Psoriasis: Association of interleukin-17 gene polymorphisms with severity and response to treatment (Review)

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Abstract. Psoriasis is a chronic, inflammatory disease with a complex pathogenesis that is not yet fully understood. Although it is a multifactorial disease, the genetic factor has a major role in the pathogenesis of psoriasis. Genome wide association studies have identified over 50 genetic loci associated with psoriasis risk. Beside TNF-α or IL-23, the IL-17 family is a newer group that has proven implications in the pathogenesis of psoriasis. The most important members of the family, with pro-inflammatory qualities, are IL-17A and IL-17F. These interleukins are produced by a varied number of cells, but by far the most important are Th17 cells. Of the patients 20-30% present moderate-to-severe psoriasis, therefore, systemic medication (phototherapy, methotrexate, cyclosporine, acitretin or biologic agents) is mandatory. The necessity of an individualized treatment plan, for each patient, is imperative in order to establish the best strategy for non-responders to classical treatment or to other biologic treatments. The discovery of Th17 pathway improved the treatment and prognosis of psoriasis. Anti-psoriatic agents against IL-17 or its receptors are a novel group of biologic agents; these include ixekizumab, secukinumab and brodalumab. Polymorphisms of IL-17 family have been correlated with the severity and response to treatment in psoriasis, and also with the risk of inflammatory, infectious, autoimmune or neoplastic pathologies. The significant difference in the presence or absence of susceptibility loci in different population is due to genetic background and environmental factors that have a major impact on disease predisposition. In this study, we reviewed the importance and influence of the IL-17 polymorphisms as predictors of response to treatment and severity of the disease.

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Abbreviations: GWAS, genome-wide association studies; HLA, human leukocyte antigen; IL, interleukin; NB-UVB, narrowband UVB phototherapy; NK, natural killer; Th17, T helper 17; TNF, tumor necrosis factor

Key words: interleukin-17, polymorphism, Th17 cells, psoriasis, ixekizumab, secukinumab

Contents

1. Introduction

Psoriasis vulgaris is a chronic immune-mediated inflammatory disease with polygenic and multifactorial background and implies negative impact on the quality of life of psoriatic patients (1-3). The disease affects approximately 2-4% of the population (4,5), but several studies indicate that there are differences between Asia and other regions, with a lower incidence of psoriasis in Asians (0.3-1.2% in China) (6). It is very important to take into consideration the genetic factor because it affects not only the overall risk, but also the clinical type, age of onset, severity of the disease and the risk for psoriatic arthritis (4,7). Many genetic studies demonstrate the major role of the immune system in the pathogenesis of psoriasis. Genome-wide association studies (GWAS) have identified approximately 50 genetic loci associated with psoriasis risk (8-12). Numerous studies have demonstrated that there is a strong link between certain polymorphisms of tumor necrosis factor-α (TNF-α) or interleukin-23 (IL-23) and the severity of the disease or the response to anti-TNF-α treatment. Another group of interleukins with proven implications in the pathogenesis of psoriasis is the IL-17 family which consists of six members (IL-17A to IL17F) and these interleukins are attached to five receptors (IL-17RA to IL-17RE) (4,13,14). The most important member of the family is IL-17A, followed by IL-17F, and both of them have pro-inflammatory qualities. These interleukins are produced

by a varied number of cells, but, by far, the most important are Th17 cells.

2. Th17 pathway and IL-17 family

Th17 pathway. After activation, macrophages and dendritic cells produce IL-23 which play a mandatory role in differentiation of naïve $CD4^+$ T cells into Th17 cells. This novel subset of Th17 cells produce IL-17A, IL-17F and IL-22, the main players in the formation of characteristic psoriasis lesions (1,13,15,16). There are other cells that are capable of producing IL-17: mast cells, NK cells, Tc17 cells, and neutrophils (17,18). Besides cutaneous psoriasis, IL-17 is also involved in other immune-mediated diseases: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, uveitis, Crohn's disease, multiple sclerosis, and asthma (19-24) (Fig. 1).

Interleukin-17A. IL-17A is a reference member of its family and a dimeric glycoprotein which in circulation can be found as a heterodimer of IL-17A with IL-17F or as a homodimer of two IL-17A chains (19,25-27). The homodimer of IL-17A has increased potency in induction of keratinocyte gene expression, compared to IL-17A/F heterodimer or IL-17F homodimer (28). IL-17A stimulate fibroblasts, epithelial and endothelial cells to produce inflammatory mediators (4,29,30). Likewise, by creating a connection between innate and adaptive immune system, mobilizes, recruits and activates neutrophils (31). In the presence of extracellular bacteria and fungi IL-17A increases the expression of chemokines on keratinocytes and leads to an immune response in the skin (32). The close relationship between IL-17A and TNF-α is highlighted by the increased response of keratinocytes to inflammatory cytokines (14,33). Though, it should be considered that in psoriasis the pro-inflammatory effects on keratinocytes and neutrophils is due to both IL-17A and IL-17F (4,34).

Interleukin-17F. IL-17F is another member of the IL-17 family, which is also secreted by Th17 lymphocytes (16). The structure of this pro-inflammatory interleukin is almost identical to that of IL-17A, sharing 50% homology (14). It induces the release of neutrophil-mobilizing and pro-inflammatory cytokines (32). IL-17A and IL-17F bind to the same receptor, which consists of two subunits: IL-17RA and IL-17RC (28). They also manifest their pro-inflammatory effects on other types of cells, such as fibroblasts, endothelial cells, chondrocytes, osteoblasts, monocytes, and synovial cells (16,19,35,36).

Interleukin-17B, interleukin-17E and interleukin-17C. IL-17B has a pro-inflammatory role, but its mechanism of action is not fully elucidated. This interleukin interferes with embryonic development, tumor progression and autoimmune diseases (37). IL-17D is linked to viral and tumor surveillance (37). IL-17E, also called IL-25, is related to Th2 cells and has the task to produce Th2 cytokines and to recruit eosinophils, thus it has a role in defending against parasitic infections (37-39). Also it exerts an inhibitory role on Th17 cells (26).

It is assumed that IL-17C, a newer member of the IL-17 family, is also involved in the pathogenesis of psoriasis. IL-17C exert its role in epithelial cells and mucosa, and modulates the innate immune system (14). It has 23% of the IL-17A structure and binds to its receptor: IL-17RC (40). Skin biopsies from psoriatic lesions revealed a significantly increased expression of IL-17C, up to 125 times higher than that of IL-17A (41).

Many cutaneous biopsy studies show that the psoriasis lesions contain cells that secrete IL-17, especially Th17 lymphocytes, in a higher number compared to normal skin (34,37,42-45). Thus, IL-17A is highly expressed in the affected skin compared to unaffected tegument (32). Patients with psoriasis have increased plasma levels of IL-17, as well as higher levels of circulating IL-17 producing cells, compared to healthy people (36,42,46-48).

3. Therapy against IL-17

Martin H. Fischer, a specialist in psychology, said that the amount of doctor's medical knowledge is not important for the patient; for him the most important thing is if the doctor can cure his disease (49). Nowadays, different therapeutic strategies are available: topical agents, ultraviolet light treatment or systemic therapies. Of the patients with psoriasis 70-80% suffer from mild disease (28) and in this case the topical treatment and phototherapy are sufficient. For about 20-30% of the patients, which present moderate-to-severe psoriasis, systemic medication (phototherapy, methotrexate, cyclosporine, acitretin or biologic agents) is mandatory (13,28). Psoriatic arthritis affects between 6-42% of patients and if early treatment is not established, local inflammation will produce joint destruction and disability (50). During the treatment, some patients can experience side effects, relapses or insufficient response (13). For example, methotrexate is an effective and well-tolerated drug but it also presents disadvantages such as: important side effects (severe headache, pancytopenia, mental/mood changes, seizures, allergic reaction, hepatitis and lung fibrosis) or large variability in response to treatment (51,52). Another example is acitretin, a drug commonly used to treat psoriasis. This therapy may seem harmless but it should be always considered that the response occurs slowly and is not recommended for women and men at reproductive age because of its major side effect of teratogenicity (53). Thus, it is very important to investigate and to take into consideration new possible therapeutic targets.

The discovery of Th17 pathway had a major impact on treatment and prognosis of psoriasis (6). Anti-psoriatic agents against IL-17 or its receptors are a novel group of biologic agents; these include ixekizumab, secukinumab and brodalumab (54), agents that have been approved for treating moderate-to-severe psoriasis. They present quite a rapid response and so far are proved to be successful therapies (4), which also supports the important role of Th17 axis in the pathogenesis of psoriasis (6). Unlike anti-TNF-α agents, anti-IL-17 therapy have a specific target and do not produce global immunosuppression (6). After administration of IL-17 blockers more than half of the 1200 genes identified in the affected skin were normalized, demonstrating its superior effect compared to anti-TNF-α agents (13); also, as predicted, these agents decrease the levels of Th17 cells and IL-17 in affected skin (37).

Ixekizumab. Ixekizumab is an IgG4 humanized monoclonal antibody that has high affinity for both IL-17A and

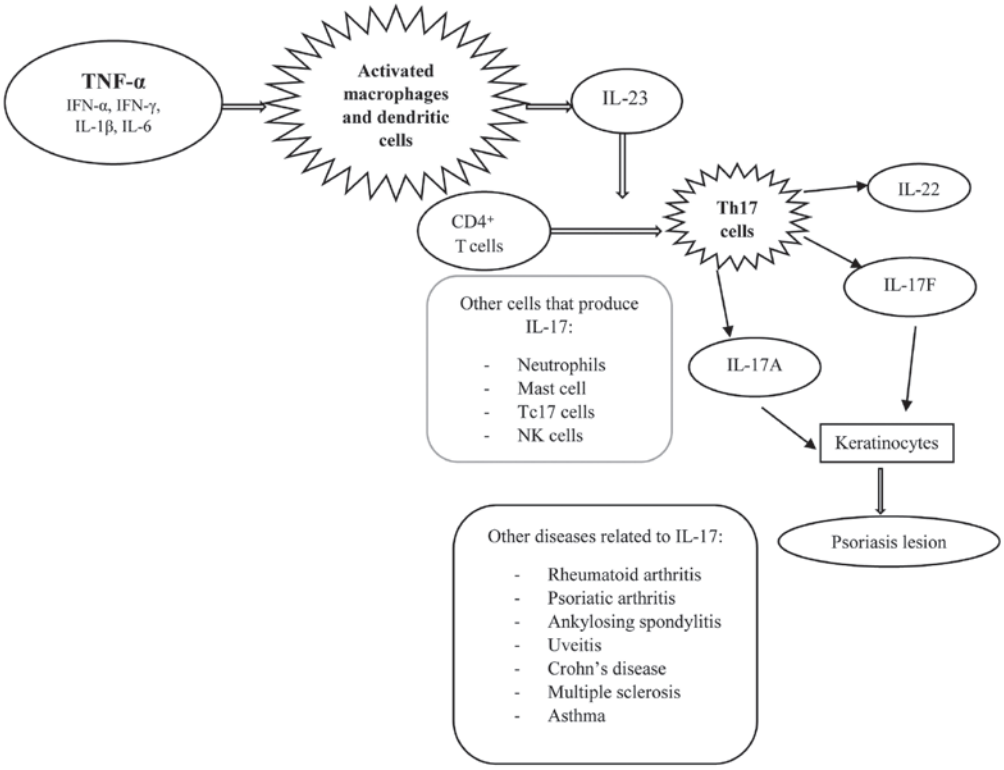

Figure 1. The IL-23, which is produced by activated macrophages and dendritic cells, stimulate the differentiation of Th17 cells from CD4+ T cells. Th17 cells produce pro-inflammatory cytokines that activate the abnormal proliferation of the keratinocytes.

IL-17A/F (55). Numerous studies paid attention to this innovative therapeutic agent including three randomized, double blind, placebo-controlled phase 3 trials (UNCOVER-1, UNCOVER-2, and UNCOVER-3) (56). These studies have shown that ixekizumab is an effective treatment for moderate-to-severe psoriasis compared to placebo and etanercept (anti-TNF agent) (57-59). Kemény *et al* have recently reported that ixekizumab has a high level of efficacy when given for up to 156 weeks. It can be said that ixekizumb is a treatment that offers a high safety profile and a high level of response when given to patients with moderate-to-severe plaque psoriasis (56).

Brodalumab. Brodalumab is a fully humanized monoclonal IgG2 antibody, anti-interleukin-17RA. By binding to the IL-17 receptor subunit IL-17RA, this therapeutic agent neutralizes the activity of IL-17A, IL-17C, IL-17F, IL-17A/F, and IL-17E (13,37,54). Response rates after 12 weeks of treatment were similar to that of ixekizumab and secukinumab, but higher than those seen with classical treatment or other generations of biologic agents (37).

Secukinumab. Secukinumab is a fully human IgG1k monoclonal antibody that has high affinity for IL-17A and blocks the activity of the cytokine (54). Compared to placebo, secukinumab is a safe treatment, regarding toxicity no difference compared to placebo and no important adverse events compared to placebo (13).

It is worth mentioning that anti-TNF-α drugs exert inhibitory effects on IL-17 signaling pathway (32). IL-17A acts in synergism with TNF-α and the efficacy of etanercept is due to suppressive effect on Th17 cells (28).

All three anti-IL-17 molecules, through their targeted action, reduce the level of IL-17 both systemically and in plaque psoriasis, demonstrating that IL-17 is a key cytokine. These agents may also influence the expression of some genes in the affected skin, but their exact role is still debated.

4. Polymorphisms of IL-17

Among the first steps that have been taken in order to understand the link between genetics and the pathogenesis of psoriasis, the identification of PSOR family was included. It consists of ten chromosomal loci (noted from 1 to 10), which are related to the onset of the disease (28). The first locus for this inflammatory disease, PSOR1, was mapped to chromosome 6p21.3 (60). Another important genetic risk factor for psoriasis is HLA-C*06:02 (60). More recently, GWAS have detected a multitude of susceptibility genes for psoriasis (28).

A question arises: what is the best strategy that clinicians can choose for non-responders to classical treatment or to other biologic treatments? Thus, the necessity of individualized treatment plan, for each patient, is imperative. A possibility is to identify markers that can predict the response to treatment or the course of the disease. Gene analysis studies suggest the direct link between genetics and response to treatment (61). Many polymorphisms of IL-17 family have been correlated with the risk of inflammatory, infectious, autoimmune or neoplastic pathologies (4,34). The genes of IL-17A and IL-17F are both located on 6p12 (32,62).

Kim *et al*, evaluated the presence of 11 polymorphisms in Korean population: IL-17A (rs2275913, rs3819025, rs3804513, and rs3748067), IL-17F (rs763780 and rs2397084), IL-17RA

(rs6518660, rs2241046, rs2241049, rs879574, and rs882643) in 208 patients diagnosed with psoriasis and in 266 healthy control. They demonstrated that the IL-17F polymorphism rs763780 T/C is strongly associated with psoriasis (1). The study found no association between the five evaluated polymorphism of IL-17RA or with the other evaluated polymorphisms and psoriasis (1).

Contrary, a study conducted by Shibata *et al*, which included 153 Japanese with psoriasis and 103 healthy controls, found no association between the IL-17F rs763780 polymorphism and psoriasis (16).

In 2015, Prieto-Pérez *et al*, studied for the first time the influence of IL-17F rs763780 on the response to biologic treatment with anti-TNF-α drugs or ustekinumab (a monoclonal antibody against IL-12 and IL-23) (32,63), in a Caucasian population. The study included 194 patients with psoriasis and 197 healthy people. Subjects who were carriers of the C allele were reported as non-responders to treatment with adalimumab or ustekinumab, but they were responders to treatment with infliximab (32).

In 2015, Batalla *et al* reported a study that was conducted on 580 Spanish patients diagnosed with psoriasis and 567 healthy controls. The subjects were genotyped for IL-17RA (rs4819554, rs879577), IL-17A (rs7747909), IL-17F (rs763780, rs2397084), and IL-17E (rs79877597) genes. The IL-17RA rs4819554 G carrier patients were much more common in psoriasis group. This polymorphism was also related to the Cw6 status: 48% of the Cw6 positive subjects presented it compared to 40% of the Cw6 negative subjects (4). The patients who were carriers for IL-17F rs2397084 TT genotype were also Cw-6 positive (4). The presence of Cw-6 is closely related to the early onset of the disease, but in this study IL-17RA rs4819554 and the age of onset were independent factors. On the contrary, IL-17F rs2397084 was linked to an early age of onset. The IL-17RA rs879557, IL-17A rs7747909 and IL-17F rs763780 polymorphisms were not included in the group of susceptibility loci because they did not show association with the disease (4). IL-17RA rs4819554, IL-17RA rs879557, and IL-17F rs2397084 were not linked to the severity of the disease, psoriatic arthritis or other characteristics of the patients (4). Among the IL-17E rs79877597 allele C carriers a more severe form of psoriasis and a higher risk for psoriatic arthritis were observed (4).

One year later, in another study, Batalla *et al* genotyped 238 Caucasian patients who underwent anti-TNF-α treatment with adalimumab, etanercept or infliximab. The investigated polymorphisms were IL-17RA rs4819554 and rs879577. The rs4819554 polymorphism was directly linked to the response to anti-TNF-α agents at week 12 (34).

In 2016, Białecka *et al*, determined the association between the IL-17A rs2275913, IL-17F rs763780, rs11465553, rs2397084 polymorphisms and psoriasis susceptibility, but also the influence of these polymorphism on topical treatment or combined therapy (topical and NB-UVB), in Polish subjects. These polymorphisms could not predict the response to treatment. Subjects carrying the IL-17F rs2397084 variant C allele, required a greater number of NB-UVB sessions in order to observe clinical improvement, than those who were carriers of TT genotype (48).

Catanoso *et al*, found a poor association between IL-17A rs7747909 and IL-17RA rs9606615, rs2241046, rs2241049 and peripheral psoriatic arthritis in a group of 118 patients (64). Three years later, Batalla *et al* did not find any association of IL-17A rs774909 with psoriatic arthritis (4).

5. Conclusions

There is a significant difference in the presence or absence of susceptibility loci in different population. The genetic background and the environmental factors have a major impact on disease susceptibilities in different populations. This leads to increased medical and socioeconomic costs and influences the patient's quality of life (65).

IL-17F polymorphism rs763780 is strongly associated with psoriasis in Korean population (1), with a good response to treatment with infliximab and with no response to treatment with adalimumab or ustekinumab in Caucasian population (32). On the other hand, no association between this polymorphism and the disease was found in Japanese and Spanish population (4,16).

In Spanish population, the IL-17RA rs4819554 was more commonly identified in the group of patients with psoriasis and was also linked to Cw6 status (4). In the same population, IL-17E rs79877597 was associated with severe forms of psoriasis and an increased risk for psoriatic arthritis (4). In Caucasian population, the rs4819554 polymorphism was linked to the response to anti-TNF-α agents (34).

The published data show the presence of a link between certain alleles and demographic, clinical and therapeutic features, but due to the limited number of published studies, the data are insufficient. In order to fully elucidate the role of polymorphisms in psoriasis, several comparative prospective studies are needed. To observe the general influence of polymorphisms these studies should be conducted in different populations on a larger number of patients.

In conclusion, the existence of many IL-17 related genes that have been linked to psoriasis (13), in association with anti-IL-17 agents that have proven their efficacy and safety, confirm the central role of IL-17 in psoriasis.

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Authors' contributions

ADP was responsible for the conception and design of the study, the analysis and interpretation of the data, as well as the drafting and writing of the manuscript, and revising it for important intellectual content. CP and IIR contributed to the conception and design of the study, the analysis and interpre-

tation of the data, as well as the drafting of the manuscript. AC, CV, MS and RIO were responsible for the conception of the study, and were involved in drafting of the manuscript and revising it for important intellectual content. All authors read and approved the final manuscript.

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Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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