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Interleukin 10 promotor gene polymorphism in the pathogenesis of psoriasis

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Abstract

Psoriasis is a chronic inflammatory T cell–mediated immunological disease. It is found to be associated with an increased expression of T-helper 1 and T-helper 17 lymphocytes and decreased expression of T-helper 2 and T-regulatory lymphocytes. Interleukin 10 (IL-10) is an important immunosuppressive cytokine mainly produced by T-helper 2 and T-regulatory cells. The main function of IL-10 is to terminate and control inflammatory processes and thereby maintain an immunological homeostasis. Because of its anti-inflammatory properties, IL-10 is a current focus of interest in research. Relative deficiency of IL-10 is found to play the main role in the immunopathogenesis of psoriasis. Analyzing the expression of IL-10 will provide a better understanding of its role in the pathogenesis of psoriasis. Only a few studies have analyzed the role of IL-10 in the pathogenesis of psoriasis, and their findings were contradictory. This article reviews and analyzes the role of IL-10 and its promoter gene polymorphism in the pathogenesis of psoriasis.

Keywords: psoriasis, interleukin 10, pathogenesis, genetic polymorphism, cytokines

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Introduction

Psoriasis is a common, chronic, inflammatory, and proliferative skin disease. It also affects the nails and joints, and it is associated with various systemic manifestations in multiple organ systems. It is a T cell–mediated disease in which deficiency of interleukin 10 (IL-10) plays a key role in its pathogenesis (1). Psoriasis is characterized by well-demarcated, erythematous, and scaly indurated plaques that are seen particularly over the extensor surfaces and scalp. It affects peoples of all age groups and there is no sexual predilection. About one-third of psoriatic cases start to manifest in childhood (2). The prevalence rate of psoriasis varies among different populations worldwide. The prevalence of psoriasis in all age groups ranged from 0.09% (Tanzania) to 5.1% (United States). In Asia, it ranged from 0.12% to 1.49% (3). These variations in the prevalence rate of psoriasis may be due to environmental factors, genetics, or climatic change (4). Psoriasis is found to be associated with increased morbidity and mortality. Early diagnosis and appropriate treatment will certainly reduce the comorbidities of this disease (5). The common clinical variants of psoriasis include generalized plaque-type, pustular, guttate, inverse psoriasis, and erythrodermic. The most common form is generalized plaque-type psoriasis. Guttate psoriasis is the most common type that occurs in children. Usually, plaque-type psoriasis has a chronic and persistent course. However, in some patients it is found to have a less stable course, with variations in the extent and degree of inflammation, which usually occur due to environmental triggers such as climate change, infections, and stress (2, 6). The exact etiopathogenesis of psoriasis still remains unclear. However, several studies have reported strong evidence suggesting that psoriasis has an important immunogenetic component in its pathogenesis (1).

Pathogenesis of psoriasis

Genetic basis of psoriasis

Psoriasis is regarded as a complex genetic disorder in which multiple genes interact with each other and the severity of the disease depends on the patient's genetic and environmental factors (7, 8). It is found to occur in families. An increased incidence of psoriasis has been found among first-degree relatives and an increased concordance rate among monozygotic twins over dizygotic twins, which strongly suggests the role of genetic factors in the pathogenesis of psoriasis (9). Major histocompatibility complex (MHC) class 1 is reported to be the main susceptibility factor for psoriasis. Psoriasis Susceptibility region 1 (PSORS 1), the major genetic determinant of psoriasis, is found to be primarily linked with the development of psoriasis (10). The PSORS 1 gene is located at chromosome 6p21 and it accounts for 35 to 50% of inheritance of psoriasis (11, 12). Family-based studies suggest that psoriasis has a multifactorial inheritance and multigenic determination (13).

Epigenetic alterations are also found to be causative factors in the pathogenesis of psoriasis (7, 8). Increased proliferation of keratinocytes and their abnormal differentiation is strongly related to the epigenetic state of keratinocytes in the basal layer (14). In addition to genetic factors, epigenetic factors and environmental factors also play an important role in the onset and progression of the disease. These environmental factors—which include cigarette smoking, alcohol intake, various infections (particularly group A streptococcal infection), obesity, stress, and drug intake (especially antibiotics, anti-inflammatory agents, and angiotensin-converting enzyme inhibitors)—are found to have a role in epigenetic alterations associated with psoriasis (7, 15, 16). DNA methylation is the main epigenetic factor responsible for psoriasis

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pathogenesis. Epigenetic alterations in psoriasis pathogenesis can also occur through abnormal histone modifications and micro RNA involvement at the post-transcriptional level (17–19).

Immunopathogenesis of psoriasis

T cells play a key role in the pathogenesis of psoriasis. T-helper (Th) 17, Th1 lymphocytes, and their cytokines play a major role in the inflammation of psoriasis. The activity of these cells is regulated by T-regulatory (Treg) cells. Treg cells suppress pathogenic T cells such as Th1 and Th17 in psoriasis. Treg cells maintain immunological homeostasis and also prevent autoimmunity against self-antigens. The pathogenesis of psoriasis is mainly due to the increased expression of Th1 and Th17 cytokines and decreased expression of Th2 and Treg cytokines (20–22). Several studies have reported that the number and activity of Treg cells are decreased in psoriasis (23). Treg cells are a type of lymphocyte that suppresses an excessive immune response by interacting directly through the receptors for immune cells and thereby produce suppressive cytokines such as IL-10, IL-35, transforming growth factor (TGF-β), and so on. Treg cells also have a direct cytotoxic action on some cells. Treg cells are divided into two types: naturally occurring Treg (nTreg) cells and inducible Treg (iTreg) cells. iTreg cells are divided into two cellular types: Treg type 1 cells (Tr 1) and Th3 Treg cells. Tr 1 cells produce high levels of immunosuppressive cytokines of IL-10 and TGF-β, and low levels of IL-2, IL-5, IL-15, and interferon (IFN-γ) (24). IL-6 is an important cytokine needed for the differentiation of Treg cells. It inhibits the activation of Th17 and thereby maintains Treg cell and Th17 balance (20). The reduced number and dysfunction of Treg cells in psoriasis interferes with the immunological homeostasis and regulation of immune response (23, 25). Studies have reported that hyperproliferation of psoriatic lesions is a result of the abnormal activity of Treg cells in the sera and skin lesions of psoriatic patients. Treg cells have been found to have an important role in the inflammation of psoriatic skin lesions (22, 26–28).

Effects of interleukin 10 on different cell populations

IL-10 is a 37 kDa homodimer with each monomer having a molecular mass of 18.5 kDa (29). Mossmann et al. first explained IL-10 as a "cytokine synthesis inhibiting factor" (CSIF) that is produced by Th2 cell lines and is capable of inhibiting IFN-γ production by Th1 cell lines (30). IL-10 is a potent anti-inflammatory cytokine mainly produced by T cell subsets such as Th2 and Treg cells. It is also synthesized by other cell types such as B cells, monocytes, macrophages, natural killer cells, and dendritic cells. Macrophages are the major source of IL-10 in vivo (31, 32). The promoter region of IL-10 contains various transcription factor regulating sites. IL-10 secretion is regulated by several mechanisms. Macrophages are stimulated by various factors such as endotoxin, catecholamines, and tumor necrosis factor (TNF-α) to produce IL-10 (33). Another mechanism is the indirect stimulation of the stress axis by endotoxins or infectious agents, which causes an increase in the production of catecholamines and thereby stimulates the production of IL-10 by macrophages. IL-10 secretion is also regulated by a p38 mitogen-activated kinase pathway. TNF-α also stimulates IL-10 production through a negative feedback mechanism by an NF-κ B dependent pathway (34).

IL-10 has various effects on the immune system and across

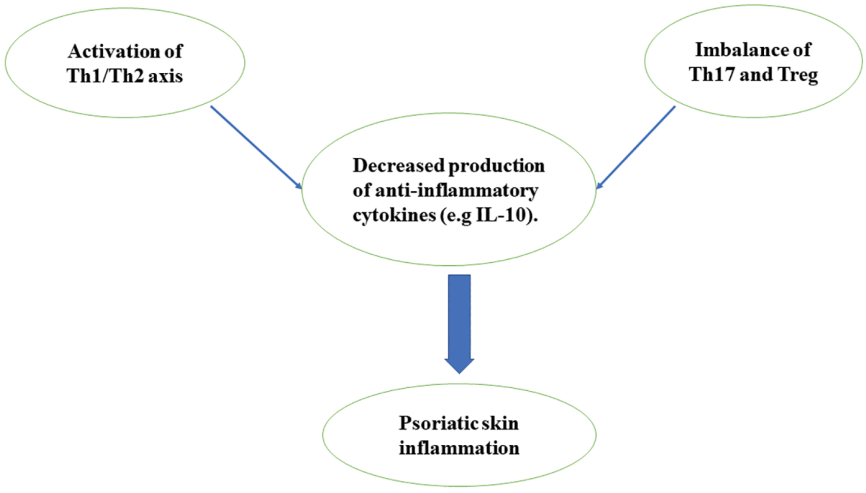

Figure 1 | The pathogenetic mechanism in psoriasis.

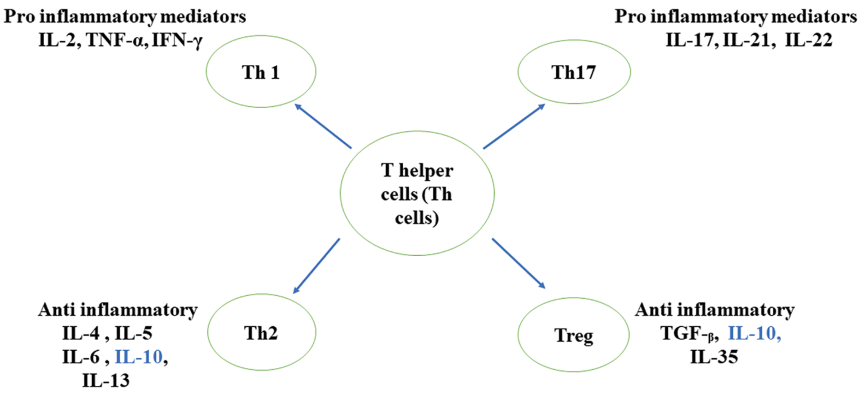

Figure 2 | T cell types and their mediators in psoriasis.

different cell types. It inhibits the production of Th1 and Th17 cytokines (29). Lymphocytes and antigen-presenting cells (APCs) are the main target cells of IL-10. IL-10 regulates the Th1/Th2 balance through its direct effects on APCs and lymphocytes. It also has a stimulatory effect on B cells, which is needed for active defense against various pathogens and natural killer (NK) cells (35). It inhibits the production of pro-inflammatory cytokines such as IL-2, IL-3, TNF-α, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF). It controls and inhibits the inflammatory processes by suppressing the expression of the inflammatory proteins, APCs, and costimulatory molecules in T cells, macrophages, and neutrophils. These pro-inflammatory cytokines are transcriptionally controlled by NF-κ_β. IL-10 exhibits its immune suppressive properties mainly by inhibiting NF-κ_β. It suppresses NO synthesis by activated monocytes (36, 37).

IL-10 binds with the IL-10 receptor (IL-10R), which is seen on a variety of immune cells. It consists of two chains: IL-10R1 and IL-10R2. Binding of IL-10 with IL-10R results in STAT3-mediated transduction of signals (38). Treg cells in psoriasis exhibit an increased STAT3 phosphorylation pathway, which leads to an increased production of pro-inflammatory cytokines (39). It also has multiple effects on hematopoietic stem cells (20). Studies have reported that suppressor of cytokine synthesis (SOCS-3) acts as a mediator in the inhibitory properties of IL-10 (38). Due to these multiple inhibitory properties of IL-10, it has been suggested as a potential therapy for various localized and systemic inflammatory diseases, tumors, and autoimmune diseases. Recent studies have also reported that IL-10 also has an immunostimulatory effect in some diseases (34). Relative deficiency of IL-10 is found to be the main role in the pathogenesis of psoriasis. The latest studies have reported another subset of IL-10 producing B regulatory cells (B regs). These cells also have the ability to inhibit the differentiation of Th1 and Th17. Psoriasis is characterized by a decrease in the number and function of B regs (40–42). IL-10 is an activator of the HLA-G molecule, which has immune-suppressive properties. Its deficiency can lead to various autoimmune diseases. It has been reported that HLA-G and IL-10 levels are found to be decreased in psoriatic patients (43–45). TGF-β is another important cytokine involved in immune homeostasis. It controls the T lymphocyte subpopulation by promoting Th17 response and by suppressing Th1 and Th2 lines (46). It is an important growth inhibitor for keratinocytes. A decrease in TGF-β has been observed in psoriatic patients, leading to hyperproliferation of keratinocytes (47).

Interleukin 10 promoter gene polymorphism in the pathogenesis of psoriasis

The IL-10 gene is located on chromosome 1 at 1q31.32. It spans approximately 4.7 kb and contains 4 introns and 5 axons. Its promoter is a highly polymorphic site. It has two microsatellites: IL-10.G and IL-10.R. These are located at 1.2 kb and 4 kb upstream of the transcription site. There are also three frequent single nucleotide polymorphisms (SNPs): –1082 G/A (rs1800896), –819 C/T (rs1800871), and –592 C/A (rs1800872) (34). These polymorphisms lie on the regulatory regions in the promoter area of the IL-10 gene. Consequently, these polymorphisms can change the transcription factor binding sites and thereby influence the production of IL-10. The decrease in the production of IL-10 alters the immunological homeostasis, which leads to the pathogenesis of various inflammatory diseases such as psoriasis (48). The IL-10 gene is a preferred gene in various studies due to its location, genetic polymorphism, and functional relevance.

Effect of interleukin 10 gene promoter (–1082 G/A, –819 C/T, –592 C/A) polymorphisms in psoriasis

Several genetic studies have been reported in the literature, showing both a strong association and a weak association between IL-10 genetic polymorphism and psoriasis among different populations. Indhumathi et al. (48) found that IL-10 gene polymorphism confers an increased risk of psoriasis in the South Indian Tamil population. The study showed that SNP at –819 C/T (rs1800871) is a risk

Table 1 | IL-10 gene single nucleotide polymorphism and association with psoriasis.

Study (reference; year)	Population studied	Polymorphism/	Association with psoriasis
Indhumathi et al. (48; 2017)	Asian (South India)	–1082 G/A	NS
		–819 C/T	Significant
Adil et al. (49; 2018)	Asian (North India)	–1082 G/A	Significant
		–592 C/A	Significant
		–819 C/T	NS
Li et al. (62; 2014)	Asian (Chinese)	–592 C/A	NS
Lee et al. (51; 2012)	Asian (Korea)	–1082 G/A	Significant risk in Asians
Wongpiyabovorn et al. (52; 2008)	Asian (Thailand)	–1082 G/A	NS
		–592 C/A	NS
Chang et al. (61; 2007)	Asian (Taiwan)	–1082 G/A	NS
		–819 C/T	NS
		–592 C/A	NS
Karam et al. (50; 2014)	Egypt	–1082 G/A	Significant
Settin et al. (53; 2009)	Egypt	–1082 G/A	Significant
Baran et al. (56; 2008)	European (Poland)	–1082 G/A	NS
		–819 C/T	NS
		–592 C/A	NS
Peddle et al. (57; 2005)	European (Canada)	–1082 G/A	NS
Kingo et al. (58; 2003)	European (Estonia)	–1082 G/A	NS
		–819 C/T	
		–592 C/A	
Windermuth et al. (60; 2003)	European	–1082 G/A	Significant
Balding et al. (59; 2003)	European (Ireland)	–1082 G/A	NS
Craven et al. (54; 2001)	European (UK)	–1082 G/A	NS
Reich et al. (55; 1999)	European (Germany)	–1082 G/A	NS

NS = not significant.

factor whereas SNP at –1082 G/A (rs1800896) is not associated with psoriasis. The mutant genotype CC is found to be common in psoriatic patients. Another recent study conducted in the North Indian population shows that –1082 G/A and –592 C/A genetic polymorphism is associated with increased risk of psoriasis (49). However, in contrast to this, Karam et al. (50) reported that there is an association of IL-10 –1082 G/A (rs1800896) polymorphism with psoriasis among Egyptians. They found a significant increase of GG genotypes and G allele in psoriatic patients. A meta-analysis study conducted by Lee et al. (51) provided evidence that –1082 G/A(rs1800896) polymorphism confers susceptibility to psoriasis in the Asian population, but there was no risk in Europeans and other study subjects, which suggests an ethnicity-specific effect. Wongpiyabovorn et al. (52) also found no risk of psoriasis among the Thai population. Another similar study by Settin et al. (53) demonstrated an increased risk of psoriasis with –1082 G/A (rs1800896) polymorphism in Egypt's Nile Delta. The majority of psoriatic patients had the GG genotype. Craven et al. (54) found that IL-10 (rs1800896) polymorphism and the GA genotype were found to be associated with late-onset psoriasis. However, in contrast to these results, Reich et al. (55), Baran et al. (56), and Peddle et al. (57) found no significant association of IL-10 –1082 G/A (rs1800896) polymorphism in psoriatic patients. Kingo et al. (58) demonstrated that IL-10 haplotype ACC is associated with lower severity of the disease. Balding et al. (59) found that IL-10 –1082 G/A (rs1800896) polymorphism was not associated with the susceptibility and severity of psoriatic arthritis. Out of eight studies conducted among European populations, only Windermuth et al. (60) showed a significant risk in the development of psoriasis associated with –1082 G/A polymorphism. Two studies from China, Chang et al. (61) and Li et al. (62), also found that IL-10 gene polymorphism does not appear to be associated with susceptibility to psoriasis and psoriatic arthritis in Chinese patients (Table 1).

There are several limitations to this review. This review article sought to determine the association of IL-10 gene polymorphism with psoriasis among different populations worldwide. However, only a limited number of studies showed an association of IL-10 gene promoter polymorphism with psoriasis. More population-based research studies are needed to reach a definitive conclusion regarding the association of IL-10 gene polymorphism with psoriasis.

Conclusions

This review surveyed IL-10 promoter gene polymorphism among different populations. This study determined that, among the three polymorphisms studied, –1082 G/A is the most common polymorphism associated with the risk of psoriasis among the Egyptian, Asian, and European population. IL-10 promoter gene polymorphisms are also found to have a significant risk with psoriasis among Asians and Egyptians than European population. Out of the seven studies conducted among European populations, only one study showed that –1082 G/A polymorphism has a significant risk with the development of psoriasis. Both of the studies conducted in Egypt showed that –1082 G/A polymorphism correlates with a significant risk of psoriasis.

Among Asians, IL-10 gene promoter polymorphism was not associated with any significant risk of the development of psoriasis in the Chinese population. Indians and Koreans have been found to have an increased risk of development of psoriasis associated with IL-10 gene polymorphism.

The majority of studies showed that –819 C/T polymorphism is not associated with a risk of psoriasis. Only one study showed a significant association. Even though studies showing –592 C/A polymorphisms are very few, the reported studies showed no significant association with risk of psoriasis.

We therefore conclude that –1082 G/A polymorphism is the most common IL-10 SNP associated with risk of psoriasis, and that –819 C/T and –592 C/A are the least common polymorphisms associated with risk of psoriasis. More population-based studies are needed to reach a definitive conclusion regarding the association of IL-10 gene polymorphism and psoriasis.

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