested, pathological role of oxidative stress in psoriasis For example, phototherapy (UVB- ultraviolet B, PUVA – photosensitizing medicaments + ultraviolet A), is one of the forms of traditional topical therapy to treat psoriasis via generation of ROS [44].

As all of the above proinflammatory mediators are under control of anti-inflammatory agents, the anti-inflammatory therapy (e.g. systemic cytokine therapy) seems to be a rational and effective strategy in the treatment of psoriasis [18].

New anti-inflammatory drugs, biologically based agents (e.g anti-TNF agents), are devoid of the side-effects characteristic for traditional systemic anti-psoriatic agents such as methotrexate and cyclosporine, and, most importantly, they can precisely target steps in the pathogenesis of psoriasis [18, 26]. All anti-TNF agents currently in clinical use, namely the monoclonal antibodies *infliximab* and *adalimumab*, as well as the soluble TNF receptor *etanercept*, markedly decrease not only joint inflammation but also skin inflammation in patients with psoriatic arthritis. In addition, they are effective in decreasing the clinical activity of skin lesions in patients with the severe form of psoriasis vulgaris [45].

In our opinion, future cytokine therapies in the treatment of psoriasis should include IL-10 therapy (for its ability to inhibit Th1 response) and anti–IL-23 therapy (for its ability to stimulate Th1 response).

Conclusions

In the present paper we have summarized the current data confirming the role of cytokines in physiological and pathological status of the skin. It is commonly accepted that cytokines of Th1-type play an essential role in the development of autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease and psoriasis. In the last decade, an enhanced understanding of the role of cytokines in pathogenesis of psoriasis has led to the development and utilization of new drugs. However, further complex studies are necessary to determine the role of cytokines, ROS and HO-1 system in the development and resolution of psoriatic lesions [46].

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