

Genes and structure of selected cytokines involved in pathogenesis of psoriasis

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Abstract: Psoriasis is a common skin disease involving 1-4% of human population worldwide, of strong genetic background. The following cytokines are directly involved in psoriasis: TNF, IL-1, IL-2, IL-6, IL-7, IL-8, IL-15, IL-18, IL-19, IL-20, IL-23 whereas IL-4, IL-10, IL-12 as well as IL-11, IL-17 and IFN-gamma are rather indirectly engaged. This work is a review of some genetic factors and structure of selected cytokines and receptors and their genes location.

Key words: Skin disease - Psoriasis - Interleukins - Receptors

Introduction

Psoriasis is a chronic recurrent skin disease of still not fully elucidated etiology, observed in both sexes [1-4]. Literature data point out at strong genetic component, however the mode of inheritance is still unclear and varies in different types of the disease [3]. In 70% of monozygotic twins, psoriasis develops concomitantly. Probability of psoriasis occurrence reaches for 70% when both parents are affected in comparison to 1-4% for the general human population [4-6]. The risk of psoriasis development is higher when the father is affected or is a psoriasis susceptibility gene carrier. This phenomenon is called "*genomic imprinting*" [5,7].

Some researchers pointed out at autosomal dominant mode of inheritance with 60% of penetrance [4,5,8], while others multigenic and multifactorial mode of inheritance with environmental factors such as mechanical traumas, dietary factors, infections, psychological stressors, drugs (including lithium, antimalarials, beta-blockers, NSAiD, salicylates) [4,5,9-14].

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Furthermore, significant positive correlation between human leukocyte antigens (HLA) and psoriasis has been observed [15] including class I HLA i.e. HLA-B13, -B17, -B39, -B57, -Cw6 (the most frequently observed), -Cw7 and class II HLA namely -DR4, DR7 (the most frequently encountered), -DR55 [4,5,16-19]. HLA-Cw6 positive individuals suffer more frequently from psoriasis than their HLA-Cw6 negative siblings. In 1985, Henseler and Christophers distinguished two types of non-pustular psoriasis namely type I, inheritant and developing before the age of 40, presenting a more severe course than type II, sporadic, developing after the age of 40 with comparatively milder course [20].

It is worth pointing out that in psoriatic patients from different cohorts various linkages and associations have been discovered. This could result from many confounding factors including ascertainment bias, gene-environment interactions, low effect size of individual genetic variation [21].

Up till now, many psoriatic susceptibility loci have been identified including the major ones located on chromosomes 6p, 17q, 4q and 1q, and called PSORS 1, 2, 3 and 4, respectively) and the minor ones discovered on chromosomes 16q and 20p [2,22,23]. Research data identified at least 20 psoriasis suscepti-

Table 1. Combined data on psoriasis susceptibility loci (with permission from authors Jullien and Barker [24]).

Locus	Region	Associated gene	Study population	Reference
PSORS7	1p	ND	British	[28]
PSORS4	1q	Many within epidermal differentiation complex	Italian and American	[29], [30]
	2p	ND	American and British	[28], [29]
	2q	ND	British	[31]
	3p	ND	Swedish	[32]
PSORS5	3q	SLC12A8	Swedish	[32], [33]
	4q13	ND	American and Swedish	[29], [32]
PSORS9	4q31	ND	Chinese, American, Northern Europe	[34], [35]
PSORS3	4q34	IRF-2	Irish	[36], [37]
PSORS1	6p21.3	HLA-C, HERV-K, HCG27, CDSN, PSORS1C3, POU5F1, TCF19, CCHCR1, LMP, SEEK1, SPR1	Many	[28], [38], [31], [34], [35], [32], [39], [40]
	6q	ND	American and German	[40]
	7	ND	American	[31]
	8q	ND	British	[31]
	10q	ND	American and German	[40]
	14q	ND	American and British	[28], [29]
	15p	ND	Swedish	[32]
PSORS2	16q		American, German, Icelandic	[40], [41]
	17q25		American and British	[42], [32], [33], [40], [43]
	18p11		Finnish	[44]
	19p13	JunB	German and British	[45], [39]
	20p	ND	German, British and American	[40], [31], [46]

ND - not determined

bility loci on 15 different chromosomes out of which nine were confirmed by studies in various populations (PSORS 1-9) [24].

Research data on susceptibility locus located on chromosome 6p, called PSORS-1 points out at this locus as the core risk haplotype [25]. Moreover, PSORS1 is the only psoriasis susceptibility locus that has been always identified in genome-wide scans responsible for about 35-50% of genetic predisposition to psoriasis development [21]. Of note, HLA-Cw6 and nine other genes (CDSN, HCR, POU5F1, TCF 19, HCG 27, PSORS-1C3, SPR1, SEEK1, STG) are located within PSORS-1 region. Furthermore, a highly polymorphic MICA gene was also discovered on chromosome 6, however still beyond PSORS-1 region [26]. It was found that MICA*017 was significantly

more frequently observed in patients with psoriasis vulgaris whereas MICA*002 in arthropathic psoriasis [27].

Clinical studies aiming at biologicals involved in psoriasis, including cytokines, their inhibitors, fusion proteins, monoclonal antibodies directed against T lymphocytes and other leukocytes, employment in psoriasis focused on pathogenic issues on immunological disturbances, which in turn depend on keratinocytes response to inflammatory stimuli. Of importance, 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) [71]. The majority of cytokines have pleiotropic effects on different cells and tissues and mutual interactions

between them are most frequently described as cytokine network.

Generally, cytokines are divided into a Th1-type and Th2-type. Psoriatic plaques demonstrate predominance of Th1-type cytokines such as IL-2 and IFN- γ [72,73]. However, different research groups revealed other cytokines involvement, which cannot be simply classified as Th1, Th0 or Th2 type, in psoriasis development [74,75].

Furthermore, in psoriasis interactions between different genes have been demonstrated thus leading to various cytokines release which can be regarded as target of future effective therapy.

The updated list of interleukins involved in psoriasis pathogenesis is presented in Table 2.

Interleukin-1

Structure. IL-1 consists of three functionally and structurally related polypeptides: two agonists of IL-1 receptor (IL-1 α and IL-1 β) and one antagonist (IL-1Ra) [76]. IL-1 α and IL-1 β are glycoproteins synthesized in a form of precursors with molecular weight of 31 kDa without signal peptide, which are then splitted to mature form of molecular weight of 17 kDa. IL-1 α is already active as a precursor, mainly intracellularly. Its mature form can be released from a cell as a result of proIL-1 α to IL-1 α splitting by calcium activated proteases, called calpains. Biological activity of IL-1 β results from intracellular cysteine protease ICE splitting (interleukin 1 β -converting enzyme) [76]. Humans have got four forms of IL-1Ra gene product: one soluble isoform (sIL-1Ra) including the signal peptide, with molecular weight of 17 kDa, as well as three intracellular isoforms (icIL-1Ra1, icIL-1Ra2 and icIL-1Ra3) [77]. sIL-1Ra is secreted by different cells and has different degree of glycosylation, thus different molecular weight ranging from 22 to 25 kDa. Intracellular isoforms arise as a result of different cutting and folding of tRNA (icIL-1Ra1) or the alternative place of initiation of gene translation (icIL-1Ra3). sIL-1Ra isoform brakes competitively bonding of IL-1 with receptor on cell surface, however the role of the intracellular isoform remains unknown [77].

Receptor. Family of IL-1 receptors belongs to TLR receptor superfamily (Toll-like receptor). Genes coding IL-1RI, IL-1RII, IL-18R and IL-18RAcP are in cluster of 530 kb on chromosome 2q12, gene coding IL-1Ra is situated on chromosome 3q28 [78]. Components of IL-1 receptor family were identified in the last years on the basis of genomic analysis of row newly recognized proteins, in majority with poorly defined function [48]. There are two receptors for IL-1: IL-1RI and IL-1RII [78]. IL-1RI receptor is a protein of 80 kDa molecular weight. It has higher affinity to IL-1 and IL-

Table 2. List of interleukins involved in psoriasis pathogenesis with corresponding genes.

Interleukin	Chromosome
IL-1 family except of IL-18	2q13 [47]
IL-18	11q22.2-22.3 [48]
IL-2	4q26-28 [49]
IL-4	5q23-31 [50,51]
IL-6	7p21 [52,53,54]
IL-11	19q13.3-q13.4 [55,56]
IL-7	8q12-q13 [57]
IL-8	4q12-4q21 [58]
IL-10, IL-19, IL-20 and IL-24	1q31.3 [59,60]
IL-12 p40	5q31-q33
IL-12 p35	3q25.33-q26 [61, 62]
IL-23 p19	12q13.2 region [63]
IL-15	4q31 [64]
IL-17	2q31 and 6p12 [65,66,]
TNF family	6p21,3 [67,68]
IFN γ	12q24.1 [69,70]

1alfa than IL1-RII receptor. It exists on majority of cells sensitive to IL-1, mainly lymphocytes T, fibroblasts, keratinocytes, endothelial cells, hepatocytes. Binding of the third protein namely IL-1RAcP (IL-1 receptor accessory protein), also belonging to IL-1 receptor family, necessary for triggering of cell signal. IL-1RII receptor of 68 kDa molecular weight has higher affinity to IL-1 β than to IL-1 α , also weak affinity to IL-1Ra. It is mainly found on neutrophils, monocytes, macrophages, B lymphocytes, bone marrow cells. It exists in a membrane bound and soluble form. Soluble form of IL-1RII also binds with IL-1 β precursor, blocking its enzymatic splitting and activation.

Interleukin-2

Structure. Mature product of gene for IL-2 is a glycoprotein with molecular weight of 15,420 kDa consisting of 133 amino acids [49]. Its structure is composed of four antiparallel amphipathic alpha helices with one intrachain disulfide bond, located between residues 58 and 105. It is worth pointing out that secondary and tertiary protein structures are required for biologic activity of IL-2 whereas the carbohydrate components are dispensable [79,80].

Receptor. Surface receptor for IL-2 is composed of three kinds of protein chains, which join together non-

covalently to create different configurations of receptor: chain alpha (CD25, Tac) with 55kDa molecular weight, beta (CD122) - 70-75 kDa and chain gamma (CD132, p56) - 64 kDa. Receptor consisting of a single chain alpha has the lowest affinity to IL-2, does not transduce signal and is located on some resting T lymphocytes. Receptor with modest affinity to IL-2 consists of chains beta and gamma, is located on monocytes and the majority of NK cells. Receptor alpha-betagamma has the strongest affinity and is located on activated T and B lymphocytes as well as on 10% of NK cells. The number of receptors on activated T lymphocytes is 10 times higher than on activated B lymphocytes. Beta chain plays the most important role in signal transmission to cell interior. Gamma chain is not specific for IL-2R and receptors for IL-4, IL-7, IL-9 and IL-15 also are composed of this chain [81,82]. The soluble form of IL-2 receptor (sIL-2R) is formed upon enzymatic cut off of the extracellular part of alpha chain. sIL-2R exerts an immunosuppressive action and competes with IL-2 membrane receptor. sIL-2R is detected in low levels in serum. sIL-2R level increases in some neoplastic and autoimmune diseases, as well as in graft rejection [82-84].

Interleukin-4

Structure. The molecular weight of this glycoprotein is about 20 kDa [85,86]. Its structure is similar to IL-2 and IL-13 and presents a globular nature composed of four short alpha helices [51].

Receptor. IL-4 acts through two types of cell surface receptors - type I and type II. One of these receptor is expressed on a wide range of cells enabling IL-4 to exert its action on various cell types [51]. IL-4 receptor complex is composed of α chain of 120-130 kDa molecular weight (800 amino acids) and γ chain CD132/common γ chain). The latter is also encountered in receptors for the following cytokines: IL-2, IL-7, IL-9, IL-15 and most probably IL-13 [87-90]. γ chain enhances affinity of α chain to IL-4. IL-4R α chain is postulated to be also a component of IL-13 receptor [87,91]. Antibodies of IL-4R α chain inhibit IL-13 binding with its receptor (IL-13R) and thus their function [91,92].

Interleukin-6 and interleukin-11

Structure. IL-6 and IL-11 belong to a larger cytokine family, sharing a four alpha helix kundle structure, comprising also LIF, CNTF, OSM and CT-1 [93,94]. IL-6 is a glycoprotein of 21-28 kDa molecular weight and consists of 184 amino acids [54]. IL-11 precursor protein consists of 199 amino acids and molecular weight of 23 kDa [56]. Although IL-11 belongs to the

same family as IL-6, no similarities are observed in amino acids sequence and in cDNA between these cytokines [56,95,96].

Receptor. IL-6, vIL-6, IL-11, LIF, OSM, CNTF, CT-1 and NNT-1/BSF-3 are also known as gp130 cytokines because they all share gp130 subunit. This subunit serves as a common transducer, by which Janus kinases (Jaks) and transcription factors of the STAT (*signal transducers and activators of transcription*) family are activated. Moreover, IL-6, IL-11, OSM and CNTF also share IL-11 specific α -receptors (IL-11R α) [97]. IL-11 effects depend on IL-11R α activity, responsible for multimeric signal transduction including gp130 subunit. Two isoforms of the human IL-11R α -chain, which differ in their C-terminus domains, have been identified and cloned. One isoform has a cytoplasmic domain and the latter lacks the entire cytoplasmic domain [98].

Interleukin-7

Structure. IL-7 is a single-chain glycoprotein and consists of six cysteine residues. Both human and mouse proteins contain three disulfide bonds which are essential for the biological activity of this cytokine. The molecular weight of IL-7 is 25 kDa [99].

Receptor. The IL-7 receptor consists of a complex of the IL-7R α chain and the γ c chain [100]. Both chains are required for the biological activity of IL-7, which was demonstrated in IL-7R α -, γ c- and IL-7-deficient mice.

Interleukin-8

Structure. There are four types of differently processed forms consisting of 69, 72, 77 and 79 amino acids. IL-8 is formed as a precursor protein composed of 99 amino acids. Most frequently it is a monocyte-derived peptide (72 amino acids). Activated epithelial cells produce a peptide which is 5 amino acids longer [56]. The molecular weight of IL-8 is 8-10 kDa [56].

Receptor. There are two receptors: IL-8 RA and IL-8 RB, expressed on neutrophils, neutrophil-like cells, monocytes, subpopulation of CD8+ T cells and CD 56+ natural killer cells. Additionally, the existence of IL-8 multi-specific receptor (CK) was confirmed and demonstrated on human erythrocytes. CK receptor was demonstrated to be a blood group antigen in the Duffy system [101]. Because of its ability to bind IL-8, this receptor regulates IL-8 level in serum. However, biological effects and stimulation pathways of the CK receptor situated on erythrocytes are still not clearly elucidated.

Interleukin-10

Structure. IL-10 belongs to the family of long-chain cytokines, which also encompasses IFN- α/β and IFN- γ . Biologically active IL-10 is a homodimer [102] with molecular weight of 37 kDa. Each monomer is composed of 160 amino acids with a molecular weight of 18.5 kDa. It is of interest that human IL-10 shares 80% homology with its murine counterpart. Literature data point out at three viral IL-10 homologs namely Epstein-Barr virus (BCRF1) [103,104], herpesvirus type 2 [105], and orf virus [106]. X-ray crystal structure analysis revealed structures of human IL-10 [107,108].

Receptor. IL-10 receptors (IL-10R) are found on normal keratinocytes. They are composed of two different chains: α and β (CRFB4) [109], which belongs to class II-cytokine receptor family. The IL-10R β chain seems to be essential for IL-10-mediated activity, because characteristic STAT transcription factor activation pattern for IL-10 signaling was observed only in cells expressing both chains [109].

Interleukin-12

Structure. IL-12 consists of a disulfide heterodimer of 40 kDa (p40) and 35 kDa (p35) subunits [110]. The peptide sequences of p35 and p40 are similar to IL-6 and the soluble form of its receptor, suggesting that IL-12 acts on target cells in a manner similar to the complex of IL-6 and soluble IL-6R [111]. There are also many similarities between IL-12 and IL-23 [111].

Receptor. The functional high-affinity IL-12R comprises IL-12R β 1 [112] and IL-12R β 2 subunits [113]. IL-12 p40 binds primarily the IL-12R β 1 subunit, whereas IL-12 p35 appears to interact mostly with the IL-12R β 2 chain [113]. Although monomeric p40 is secreted in larger quantities than p70 heterodimer, only the latter is biologically active [114]. This heterodimer is produced after co-expression of both the p40 and the p35 genes in the same cell [115]. The homodimer binds with a much lower affinity than the heterodimer and therefore acts as an antagonist only at much higher concentrations [116].

Interleukin-15

Structure. IL-15 is a glycoprotein with molecular weight of 14-15 kDa. Its active form consists of 114 amino acids [117,118]. It is a member of 4 alpha helix bundle family of cytokines.

Receptor. IL-15 type 1 receptor is found on T lymphocytes and NK cells. It consists of three subunits. Two of them - β chain (protein p75) and γ chain (protein

p64) are components of IL-2 receptor [118, 119]. The third element is a special α chain for IL-15 receptor [120]. The second type of IL-15 receptor is located on mast cells and probably it does not share the same elements with IL-2 receptor. Second type of receptor, which is activated by IL-15 in mast cell proliferation, is characterized by a new subunit initially defined as IL-15RX [121], and now described as an isoform of IL-15R α chain [122].

Interleukin-17

Interleukin-17 (IL-17) is a first member of a new cytokine family. Of note, up till now it has been discovered only in six species. Whereas, IL-17 is produced mainly by activated CD4⁺ and CD8⁺ T lymphocytes, its receptor can be found ubiquitously in the organisms [123].

Structure. Human IL-17 is a protein composed of 155 amino acids and shares about 75% homology at the nucleotide level and 72% at the amino acid level with the thirteenth open reading frame of the T lymphotropic Herpesvirus saimiri (HVS13) [123,124]. IL-17A structure sequence does not resemble any other cytokine or mammalian protein [125]. That is why the IL-17 cytokine family seems to represent a distinct ligand-receptor signaling system.

Receptor. As opposed to a relatively restricted expression of IL-17, IL-17 receptor (IL-17R) are ubiquitously expressed in all types of cells and tissues [65,125,126]. It appears, that protein structure of IL-17R is unrelated to those of other cytokine receptor families. The IL-17R chain contains at least seven N-linked glycosylation sites and the molecular weight of nascent IL-17R protein is approximately 112 kDa. IL-17R mRNA was detected in epithelial cells, fibroblasts, lymphocytes, myelomonocytic cells and marrow stromal cells [127]. The IL-17R protein as found in peripheral blood T lymphocytes and vascular endothelial cells [65]. Recent studies have demonstrated other forms of IL-17 receptors, subsequently called IL-17RB-E. The above receptors, similarly to IL-17R, are type I transmembrane proteins, but display significant alternative splicing [65].

Interleukin-18

Structure. IL-18 is produced as a 24-kD inactive precursor lacking a signal peptide (pro-IL-18) [128]. Pro-IL-18 is cleaved after Asp35 by the endoprotease IL-1 β -converting enzyme (ICE; caspase-1) to generate a biologically active, mature 18-kD fragment [128]. IL-1 β and IL-18 are closely related. Both interleukins have a similar three-dimensional structure [129].

Receptor. Interleukin-18 and its receptor, IL-18R, are structurally related to IL-1 and the IL-1R family. All members of the IL-1R family are composed of two chains: the binding chain (IL-1R related protein, IL-18R α) and the signaling chain (IL-1R accessory protein-like, IL-18R β) [128-132].

Interleukin-19

Structure. IL-19 is secreted as monomer. The crystallized monomer has seven helices able to bind to its two-chain receptor [133].

Receptor. Three members of the IL-19 family (IL-19, IL-20 and IL-24) act through the receptor originally defined as the IL-20 receptor [134,135]. Interestingly, IL-20 and IL-24 can also use an alternative receptor and indeed, recent investigations have suggested, that the IL-20 receptor, as originally defined, may be the true IL-19 receptor [136-138]. IL-19 act through the IL-20R(1 or α)/IL-20R(2 or β) heterodimer which have been involved in triggering abnormal keratinocyte differentiation and proliferation [135]. IL-19 receptor binding results in a rapid activation of the transcription factor STAT3 (signal transducers and activators of transcription 3) [136, 37].

Interleukin-20

Structure. The entire coding sequence translated from full-length IL-20 cDNA clone indicates, that IL-20 is a member of the IL-10 family and it is mostly similar to IL-19 (40% of sequence identity) [139]. Recombinant human IL-20 produced in BHK (renal cells of new born Syrian hamsters) and baculovirus cells is a monomer [134]. The IL-20 mRNA contains motifs in its 3' untranslated region, that are associated with instability. IL-20 mRNA appears to be rare and short-lived. The polypeptide sequence of IL-20 is similar (20-40% identical) to that of IL-10 and four other mammalian cytokines [140]. In contrast to IL-10, which only has four conserved cysteine residues in its mature protein sequence, IL-20 contains six of them. However, Gln81 and Asn134 residues in IL-10, corresponding to Cys81 and Cys134 in IL-20, have a separation of 11.6Å. IL-10, which forms an intercalating dimer contains Asn116 in a potential flexible hinge region between the core of one monomer and the helix contributed by the other monomer [134]. Based on a structural analysis, IL-20 is assumed to share a similar three-dimensional structure [141].

Receptor. Recombinant IL-20 protein stimulates a signal transduction pathway through STAT3 in a keratinocyte cell line, demonstrating a direct action of this ligand. IL-20 receptor is the same as for IL-19

and was identified as a heterodimer of two orphan class II cytokine receptor subunits, which are both expressed in the skin [134]. Binding of the IL-20 ligand depends on a connecting recombinant monomer of IL-20 to IL-20RA/IL-20RB heterodimer complex. The ligand does not bind itself, in any detectable way, with any subunit, which can point that IL-20 does not built homodimer causing impossible ligand-induced homodimerisation of 2 α subunits. It is rather unique, that IL-20RA, as well as IL-20RB are required for binding the IL-20 ligand. Each of three IL-20 receptor subunits (IL-20RA, IL-20RB and IL-22RA) has an individual expression pattern in tissues [142].

Interleukin-23

Structure. IL-23 is a heterodimer, sharing a p40 subunit with IL-12 [143], but containing a distinct p19 subunit. Thus a human antibody directed against p40 effectively blocks the action of both IL-12 and IL-23 [143]. Interestingly, IL-12 and IL-23 are both produced by activated (mature) dendritic cells (DCs) and play a key role in promoting differentiation and proliferation of type 1 cytokine-producing naive and memory T cells, respectively [144].

Receptor. IL-23 binds to IL-12R1, but not to IL-12R2. This cytokine has a heterodimeric receptor, which uses a novel second subunit, IL-23R, a member of the hematopoietin receptor family [145]. The receptor complex for IL-12/IL-23 is expressed or upregulated on natural killer (NK) and T cells, as well as on cells of the myelomonocytic lineage including DCs. The presence of IL-23R in macrophages and dendritic cells suggests, that IL-23 acts in an autocrine manner [145-148].

Tumor Necrosis Factor

Structure. The overall structure of TNF is described as a " β -jellyroll" in which eight antiparallel β -strands form a sandwich 3D structure. TNF precursor is a 233 amino acid, 26 kDa transmembrane glycoprotein type II, comprising cytoplasmic domain and extracellular C-terminus. As a mature form, TNF is released as an 17 kDa extracellular precursor fragment, consisting of 157 amino acids, as a result of TACE family metalloproteinases activity (TNF- α converting enzyme). Biologically active forms, both membrane and soluble ones, are homotrimers consisting of 3 identical protein chains of non-covalent bindings [149,150].

Receptor. Two TNF cell receptors i.e. TNFR1 (also called TNF-R55, TNFR β , p55, CD120a) of 55 kDa molecular weight and TNFR2 (TNF-R75, TNFR α ,

p75, CD120b) of 75 kDa molecular weight can be demonstrated. There are transmembrane glycoproteins of different degree of glycosylation, molecular weight, affinity and type of signal transduction. TNFR1 seems to be responsible for the majority of TNF activity. However, TNFR2 exerts a stronger affinity to transmembrane pro-TNF [149,151]. TNFR1 and TNFR2 are present on all cell types except for erythrocytes. TNFR1 expression is constitutive in most cell types, whereas expression of TNFR2 appears to be inducible [150]. Soluble forms of both TNF receptors -TNFR1 and TNFR2 are encountered in the blood. The above forms are formed through proteolysis of extracellular fragment, like the mature TNF. By binding TNF, soluble receptors exert an inhibitory or modulatory effect on TNF itself. On the other hand, however, they block dissociation of the active homotrimer to biologically inactive monomers thus prolonging TNF activity [149,152]. Both receptors, apart from TNF, bind to LT- and one of LT- β (LT- α 2 β 1). TNF receptors are discovered on all nuclear mammal cells and their number does not correlate with response to TNF. IL-1, IL2, IFN- γ and TNF itself enhance the expression of TNF receptors. Stimulation of TNF receptors leads to protein kinases A and C activation together with NF-AT, NF- κ B and AP-1 transcription factors [151,153,154].

Interferon- γ

Interferons form a separate groups of proteins produced by numerous cells as a result of viral infection or antigen stimulation [56,155].

Structure. IFN- γ is the only type II interferon, classified to this group because of its unique amino acid sequence. IFN- γ in its biologically active form is a 34kDa homodimer stabilized by non-covalent forces. The peptide is heterogenous in size and charge, due to enzymatic trimming of the C-terminus and to variation in degree of glycosylation. This heterogeneity seems to be unimportant for biological activity on cells but might well influence the dynamics of tissue distribution [1,156].

Receptor. Receptors for IFN- γ are located on the surface of most of the cells of the body, so that many organs and systems are sensitive to IFN- γ action. Expression of IFN- γ receptor differ from cell to cell. The highest expression of receptors is observed on T- and B-lymphocytes, NK cells, monocytes, macrophages, fibroblasts, neutrophils, endothelial and smooth muscle cells. The receptor for IFN- γ is composed of two structurally homologous polypeptides - IFN- γ -Ra and IFN- γ -Rb. The signal transduction is mediated by Jak1, Jak2 and STAT1a [156,157].

Conclusions and summing-up

Since mid of the twenties century, dynamic development on cytokine knowledge allowed not only to elucidate mechanism of traditional anti-psoriatic treatments but create the basis for elaboration of new effective biologicals. Fairly recently first cytokine antagonists were registered for the treatment of autoimmune-inflammatory diseases, including skin and arthropatic psoriasis, demonstrating much higher efficacy than traditional therapies [150,155,158-160].

When thinking about biologicals employment, detailed knowledge on genes and receptors of cytokines and their structure is of importance for psoriasis. Data on this subject allow to understand treatment failures observed during many anti-cytokine therapies as for example when anti-IL-8 is used. Despite many theoretical aspects pointing out at anti-IL-8 as a very effective anti-psoriatic component, this anti-cytokine effects observed in practice were totally disappointing. This lack of efficacy could at least be partly explained by the presence of additional IL-8 receptors on erythrocytes. On the other hand, further, still not fully elucidated, interactions of cytokine network could be to blame. This is why a single cytokine introduction to anti-psoriatic treatment could at first lead to clinical improvement, expressed as decrease in PASI score (Psoriasis Area and Severity Index). However later usually a quick relapse of psoriasis follows.

Literature data report both most spectacular successes and disappointments of anti-cytokine treatments in selected diseases, as for example in septic shock [76]. Specially, the latter suggest the necessity of more advanced therapeutic strategies implementation taking into account considerable diversity of signal transduction and mutual interactions between different cytokines and their receptors. It is of importance that cytokine expression alters with the disease progression. However, up till now, only single cytokines at a time are used in therapy. There are no schemes of combined anti-cytokine treatment taking into account multi-cytokine approach. Multi-drug schemes of different anti-cytokine treatment, administered at different stages of the disease should be elaborated in the near future.

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