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Review

The association between the interleukin-10 gene polymorphism (-1082 G/A) and allergic diseases

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Abstract. IL-10 is an important immunoregulatory cytokine mainly determining the suppression of immune responses. There are many genetic variants of the IL-10 gene, but the promoter region polymorphisms are the most studied ones, especially the IL-10 -1082 G/A polymorphism. Several studies have shown that the IL-10 -1082 G/A polymorphism is associated with different diseases, including allergies, playing an important role in their pathophysiology and evolution.This review summarizes published literature data about the association between IL-10 -1082 G/A polymorphisms and expression patterns with asthma, atopic dermatitis or food allergy.

Key Words: IL-10, genetic polymorphism, allergy.

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Introduction

Cytokines are a heterogeneous group of regulatory molecules, key mediators in immune and inflammatory processes. Constitutive production of cytokines is usually low or absent, their secretion being regulated by several stimulatory transcription or translation factors. They are produced by several immune cells after stimulation (Trifunović et al 2015; Cristea&Crisan 2004). Cytokine production is stimulated by bacterial and viral agents, complement or cancer cells (Cristea&Crisan 2004, Borish&Rosenwasser 2008). Cytokines act in very low concentrations, through binding to specific receptors. They can upregulate cytokine receptors' expression, proliferation and differentiation of several target cells, mediate or modulate immune responses, and modulate the secretion of other cytokines (Trifunović et al 2015; Cristea&Crisan 2004; Borish&Rosenwasser 2008). Based on their functional role, there are pro-inflammatory and anti-inflammatory cytokines (Trifunović 2015; Cristea 2004). Imbalance of pro- and anti-inflammatory cytokines induces a malfunction of the immune system. Cytokines may have pleiotropic effects, the same molecule acting on different types of cells that are nearby (paracrine) or at a distance (endocrine). They induce multiple biological effects depending on how the target cell understands the cytokines' signal messages. The same cytokine may exert multiple roles according to the generating or target cell, or to the immune response phase in which it is present. Some cytokines may have both pro- and anti-inflammatory effects (IL-4, IL-6, IL-10, IL-13) (Cristea 2004; Borish&Rosenwasser 2008).

Characteristics of Interleukin-10

IL-10 is an important pleiotropic cytokine that acts on different cells, having an immunoregulatory role. It is a 37 kDa homodimer that belongs to the cytokine family that also includes IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, and IL-29 (Commins et al 2008; Swiątek 2012; Pestka et al 2004). The primary source of IL-10 is macrophages (Trifunović et al 2015), as well as B and T lymphocytes, especially regulatory T cells (Tregs) that produce IL-10 (Del Prete et al 1993). IL-10 is also synthesized by Th1 and Th2 lymphocytes, cytotoxic T cells, dendritic cells, monocytes and mast cells (Trifunović et al 2015; Del Prete et al 1993), but also by some human carcinoma cell lines (Gastl et al 1993). IL-10 exerts its biological effects acting on a specific receptor complex formed by two subunits: IL-10R1 and IL-10R2. IL-10R1 is the signaling subunit, while IL-10R2 is the common component of the entire family (Commins et al 2008). Receptor stimulation induces a consecutive activation of JAK1 and tyrosine kinase 2, signal transducer and activator of transcription STAT1, and STAT3 (Commins et al 2008). Some studies assumed that other kinases and enzymes could be involved in IL-10 receptor signaling (Commins et al 2008; Swiątek 2012).

Although IL-10 was first considered a Th2-type cytokine with an anti-inflammatory effect (Commins et al 2008), it has been proven that it has multiple immunoregulatory functions, mainly determining the suppression of immune responses. Under certain conditions, it may trigger a stimulatory activity (Commins et al 2008; Swiątek 2012; De Vries 1995; Akdis&Blaser 2001). IL-10 plays an important role as a regulatory factor of immune responses in both health and immune-mediated diseases (Swiątek 2012). On one hand, it is involved in innate and adaptive immune responses, being associated with the persistence of viral and bacterial infections (Swiątek 2012; Zdrenghea et al 2015). On the other hand, IL-10 prevents the development of pathological lesions that result from an exacerbated protective immune response (Mege et al 2006). In cancer cells, IL-10 has

Table 1. The pleiotropic effects of IL-10 (Trifunović et al 2015; Commins et al 2008; Swiątek 2012; Groux&Cottrez 2003)

Inhibitory effects	Stimulatory effects
·Down-regulation of MHC II expression	·Enhancement of B cell proliferation and differentiation
·Inhibition of Th1 effector mechanisms	·Stimulation of the proliferation and cytotoxic activity of NK cells and CD8 cytotoxic lymphocytes
·Inhibition of antigen presenting capacity of monocytes/ macrophages	·Stimulation of NK cell cytokine production
	·Stimulation of immunoglobulin synthesis
·Inhibition of pro-inflammatory cytokine secretion and release (IFN-γ, TNF-α, Il-1, Il-1β, IL-2, Il-6, Il-8, Il-12,G-CSF, GM-CSF)	·Regulation of certain cell growth and differentiation (T cells, dendritic cells, mast cells, endothelial cells, granulocytes and keratinocytes)
·Inhibition of eosinophil and B cell apoptosis	·Enhancement of monocyte/macrophage phagocytosis
·Inhibition of the synthesis of PG, free oxygen radicals, pro-coagulation factors	
·Suppression of mast cell development	
·Inhibition of antigen-stimulated proliferation of CD4+ T cells	
·Reduction in the expression of the IgE receptor	

a dual role: promoter, due to its anti-inflammatory properties, and inhibitor, due to its anti-angiogenic effect (Swiątek 2012; Howell&Rose-Zerilli 2006). Both overproduction and deficiency of IL-10 are responsible for potential lesions. The main effects of IL-10 are described in table 1.

Lack of IL-10 determines an exacerbation of inflammatory responses as IL-10 assures no suppression of pro-inflammatory cytokine responses. Thus, IL-10 deficiency leads to autoimmune diseases (systemic lupus, Sjögren syndrome, rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease) (Swiątek 2012; Groux&Cottrez 2003). However, the overproduction of IL-10 produces an increased susceptibility to viral (HCV, HVB, HIV or EBV) and bacterial infections or tumors (skin, gastric or hepatic cancer) (Commins et al 2008; Swiątek 2012; Akdis&Blaser 2001; Zdrenghea et al 2015).

Interleukin-10 gene polymorphism

In the last years, the research has started to focus on understanding how the same molecule may have different roles in specific clinical conditions. Differences in cytokine secretion (deficiency or overproduction) showed an association with certain allelic variants of mediators genes (Trifunović et al 2015). Therefore, the polymorphisms of genes that encode cytokines might play an important role in disease pathophysiology.

Single nucleotide polymorphisms may change the structure or the function of the protein coded by a gene, especially the polymorphisms located in the promoter region. The gene encoding IL-10 synthesis is located on chromosome 1q31-32, consisting of four introns and five exons (Spits&De Waal 1992).

The polymorphisms located in the promoter regions of the IL-10 gene have been the most intensely studied until now, identifying at least 23 different SNPs (Opdal 2004). Some of them were related to an altered IL-10 level (Zheng et al 2014). These polymorphisms include 3 biallelic SNPs (single nucleotide polymorphisms) located at position -592 (C/A), -819 (C/T) and -1082 (G/A) from the transcription start site (Eskdale et al 1997; Eskdale et al 1998; D'Alfonso et al 2000; Tountas & Cominelli 1996). These form 3 distinct haplotypes (ATA, CCA and CCG), the forth one, ATG, being extremely rare (Swiątek 2012; Eskdale et al 1997; Eskdale et al 1998). Two other sites of the promoter region where the microsatellite polymorphisms may occur, were also studied: IL-10.R and IL-10.G. These 2 sites are located at 1.2 kb and 4 kb, upstream of the transcription start site (Swiątek 2012; Eskdale et al 1996). Polymorphisms in non-coding regions were also described, but they are not associated with the IL-10 function (Donger et al 2001).

Some of the described polymorphisms may influence the constitutive and induced level of IL-10. It is estimated that 50-70% of IL-10 synthesis variation is due to genetic factors (Swiątek 2012). IL-10 level differs from one person to other depending on the distinct presence of SNPs (Eskdale et al 1997; Donger et al 2001; Eskdale et al 1999). Deficiency and overproduction of IL-10, resulting as a consequence of a specific genotype or haplotype, might influence the pathogenesis of several diseases, including allergic ones.

The IL-10 -1082 G/A polymorphism

Among the polymorphisms mentioned above, the IL-10 gene polymorphism -1082G/A seems to have an important role in the modulation of IL-10 production. The presence of the A allele induces a reduced transcriptional activity, but its full functional role is not well known (Reuss et al 2002). Published data are still inconsistent as both A and G alleles at position -1082 might be associated with an overexpression of IL-10 (Suarez et al 2003; Rees et al 2002). However, it is considered that IL-10 levels are not dependent on -819 C/T or -592 C/A polymorphisms (Turner et al 1997), even if there are studies that revealed a low production of IL-10 in patients with the A allele at position -592 (Clerici et al 1994).

The distribution of alleles, genotypes and haplotypes has an important interethnic variation. The G allele at the position -1082, which correlates with overproduction of IL-10, is more frequently observed in Caucasians than in Asians, the GCC haplotype being present in over 50% of the general population (Suarez et al 2003; Turner et al 1997; Meenagh et al 2002). In a study conducted on Spanish people, Suarez et al (2003) observed that the polymorphism at position -1082/G is correlated with a serum level of IL-10 of over 2 pg/ml. Kurzawski et al

(2005) published the results of a study performed on 205 healthy volunteers and reported that the GCC haplotype is the most frequent in different Caucasian subgroups (over 40%), except for Italians (37%) (Poli et al 2002). But the G allele at the position -1082 and the GCC haplotype are less frequent in Asians (GCC haplotype 17.2%) (Mok 1998) and Africans (GCC haplotype 31.8%) (Hoffmann et al 2002).

A comparative study published in 2002 (Meenagh et al 2002) analyzed the -1082 G/A polymorphism in different populations: Caucasians, Africans, Chinese, Spanish and Arabians. The GG genotype is the most frequent genotype in Caucasians (34.4%), but it is absent in Asians. The AA genotype is exclusively specific in Asians (97.5%), and more frequent in Spanish, Africans and Arabians than in Caucasians (46.2%, 33.4%, and 44.3%). Same data on the infrequent presence of the GG genotype in Asians were also mentioned in other studies (Hoffmann et al 2002; Kusumoto et al 2006; Chen et al 2007).

The IL-10 -1082 G/A polymorphism in respiratory allergic diseases

Allergic diseases are IgE-mediated disorders, with Th2 lymphocytes playing a major role in chronic allergic inflammation. Activated Th2 lymphocytes are responsible for the release of specific cytokines that are involved in the stimulation of IgE synthesis (IL-4, IL-13) or in the recruitment and activation of eosinophils (IL-5, GM-CSF). Eosinophils are the main cells involved in chronic allergic inflammation. IL-10 is the intrinsic inhibitory mechanism of pro-inflammatory cytokine synthesis (Borish et al 1996).

Bronchial asthma is a Th2-mediated disease, produced by genetic and environmental factors. In the lung of healthy individuals, the main source of IL-10 is represented by alveolar macrophages and circulating monocytes (Rosenwasser&Borish 1997). As alveolar macrophages account for more than 80% of the cells in the bronchoalveolar lavage (BAL), compared to Th1 and Th2 lymphocytes that are less than 10% (Borish et al 1996), it is expected that IL-10 reduces the development of chronic inflammation. However, an inverse correlation between IL-10 levels and disease severity was noticed in patients with asthma (Borish et al 1996), thus permitting a continuous production of some pro-inflammatory cytokines, like IL-1 beta, IL-6 and TNF-α, which promote the development of chronic inflammation in the lower airways (Trifunović et al 2015).

Based on this observation, research was performed in order to assess if a specific polymorphism influences asthma susceptibility and phenotypes, but the published data are inconsistent. The A allele at position -1082 of the Il-10 gene, which determines an impaired secretion of IL-10 in asthma patients, was more frequent in patients with asthma than in the control group in a study conducted on Indians (Chatterjee et al 2005). Trajkov et al. (2008) analyzed the role of 22 cytokine polymorphisms in 74 patients with asthma and 301 controls and reported no correlation between a specific allele at position -1082 and asthma. However, genotype analysis revealed a positive association between GG and AA genotypes and asthma in Macedonians (Trajkov et al 2008). Karjalainen J et al (2003) reported no correlation between this allele and asthma susceptibility in Finnish, but an association with eosinophilia and high total plasma IgE levels that might contribute to a greater asthma severity. The last observation was also present in a previous study, where there was a correlation between the A allele and high total IgE levels in asthma patients compared to controls in a study conducted on Caucasians (Hobbs et al 1998). Similar data were also reported in Arabs, with a correlation between the A allele and elevated plasma IgE levels, but no correlation with IL-10 levels (Hussein et al 2014), suggesting that there are also other IgE-dependent mechanisms involved in asthma severity.

The relationship between the -1082 G/A polymorphism and the pulmonary function has also been analyzed as an expression of asthma severity. There was a correlation between the A allele and FEV1 reduction, indicating an association with severe types of asthma in children (Weiss et al 2000, Lyon et al 2004), but not in adults (Burgess et al 2004). There was also a correlation between the AA genotype and the reduced pulmonary function observed in Kim's study (Kim et al 2011). This genotype is associated with a 20% FEV1 reduction after the methacholine challenge test. Kim et al (2011) observed no correlation between IL-10 -1082 genotypes and IL-10 levels, total IgE levels, eosinophil count or asthma susceptibility.

Starting from these inconsistent data, three meta-analyses were performed and published, trying to find a better answer for a possible connection between IL-10 gene polymorphisms and asthma susceptibility or severity. The first meta-analysis included 18 studies, with 4,478 asthma patients and 4,803 controls (Nie et al 2012). Nine of these studies revealed an association between IL-10 -1082 G/A polymorphism and asthma susceptibility. Individuals with the AA genotype have a 27% higher risk of asthma. Analysis of different subgroups showed that the highest risk was noticed in patients with atopic asthma and among Asians.

The second meta-analysis published by Hyun et al. (2013) included 11 studies, with 2,215 asthma patients and 2,170 controls. Hyun mentioned no association between a specific IL-10 genotype at position -1082 and asthma susceptibility, even if the G allele is more frequently observed in East Asians and adults. Compared with the previous one, there is no correlation mentioned in children (Hyun et al 2013).

The most recent meta-analysis of Zheng et al (2014) included 12 studies, but a pooled analysis was conducted in eight studies with Hardy Weinberg equilibrium. This analysis involved 2,448 asthma patients and 2,146 controls. The AA genotype was associated with a higher risk of asthma when compared to GG or AG (43% and 17%). Stratification by ethnicity, etiology and age revealed a higher risk in adults, Asians and patients with atopic asthma (Zheng et al 2014).

The hypothesis arising from these studies regards the possible association between the presence of a specific IL-10 genotype at position -1082 and a risk of asthma development in non-asthma patients that have other risk factors for this disease. Koponen et al (2013) analyzed the polymorphism in children with viral bronchiolitis within the first 6 months of life and in controls. There was a correlation between the AA genotype and rhinovirus-induced bronchiolitis, but not syncytial virus-induced, concluding that the pathophysiological mechanisms are different in these two respiratory infections. The authors also noticed that there is no correlation between a polymorphism at position -1082 and the presence of wheezing at 6 or 18 months

of life. The presence of the G allele had a protective effect for the development of post-bronchiolitis asthma, even if the AA genotype was more frequent in patients with bronchial asthma at preschool age, but the difference did not reach statistical significance (Koponen et al 2013).

There is insufficient data regarding the influence of this polymorphism on allergic rhinitis. There is only one published study conducted in Northern India, which included 95 patients with different forms of allergy (asthma, rhinitis and urticaria). There was a significant association between the GG genotype and the presence of allergy (OR=2.47, 95%CI 1.003-4.96), but the authors did not perform a detailed analysis for each form of allergy (Gaddam et al 2012).

The IL-10 -1082 G/A polymorphism in atopic dermatitis

Atopic dermatitis (AD) is another clinical manifestation of atopy, a Th2-mediated disease. Atopic dermatitis is more frequently observed in children, as the first manifestation of atopy. Even if the entire pathophysiological mechanism is not well-known, atopic dermatitis is considered the initial skin manifestation of a systemic disease, which can advance to respiratory manifestations, like bronchial asthma or rhinitis (Eichenfield 2003). The published data revealed a close relationship between severe forms of atopic dermatitis and sensitization to respiratory allergens, the main cause of asthma and rhinitis symptoms (Dunstan et al 2005). The understanding of Th2 response dependent immune mechanisms in these patients could prevent the development of respiratory allergies.

Dunstan et al (2005) observed that a more intense Th2 response in patients with atopic dermatitis is partially associated with a low production of IL-10 as a response to different exogenous and endogenous stimuli, such as foods, respiratory allergens, intestinal flora, Staphylococcus Aureus or vaccines. This connection had already been demonstrated in bronchial asthma, another Th2-mediated disease. Therefore, Sohn et al (2007) investigated the influence of polymorphisms within the promoter region of the IL-10 gene and the susceptibility and phenotypes of atopic dermatitis. There is no association between a specific allele or genotype and atopic dermatitis or elevated total IgE levels or eosinophilia. The other two promoter region polymorphisms (-592 C/A and -819 C/T) are related to eosinophil activation and specific phenotypes of atopic dermatitis in children (Sohn et al 2007).

Similar observations were reported by Raedler et al (2013), who investigated the risk of wheezing and atopic dermatitis in newborns of atopic mothers. The authors determined IL-10 gene polymorphisms in 200 newborns (72 of atopic mothers and 128 of controls) and concluded that the investigated polymorphisms are risk factors for atopic dermatitis at the age of three. They suggested that IL-10 influences early-life immune maturation, favoring the atopic status (Raedler et al 2013).

Despite several studies that revealed an association between the AA genotype and elevated total IgE levels in patients with bronchial asthma (et al 2014, Hobbs et al 1998, Hussein et al 2014), this observation was not confirmed in patients with atopic dermatitis. Shin et al (2005) analyzed the role of -1082 G/A polymorphism and serum IgE levels in 334 patients with atopic dermatitis, reporting no association. But this study mentioned the role of the other 2 promoter region polymorphisms, especially -592 C/A and a specific haplotype in atopic dermatitis (Shin et al 2005), results which were also confirmed in further studies (Sohn et al 2007, Raedler et al 2013). The author suggested the combined role of these polymorphisms in atopic dermatitis, not taken individually.

The IL-10 -1082 G/A polymorphism in food allergy

Food allergies are IgE or non-IgE-mediated reactions. IgE-mediated reactions are immediate anaphylactic reactions, being the most frequently studied. IL-10 is an anti-inflammatory cytokine that limits the production of IgE in favor of non-inflammatory IgG4 and IgA (Taylor A 2006) and that could inhibit the inflammatory response in food allergies. As there is a correlation between the G/A polymorphism at position -1082 and asthma susceptibility and elevated IgE levels, there is a hypothesis stating the possible modulation of food allergy evolution.

Campos et al (2008) studied the polymorphism in 111 patients with food allergy and 115 atopic control children and concluded that carriers of the AA genotype have a 2.5-fold increased risk of developing food allergies (95% CI, 1.0-6.4) compared to controls. However, the authors noticed no correlation between G/A polymorphisms at position -1082 and total IgE levels in Japanese atopic children. Different results were obtained by Chen et al (2012) in their study on Taiwanese people. There is no correlation between the G/A polymorphism at position-1082 and food allergy susceptibility, IL-10 and IgE levels or clinical manifestations of food allergy. Nevertheless, there were fewer patients included in this second study (Chen et al 2012). In accordance to data published on atopic dermatitis, the influence of -592 C/A polymorphism was reported in the modulation of IL-10 immune responses in food allergies.

Jacob et al (2013) analyzed five IL-10 gene polymorphisms, including -1082 G/A, in 50 patients with cow milk allergy and 224 healthy volunteers. There was a correlation between this polymorphism and cow milk allergy, the GG genotype being more frequent in allergic patients than in controls. The G allele has a 2-fold increased risk of persistent forms of cow milk allergy (OR=2.43, 95%CI=1.75-4.08) in Brazilian people (Jacob et al 2013).

Conclusions

There is a deficiency in the production of IL-10 in bronchial asthma and atopic dermatitis. There is a correlation between the IL-10 G/A polymorphism at position -1028 and asthma susceptibility, particularly in Asians, children and atopic asthma, and food allergy, but no correlation with susceptibility for atopic dermatitis. Different genotypes are associated with asthma or food allergy phenotypes and with greater IgE synthesis and eosinophilia in asthma.

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