

REVIEW ARTICLE

Cytokine network in psoriasis revisited

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ABSTRACT. Psoriasis is a chronic genetically determined, erythematous-squamous disease associated with many comorbidities. Evidence from clinical studies and experimental models support the concept that psoriasis is a T cell-mediated inflammatory skin disease and T helper (Th) cells – Th1, Th17 and Th22 – play an important role in the pathogenesis. Th1 cytokines IFN γ , IL-2, as well as Th17 cytokines IL-17A, IL-17F, IL-22, IL-26, and TNF α (Th1 and Th17 cytokine) are increased in serum and lesional skin. IL-22 produced by Th17 and new subset of T helper cells, Th22, is also increased within psoriatic lesions and in the serum. Other recently recognized cytokines of significant importance in psoriasis are IL-23, IL-20 and IL-15. The IL-23/Th17 pathway plays a dominant role in psoriasis pathogenesis. Currently due to enormous methodological progress, more and more clinical and histopathological psoriatic features could be explained by particular cytokine imbalance, which still is one of the most fascinating dermatological research fields stimulating new and new generations of researchers.

Key words: psoriasis, interleukin, cytokine, Th1, Th17, Th2

INTRODUCTION

Psoriasis is a chronic genetically determined, erythematous-squamous disease affecting approximately 2-3% of the world's population. About 6-20% of psoriatic patients develop a chronic inflammatory arthritis or enthesitis [1]. Comorbidities associated with psoriasis include other inflammatory conditions such as Crohn's disease and an elevated risk of cardiovascular diseases, lymphomas, diabetes, metabolic syndrome, depression and mortality [2-4].

The histological changes observed within lesional skin include acanthosis, hypogranulosis, parakeratosis, marked dilatation of blood vessels in the papillary dermis, and infiltration of monocytes, dendritic cells (DCs) and T cells. Evidence from clinical studies and experimental models support the concept that psoriasis is a T cell-mediated inflammatory skin disease and T helper (Th) cells – Th1, Th17 and Th22 – play an important role in the pathogenesis [4, 5] (*figure 1*).

Th1 cytokines IFN γ , IL-2, as well as Th17 cytokines IL-17A, IL-17F, IL-22, IL-26, and TNF α (Th1 and Th17 cytokine) are increased in serum and lesional skin [5]. IL-22 produced by Th17 and Th22 is also increased within psoriatic lesions and in the serum [5-8]. Differentiation of naive CD4+ cells into different T cell subsets depends on specific immune conditions (*figure 2*).

Th1 cells differentiate from naive CD4+ cells in the presence of IL-12, IL-18 and IFN α and γ . Th1 cells have been associated with the development and maintenance of chronic inflammatory diseases, such as psoriasis, inflammatory bowel disease (IBD), multiple sclerosis (MS), and rheumatoid arthritis (RA), through Th1 cytokines have an effect on macrophage, neutrophil and CD8+ cytotoxic T cell activation [9].

Th17 cells require a combination of TGF- β 1 and proinflammatory cytokines (IL-1b, IL-6 and/or IL-21) to differentiate. This finding was initially surprising because TGF- β 1 is known to induce the development of regulatory T cells with a potent suppressor function [10, 11]. TGF- β 1 may be secreted by activated T cells to initiate T cell and fibroblast activation, as well as angiogenesis and neovascularization [12-16]. IL-6 is secreted by macrophages, endothelial cells, and epithelial cells, and augments keratinocyte hyperplasia and invasion of macrophages and T cells [16, 17]. Upregulation of the IL-23 receptor makes Th17 cells responsive to IL-23. Some studies suggested that IL-15, produced by monocytes, macrophages, DCs, and T cells, can also induce Th17 cells [16-19]. IL-15 can appear to induce angiogenesis, immune cell (including Langerhans cells [LCs]) recruitment, and activation of keratinocytes (KCs) [12, 20, 21].

Th22 cells have been recently described as inflammatory CD4+ T cells that produce cytokines such as IL-22, IL-26,

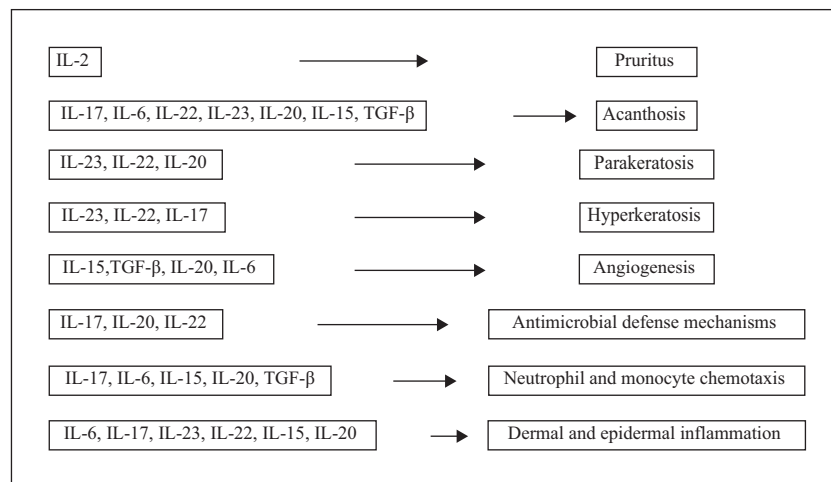


Figure 1
Influence of the cytokines on main features of psoriasis.

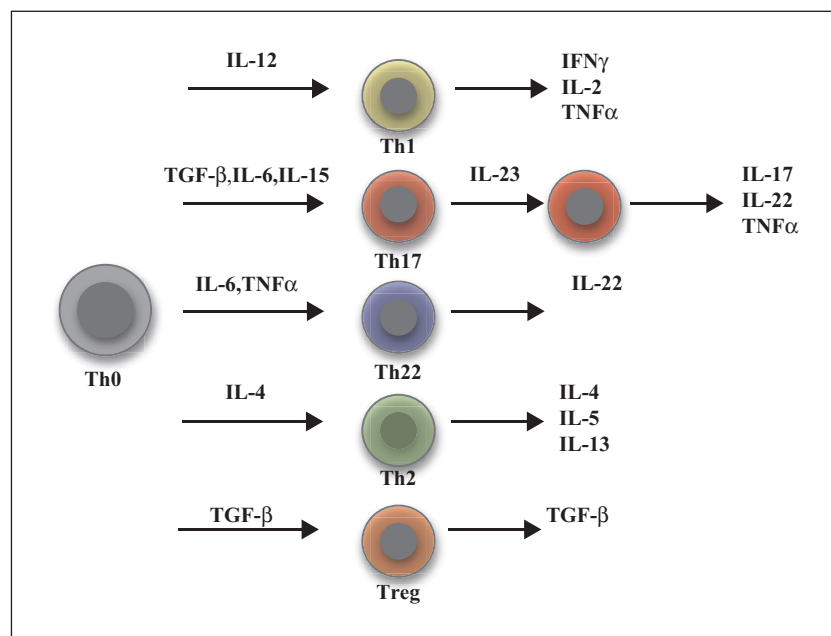


Figure 2
Naive (Th0) T cells differentiation into Th1, Th17, Th22, Th2 and T-regulatory cells. Main cytokines involved in this process.

and IL-13, of which IL-22 is the most important functional cytokine. Recent studies indicate that IL-6 and TNF α , along with the help of plasmacytoid dendritic cells (pDCs), can promote the Th22 phenotype [7, 22].

TH1 CYTOKINES

Interleukin 2 (IL-2)

IL-2 is produced by T cells upon antigen binding to the T-cell receptor (IL-2R). The IL-2 receptor plays a key role in the antimicrobial response and in discrimination between non-self and self immune response. The IL-2R is present in three different forms: high, intermediate and low-affinity complexes. The high-affinity receptor consists of three subunits: α (CD25, Tac), β (CD122), and γ (CD132). The intermediate and low-affinity receptors consist of the β and γ subunits, and the α subunit, respectively [23, 24]. The high-affinity IL-2R is present on actively proliferating

T lymphocytes, recently activated B cells, monocytes and a small population of resting natural killer (NK) cells, although most NK cells express the intermediate affinity receptor isoform [23].

The IL-2/IL-2R interaction stimulates the growth, differentiation and survival of antigen-selected CD8 $^{+}$ T cells via the activation of the expression of specific genes. IL-2 is also necessary during T cell development in the thymus for the maturation of regulatory T cell subset. It stimulates activity and proliferation of NK cells, monocytes, macrophages, stem cells in bone marrow, lymphokine-activated killers (LAK) and tumour infiltrating lymphocytes (TIL), as well as differentiation of B cells (together with IL-15). IL-2 induces production of IFN γ , TNF, IL-6, GM-CSF, IL-2R and IL-2 [25]. IL-2 has a well documented role in induction of pruritus in atopic dermatitis, psoriasis and uraemia [26, 27].

Many drugs used in therapy of psoriasis reduce IL-2 activity by blocking the T cell production of IL-2 (ciclosporin

A, tacrolimus, vitamin D3 analogues) and/or by decreasing the expression of IL-2R (cyclosporin A, UVB and PUVA) [28].

Interferon gamma (IFN γ)

IFN γ is the only type II interferon, classified to this group because of its unique amino acid sequence. Receptors for IFN γ are located on the surface of many cells, but its expression differs from cell to cell. The highest expression is observed on T and B cells, NK cells, monocytes, macrophages, fibroblasts, neutrophils, endothelial and smooth muscle cells [23].

IFN γ influences the immune response regulating activation, proliferation and differentiation of T cells, B cells, macrophages, NK cells, fibroblasts and endothelial cells. IFN γ stimulates production of many proinflammatory factors like IL-1, IL-6, IL-8, IL-12, IL-15, TNF, IFN γ -induced protein 10 (IP-10), inducible NO synthase (iNOS), caspase-1 and gp91^{phox} (NOX2), a subunit of NADPH oxidase [23]. IFN γ has been shown to stimulate DCs to produce IL-1 and IL-23, which are Th17 and Th22 promoting cytokines [29, 30]. Recently a distinct subset of human Th17 cells have also been shown to produce IFN γ [31-33]. IFN γ increases the production of antibodies in response to antigens administered simultaneously with IFN α , expression of MHC class I and II molecules on antigen presenting cells (APCs) as well as expression of ICAM-1 on KCs and endothelium [25, 34].

Literature data on the IFN γ levels in serum and lesional and nonlesional skin in psoriatic patients are controversial. However more authors demonstrated elevated serum IFN γ level in psoriatic patients and correlated it with the clinical severity of psoriasis [31, 35-39]. Uyemura *et al.* observed strong IFN γ expression not only in psoriatic lesions, but also in the nonlesional skin [40]. Many authors state that IFN γ detected in the psoriatic skin is locally produced and does not originate from the peripheral blood [25]. Barna *et al.* obtained clones of different T cells from psoriatic lesions, producing different levels of IFN γ and IL-4, suggesting presence of both Th1 and Th2 cells [41].

A significant decrease in expression of IFN γ and biologically active IL-23 (IL-12/IL-23p40+IL-23p19) in the epidermis and dermis of psoriatic lesions was observed after PUVA therapy [42].

Th1/Th17 cytokine: tumor necrosis factor alpha (TNF α)

Biologically active forms of TNF α , both membrane and soluble ones, are homotrimers consisting of 3 identical protein chains of non-covalent bindings [43, 44]. There are two TNF cell receptors: TNF-RI (also called TNF-R55, TNF-R β , p55, CD120a) and TNF-RII (TNF-R75, TNF-R α , p75, CD120b) presented on all cell types except for erythrocytes. TNF-RI seems to be responsible for the majority of TNF activity. Soluble forms of both TNF receptors, TNF-RI and TNF-RII, are encountered in the blood. By binding TNF, soluble receptors exert an inhibitory or modulatory effect on TNF itself [43, 45].

TNF α is a prominent mediator of psoriatic inflammation and therefore it is a major target of biologic therapeutics. TNF α appears to be a point of convergence for Th1 and Th17 cells. Proteins of TNF superfamily influence

the proliferation, activation and differentiation of many cells and even stimulate apoptosis [25, 45, 46]. TNF enhances the synthesis of IL-1, IL-6, GM-CSF, leukemia inhibitory factor (LIF), TGF, B4 leukotriene (LTB4), PGE2 and expression of some adhesion molecules (E-selectin, ICAM-1, VCAM-1) [46-48]. TNF α induces APCs to secrete IL-23 and upregulate the Th17 cell response [49-51].

An elevated level of TNF in the lesional psoriatic skin in comparison to both nonlesional and normal skin was observed [52, 53]. Overexpressed TNF is localised in the epidermis and around blood vessels in the upper dermis [54]; its sources are KCs, epidermal LCs and macrophages in the papillary dermis [54]. The majority of authors observed increased plasma TNF levels in active psoriatic patients [37, 52, 55]. It is worth underlining that plasma TNF levels are significantly lower than the ones found in suction blister fluid, which suggests that this cytokine is produced locally [25]. A positive correlation between serum TNF levels and PASI score was demonstrated [52, 55, 56]. In the normal skin and unaffected skin of psoriatic patients, TNF-RI is expressed on epidermal KCs and on dermal DCs. In lesional psoriasis skin, TNF-RI, and soluble TNF-RI and TNF-RII were detected in the parakeratotic stratum corneum. Moreover, plasma TNF-RI levels in psoriatic patients were significantly increased compared to those in healthy people [25, 57].

A decrease in TNF cytokine levels after successful anti-psoriatic treatment using different methods, including PUVA, UVB plus topical corticosteroids and dithranol, was observed [37, 55, 58]. The treatment with cyclosporin A, acitretin or Goeckerman method did not exert any influence on TNF protein levels [59]. The TNF antagonist treatment of both psoriasis arthropatica and vulgaris is most widely used and thoroughly studied in clinical practice amongst all anti-cytokine therapies for psoriasis [60].

TH17 CYTOKINES

Interleukin 17 (IL-17A)

IL-17 (IL-17A) is a member of a newly identified cytokine family comprising IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. Very little is known about IL-17B, IL-17C, and IL-17D, which are produced by non-T-cell sources, whereas IL-25 and IL-17F share many features with IL-17A [10, 61]. T cells producing IL-17 are now recognized as a third Th cell subset: Th17 cells [62, 63]. Other IL-17A-producing cells have also been reported, including CD8+ cells [64], $\gamma\delta$ -TCR cells [65-67], DCs [68] and NK cells [69, 70]. IL-17F and IL-17A have 50% sequence homology and they can form IL-17A and IL-17F homodimers or IL-17A-IL-17F heterodimers [10].

There are two receptors for IL-17: IL-17 receptor A (IL-17RA) and IL-17RC. IL-17RA and RC interact together for an optimal response. The inhibition of the two receptors is needed to reduce the response to the combination of IL-17 with TNF [63]. IL-17 and IL-17F have a proinflammatory activity inducing the expression of proinflammatory cytokines, colony-stimulating factors, and chemokines from DCs, neutrophils, T cells, monocyte/macrophages, and epithelial cells [10, 71]. Cells selectively producing IL-17 express the chemokine

receptors CCR6 and CCR4, whereas cells producing both IL-17 and IFN γ express CCR6 and CXCR3 [72, 73]. Hirota *et al.* reported that CCR6 was critical for leukocyte migration into inflamed joints in a mouse model RA [74]. IL-17 expression is increased in inflammatory tissues [9, 71]. IL-17A and IL-17F link also specific and non-specific immune response, because they can mobilize, recruit, and activate neutrophils [10, 61]. In keratinocyte experimental systems, IL-17 and IL-22 act together to induce the proliferation and expression of co-stimulatory immune molecules and downstream immune modulators such as neutrophilic and monophilic chemokines, cellular adhesion molecules, and intracellular transcription factors [12]. IL-23/IL-17 pathway is linked to mucosal host defense against extracellular pathogens [75, 76] and to the induction and progression of many inflammatory diseases, including psoriasis [9, 32, 33]. Normally, IL-17A is present in extremely low or undetectable concentrations in human sera but it is increased in serum and tissue in IBD, MS, and RA [10, 71].

Th17 cells and the cytokines produced by these cells are found in increased levels within skin affected by psoriasis [30, 31, 33, 49, 77, 78]. IL-17-producing cells have been isolated from the dermis of psoriatic lesions by flow cytometry [77] and surface phenotypic analysis of these cells showed a predominantly CD161+ phenotype [79]. DCs isolated from psoriatic skin are able to increase the percentage of IL-17A production in allogenic T cells [49]. IL-17A and IL-17F mRNA were observed in psoriatic skin lesion comparing to nonlesional or healthy skin [5, 33, 49, 73, 78]. In psoriasis no statistically significant differences in peripheral levels of IL-17A have been found. IL-17 and IL-22 may act cooperatively in mediating tissue inflammation by upregulation of antimicrobial peptides human β -defensin (hBD-2), S100A7 (psoriasin), S100A8, S100A9 and matrix metalloproteinase 3 (MMP-3) transcripts in primary KCs [9, 80].

Th17/Th22 cytokine: interleukin 22 (IL-22)

IL-22 is a member of the IL-10 cytokines family, and is mainly produced by Th17, Th22 and mucosal NK cells [75, 78, 81]. This subset of NK cells (NK-22 cells) produces IL-22 in response to IL-23 and may inhibit inflammation (through IL-10 production) and provide mucosal protection (via epithelial cell proliferation) [81]. Th22 cells are recently described inflammatory CD4+ T cells that produce IL-22, but do not express IL-17A or IFN γ [29, 82-84]. Th22 cells are also increased within psoriatic lesions [29, 31, 84].

The IL-22 receptor (IL-22R) is part of the cytokine receptor family class 2 and consists of two subunits, IL-22R1 and IL-10R2 [85, 86]. IL-10R2 is expressed on immune cells (T, B, and NK cells), and IL-22R1 in a variety of non-immune tissues: skin, lung, small intestine, liver, colon, kidney, and pancreas [84]. In KCs the expression of IL-22R1 and IL-10R2 is increased by IFN γ . There is also a soluble, secreted IL-22 receptor called IL-22-binding protein (IL-22BP), which is encoded by a different gene [85, 86]. The affinity of IL-22 to IL-22BP is about four times higher than that of IL-22 to IL-22R1. IL-22 increases the cellular level of STAT3 in the three-dimensional epidermis model which suggests a further positive feedback

mechanism for IL-22 effects [85]. Many IL-22 effects can be amplified by TNF α , IL-17, IFN γ or IL-1 [80, 85, 87, 88]. IL-22 promotes antimicrobial defense mechanisms, protects against tissue damage, and reorganizes non-immune tissues, such as epithelia [85]. IL-22 upregulates the expression of acute phase proteins: serum amyloid A (SAA) in the liver and pancreatitis-associated protein 1 (PAP1) in the pancreas [85]. IL-22 increased the expression of the hBD-2 and hBD-3 in human KCs and MMP1 and MMP3 in the skin and MMP1, MMP3, and MMP10 in the digestive tract [85, 86, 89].

Increased IL-22 mRNA and protein levels have been found both in the skin and blood of psoriatic patients compared to healthy controls [5, 6, 8, 78, 90]. IL-22 mRNA levels were higher in lesional skin than in psoriatic peripheral monocytes [90]. IL-22 levels in plasma correlated with psoriasis severity [78]. The treatment with TNF inhibitor (etanercept) reduced serum levels of IL-17 and IL-22 [91]. IL-22 upregulates keratinocyte proliferation and migration, inhibits keratinocyte differentiation by downregulating a variety of genes as filaggrin and involucrin genes [87, 92], and augments the expression of inflammatory molecules by KCs, which leads to an increase in skin thickness *in vitro* and *in vivo* [93-95]. IL-22 can also stimulate epithelial cells to release chemokines, such as IL-8 [5, 80].

Interleukin 26 (IL-26)

IL-26 is a member of the IL-10 cytokine family with almost 25% identity to IL-10. IL-26 is often co-expressed with IL-22 by activated T cells, especially Th17 cells. IL-22 induced IL-20 mRNA and protein in human KCs and had only a minimal effect on IL-19 and IL-26 [96, 97]. IL-26 is a secreted protein, and may be functional either as a monomer or homodimer and signals through a heterodimeric receptor complex composed of the IL-20R1 and IL-10R2 chains. IL-26 receptors are primarily expressed on non-hematopoietic cell types, particularly epithelial cells. Signaling through IL-26 receptor complexes results in the activation of STAT1 and STAT3 with subsequent induction of IL-26-responsive genes. The biological functions of IL-26 is not well known [96].

OTHER RECENTLY RECOGNIZED CYTOKINES OF SIGNIFICANT IMPORTANCE IN PSORIASIS

Interleukin 23 (IL-23)

IL-23 together with IL-12 belongs to the IL-12 family and are both structurally related; IL-12 is formed by the p40 and p35 subunits; IL-23 consists of p40 and p19 subunits, and it was discovered in 2000 by Oppmann and co-workers [10, 98]. IL-23 is expressed by activated mouse and human monocytes, macrophages, CD11c+ DCs, T cells, B cells, KCs and endothelial cells [9, 10, 98, 99]. IL-23 production is stimulated by many microorganisms [100] and by the activation of receptors involved in innate immunity, including toll-like receptor-4 (TLR4) [101].

IL-23 exerts its biological activities through the interaction with a heterodimeric receptor complex composed of IL-12R β 1 and IL-23R [9, 10, 102, 103]. IL-23R is unique to the IL-23 receptor complex and is mainly expressed by

T cells, NK cells, and to a lower extent by monocytes and DC populations [9, 102]. The large-scale genomic studies have identified IL-23R as a psoriasis susceptibility gene, whereas no psoriasis association was found for IL-12R β 1, the signaling receptor for IL-12 [31, 104, 105]. IL-23R expression is enhanced on human memory T cells more than on naive cells [9, 11, 23], suggesting that TCR activation of naive human T cells leads to an upregulation of low levels of IL-23R expression, causing sensitization of the cells to IL-23. Furthermore, IL-23 increases its own receptor expression on activated naive T cells [9, 23]. IL-23 is a key cytokine in bridging the innate and adaptive immune response [106, 107]. Interaction of IL-23-IL23R augments the proliferation of the differentiated Th17 cells characterized by the production of IL-17A and other related proinflammatory cytokines, activates NK cells, and regulates antibody production [10, 16, 108, 109]. In IL-23 knockout mice Th17 cells were not detected, which can suggest a critical role for IL-23 in the development and expansion of that T cell subset [106, 110]. IL-23 also regulates proinflammatory cytokines which are important in cell-mediated immunity against intracellular pathogens [106].

Although both IL-12 and IL-23 are present in psoriasis, studies support that IL-23, rather than IL-12, is crucial in psoriasis pathogenesis. IL-23 is overexpressed in psoriasis lesional skin, as shown for example by increased p40 and p19 mRNA levels, but not always p35 [9, 31, 33, 49, 111-115]. IL-23 is overproduced by dermal DCs [33, 114] and KCs [112] in lesional psoriatic skin, and is able to induce the Th17 cytokines release that act on KCs which produce more IL-23 as well as pro-inflammatory cytokines, chemokines, members of the S100 family and antimicrobial peptides. They exert their influence on sustenance and amplification of the chronic inflammation in psoriasis [116]. In contrast, most recent reports show no increased expression of IL-12 in psoriasis [16, 49, 113, 114]. It was observed that intradermal injection of IL-23 in mice induced a psoriasis-like phenotype including a dramatic increase in erythema, induration, acanthosis and parakeratosis of the skin [9, 113, 117]. Furthermore, IL-23 was shown to mediate epidermal hyperplasia, acanthosis, hyperparakeratosis, and orthohyperkeratosis through TNF α and IL-20R2 [113]. It was shown that clinical improvement in psoriatic patients, who were put on anti-IL-12p40-neutralizing antibodies, was associated with reduced expression of IL-12p40 and IL-23p19 but not of IL-12p35 [9, 118]. Genetic studies revealed that single nucleotide polymorphisms in both the IL12B and IL23R genes, coding for IL-12/23p40 and IL23R subunits, respectively, are associated with higher risk of susceptibility to psoriasis [9, 104, 105, 116], making it very likely that the IL-23/Th17 pathway plays a dominant role in this disease.

Interleukin 20 (IL-20)

IL-20 resembles IL-22 structurally and belongs to the same cytokine family. IL-20 is produced by KCs in the presence of IL-22, TNF α and IL-17 but not IFN γ or IL-20 itself [84, 119]. Stimulated monocytes and DCs are also capable of producing this cytokine [120-122]. There are two different receptor complexes for IL-20: IL-22R1/IL-20R2 and IL-20R1/IL-20R2 [84, 123]. Thus the IL-22R1 chain

is a component of both the IL-22 as well as the IL-20 receptor system. The receptors for IL-20 are found exclusively on non-hematopoietic tissue cells [120-122]. Most effects of IL-20 on KCs are primarily mediated by the IL-22R1/IL-20R2 receptor.

Psoriasis patients exhibit increased levels of IL-20 in the lesional skin as well as in the blood [122]. IL-20 blood levels correlate with PASI scores of the patients [119]. IL-20 can play an important role in the later effector phase of psoriasis pathogenesis, in which inhibits terminal differentiation, increases antimicrobial competence and production of chemokines for neutrophils in KCs [119, 124].

Interleukin 15 (IL-15)

IL-15, an IL-2-like cytokine, is a proinflammatory cytokine. IL-15 recruits and activates T cells and other inflammatory cells and can induce TNF α , IFN γ and IL-17 production as a downstream cascade [25, 125, 126]. IL-15 upregulates Th17 response [16, 17, 19, 127]. It has also an antiapoptotic function, and can induce angiogenesis, immune cell recruitment, and activation of KCs [12, 20, 21, 25, 128].

IL-15 is expressed in psoriatic skin lesions and is also present in the synovium of patients with psoriasis arthritis [1, 128-130]. IL-15 has a great influence on pathophysiologic components of psoriatic skin including angiogenesis, neutrophil and macrophage recruitment and activation, activation of cytotoxic T cells, and acanthosis [128, 129, 131-133]. When anti-IL-15 antibodies were injected into immunocompromised mice with xenografted psoriatic skin, resolution of psoriatic lesions with a downregulation of hyperkeratosis, parakeratosis, and inflammatory cell proliferation were observed [134]. Genetic polymorphisms in the IL-15 gene are linked to a genetic susceptibility to psoriasis [135, 136].

SUMMING-UP

A few years ago scientists deeply engaged in dermatological research were quite firmly convinced that psoriasis is a fairly stabilized disease from the therapeutic and pathogenetic point of view, bearing in mind that psoriasis pathogenesis was not fully elucidated, just like nowadays. Much to all dermatologists surprise, breakthrough research and biologic agents efficacy in psoriasis treatment urged a new wave of intensive work in this subject. Professor Enno Christophers used to say that if someone starts to investigate psoriasis as a resident, will still be full-time occupied with this fascinating condition when preparing oneself for a pension benefit. And this statement still continues to be a very true one.

Currently, due to enormous methodological progress, more and more clinical and histopathological psoriatic features could be explained by particular cytokine imbalance, which is still one of the most fascinating dermatological research fields, stimulating new and new generations of researchers. Let explanation of cytokine network thrive in this disease!

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