IL-10 Implications in Psoriasis

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Abstract: Interleukin (IL)-10 is a pluripotent cytokine with effects on numerous cell populations, in particular circulating and resident immune cells as well as epithelial cells. With its potent immunoregulatory capacities, its main biological function seems to be the limitation and termination of inflammatory responses. Hence, its low level expression found in psoriasis may have pathophysiological relevance to this immune disease. Remarkably, the induction of IL-10 expression was found by conventional antipsoriatic therapies, supporting the hypothesis that it may be a key cytokine in psoriasis. Furthermore, the first use in clinical trials in patients with established psoriasis showed that it had moderate antipsoriatic effects and was well tolerated. Moreover, long-term application in psoriatic patients in remission showed that it decreases the incidence of relapse and prolongs the disease free interval. The IL-10 antipsoriatic activity is suggested to be due to the effects on different cell populations, including antigen presenting cells and T-cells (type 1 / type 2 balance shift), but not through direct effects on keratinocytes. In conclusion, IL-10 seems to have major clinical and therapeutic implications in psoriasis. Further multicenter, placebo-controlled, double blind trials are required to be an established antipsoriatic therapy. We can come to the conclusion that IL-10 genetic polymorphism and expression is potentially a key immune marker in psoriasis.

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Introduction

Clinical and genetic background of psoriasis

Psoriasis is a chronic, T lymphocyte–mediated inflammatory disorder that affects the skin, joints, and tendons in up to 4.8% of the worldwide population [1]. A population-based study in the United States estimated that the prevalence of psoriasis was 2.5% in Caucasians and 1.3% in African-Americans [2]. Environmental and behavioral factors may play a role. Smoking and alcohol appear to be associated with an increased risk and the severity of psoriasis [3-5]. Psoriasis can begin at any age, although epidemiological studies demonstrate that it most commonly appears for the first time between the ages of 15 and 25 years [6].

Psoriasis affects areas of skin that are dry or red, usually covered with silvery-white scales, and sometimes with raised edges, rashes on the genitals or in the skin folds, small red dots on the skin, itching, joint pain or aching and nail abnormalities, such as pitted, discolored, or crumbly nails. Several clinical types of psoriasis have been described including:

- Plaque psoriasis that tends to affect young adults in which, the skin patches usually spread evenly across a person's scalp, elbows, knees, and back.
- Guttate psoriasis which may be linked to a recent streptococcal infection, usually pharyngitis.
- Pustular psoriasis which is the most severe form of psoriasis.
- Inverse psoriasis which affects less visible body areas, such as the perineum and in the genitals.
- Nail psoriasis manifested with nail problems, as tiny pits over the surface of the nails.
- Psoriatic arthritis that is accompanied by joint pain and swelling.
- HIV-associated psoriasis that may develop in people infected with the human immunodeficiency virus [7-14].

Psoriasis has long been known to occur in families. Approximately 40% of patients with psoriasis or psoriatic arthritis have a family history of these disorders in first degree relatives [15]. Psoriasis tends to be concordant among monozygotic twins more commonly than among dizygotic twins [16]. A genome wide analysis suggested that a gene or genes located within the major histocompatibility complex and close to the class I HLA loci was the major determinant of the genetic basis of psoriasis [17]. Other genetic loci have been identified, and early-onset psoriasis may have different genetic determinants than later-onset psoriasis [18].

Pathophysiology and immunology of psoriasis

Although not completely understood, a great deal is known about the pathophysiology of psoriasis. The typical clinical findings of erythema and scaling are the result of hyperproliferation and abnormal differentiation of the epidermis, plus inflammatory cell infiltrates and vascular changes. Abnormal differentiation in psoriatic skin is evidenced by a delay in the expression of keratins 1 and 10 (seen in normal skin), and an over-expression of keratins 6 and 16 (seen in reactive and healing skin) [19].

The immune system plays an important role in the pathogenesis of psoriasis. Since the early 1990s, it has been assumed that T1 cells play the dominant role in the initiation and maintenance of psoriasis. However, the profound success of anti-tumor necrosis factor-alpha therapy, when compared with T-cell depletion therapies, should provoke us to critically re-evaluate the current hypothesis for psoriasis pathogenesis. Recently made discoveries regarding other T-cell populations, such as Th17 and regulatory T cells, dendritic cells, macrophages, the keratinocyte signal transduction and novel cytokines including interleukin (IL)-22, IL-23 and IL-20, let us postulate that the pathogenesis of psoriasis consists of distinct subsequent stages, in each of them different cell types playing a dominant role [20]. Also, polymorphisms in regulatory (promoter) regions of immune genes are claimed to have an impact on proper immune synapse function with emergence of autoreactive T cells [21].

IL-10 gene and immune function

The IL-10 gene maps to chromosome 1q31–q32 encodes for 5 exons (5.1 kb) [22, 23]. Its promoter region contains several polymorphic elements. Approximately 1.1 kilobase pairs (kb) upstream of the transcription initiation site the microsatellite IL10.G, a CA dinucleotide repeat with at least 11 alleles, is found [24]. In addition, 3 polymorphic sites exists within the IL-10 promoter region, -1082(G/A), -819(C/T), and -592(C/A) [22, 25, 26] (Fig. 1).

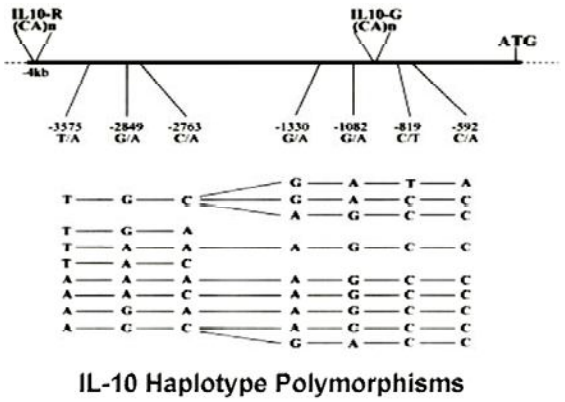

Fig. 1. Single nucleotide polymorphisms (SNPs) as well as $(CA)^n$ satellite.

Polymorphisms related to IL-10 gene on chromosome 1:

Interleukin (IL)-10 is a pleiotropic cytokine with effects on numerous cell populations, in particular circulating and resident immune cells as well as epithelial cells. IL-10 is produced by monocytes and Th2 cells, mast cells and also in a certain subset of activated T cells and B cells [27]. IL-10 can exert either immunosuppressive or immunostimulatory effects on a variety of cell types. It is a potent inhibitor of monocyte/ macrophage function, suppressing the production of a number of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6,MIP-1α and IL-8 although the release of MCP-1 is increased [28-30]. IL-10 inhibits monocyte MHC class II, B7.1/ B7.2 and CD23 expression and accessory cell function. Accessory signals mediated by B7 molecules through CD28 on the surface of T cells are essential for T cell activation. The expression of IL-10 by antigen presenting cells may be an established pathway for the induction of antigen specific tolerance such as that to allergens. By contrast, IL-10 upregulates the monocyte expression of IL-1Ra, another anti-inflammatory cytokine [29]. IL-10 suppresses the synthesis of superoxide anions and NO by activated monocytes/macrophages [31]. IL-10 is also a growth co-stimulator for thymocytes and mast cells [32], as well as an enhancer of cytotoxic T cell development [33]. It also activates the transcription of genes for mast cell derived proteases and enhances the production of the tissue inhibitor of metalloproteinases of monocytes and tissue macrophages while decreasing metalloproteinase biosynthesis [34].

IL-10 gene expression and polymorphisms in psoriasis:

A relative deficiency in cutaneous IL-10 mRNA expression was found in psoriasis compared with other inflammatory dermatoses [35]. Interestingly, patients during established antipsoriatic therapy showed a higher IL-10 mRNA expression of peripheral blood mononuclear cells than patients before the therapy. This suggested that IL-10 may have antipsoriatic capacity [36].

Regarding IL-10 gene polymorphism, Asadullah et al. reported no difference in allele distribution was observed; however, a clear differential distribution was revealed at the interleukin 10.G locus when patients were stratified according to whether they had a positive family history of psoriasis ($p = 0.04$). This difference was due to an over-representation of the interleukin 10.G13 allele in those patients with familial disease (40.4% vs 19.6%, $p = 0.007$) [37]. Also, Hensen et al. failed to confirm the susceptible effect of the G13 allele found in previous studies, but provided the first data for a protective effect of allele 3 (IL10.G9) for familial psoriasis. Their results suggested that the IL10.G polymorphism is not a major locus, but acts as a minor locus [38].

Other authors stated that IL-10 genetic polymorphisms of cytokine genes do not appear to be associated with susceptibility to psoriatic arthritis (PsA) [39-42]. On the other hand, Hassan in a study on Egyptian cases with psoriasis reported that the analysis of $IL\text{-}10^{-1082}$ (G/A) polymorphism among cases compared to controls showed that homozygous form GG was found significantly high in total cases ($OR=3.9$, $P<0.05$). This was also noted in case subgroups, especially in cases with moderate severity ($OR=4$, $P<0.05$) and in plaque psoriasis ($OR=4.9$, $P<0.05$) [43].

Kingo et al. reported that no difference was found in the frequencies of SNPs haplotype distribution between healthy controls and patients with psoriasis from Estonia with no relation to the age of onset and the family history of psoriasis. However, the results of their study demonstrate that the IL-10 haplotype has a role in determining the severity and course of the plaque type of psoriasis so that IL-10 ACC haplotype ($P<0.05$) is likely to be defining a lower activity of disease (PASI < likely=10%) [44].

English researchers reported no significant differences in the genotype distribution of IL-10-1082 with respect to the age of onset of psoriasis, gender or between patients with early onset psoriasis and the control population. However, in comparing patients with late onset psoriasis with controls, a borderline result is seen for IL-10 (P = 0.02). This group of patients with late onset psoriasis has a higher frequency of the heterozygous (G/A) genotype (corresponding to an intermediate production of IL-10) and lower frequencies of both G/G and A/A genotypes [45]. It is also worth mentioning that Reich et al. found no association between atopic dermatitis (AD) and (IL10-1082 A/G) polymorphism in German patients [46].

IL-10 therapeutic trials in psoriasis

Therapeutic effects of recombinant human (rh) IL-10 in psoriatic patients has been studied in seven trials to date (Schering Plough Research). In a pilot trial starting in 1997, daily injections of 8 µg of rhIL-10/kg body weight directly under a psoriatic plaque over a 24-day period led to the complete clearance of the plaque in one of two patients [47]. Moreover, some systemic antipsoriatic effects were observed in all three patients treated in this pilot trial through subcutaneous injections under non-lesional skin.

In a second trial (open-label phase II), 10 psoriatic patients received subcutaneously rhIL-10 over a 7-week period in a dosage of 8 µg/kg daily (n = 5) or 20 µg/kg three times per week (n = 5), respectively. The patients were followed up for an additional 7 weeks. The treatment was well tolerated. They found antipsoriatic effects in 9 of 10 patients resulting in a significant decrease of the psoriasis area and severity index (PASI) by 55.3 ± 11.5%, ($p < 0.02$). The clinical response was associated with a significant decrease of cutaneous cell infiltration and the lesional expression of type 1 cytokines (IFN-γ, TNF), IL-17, IL-8, and IL-8 receptor CXCR2 [48].

Interestingly, there was some evidence that genetic factors are involved in the response to IL-10. Thus, in a study, 28 patients with moderate-to-severe psoriasis received rhIL-10 (20 µg/kg) or placebo subcutaneously three times weekly for 12 weeks in a randomized, double-blind manner. Remarkably, the treatment with rhIL-10 resulted in only temporary clinical improvement after 6 and 8 weeks, despite sustained systemic decreases in proinflammatory and type 1 cytokine production [49, 50].

The effect of IL-10 in psoriatic arthritis patients has been investigated by McInnes et al. IL-10 was given subcutaneously for 28 consecutive days in a double-blind, placebo-controlled study including 29 patients (0, 1, 5 or 10 µg/kg). Modest, but significant, clinical improvement in skin but not articular disease activity scores with only minor adverse effects was observed [51].

Interestingly, IL-10 therapy led to a decrease in cutaneous IL-8 and an increase in IL-4 expression, both of which might contribute to the antipsoriatic effect. They reported that direct effects of IL-10 on keratinocytes are unlikely to have contributed to the clinical response. Overall, IL-10 therapy seems to be well tolerated and immunologically effective in psoriasis [37, 49].

Conclusion

We can come to the conclusion that IL-10 genetic polymorphism and expression is potentially a key immune marker in psoriasis.

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