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Review article

Influence of genetic polymorphisms (IL-10/CXCL8/CXCR2/NFκB) on the susceptibility of autoimmune rheumatic diseases

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ABSTRACT

The autoimmune rheumatologic disorders mostly have a common genetic path to the autoimmunity. Several genes have been associated with rheumatologic disorders; therefore, we are analyzing just the ones in those containing several evidences of the existence of association with the risk or protection from autoimmune disorder. The nuclear factor kappa beta (NF-kappa B), which regulates the autoimmune and anti-inflammatory responses, is associated with systemic sclerosis (SS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), just as the CXCR2 e CXCL8 genes. On the other hand, the interleukin-10 (IL-10), which is an anti-inflammatory cytokine, is associated with almost all rheumatologic disorders. In this article, we are reviewing the potential roles of these genes in the immune system and in several rheumatologic disorders. In relation to IL-10, several studies have been carried out, but most of them are controversial – some detected the absence of association, and others found association in different genetic polymorphisms. Conversely, in relation to NF-kappa B, it was studied just in RA and SLE, and no relevant significant analyses were observed. The genetic polymorphisms of the CXCR2 gene were associated with SS, but not with RA e SLE. On the other side, the genetic polymorphisms of the CXCL8 gene are not associated with SS, but with RA.

Influência dos polimorfismos genéticos (IL10/CXCL8/CXCR2/NFκB) na susceptibilidade das doenças reumatológicas autoimunes

Palavras-chave:
Doenças reumatológicas
Quimiocinas
Citocinas
NF-kB

RESUMO

As doenças reumatológicas autoimunes, na maioria das vezes, possuem uma via genética comum para a autoimunidade. Vários genes foram associados com as doenças reumatológicas, para tanto iremos analisar somente alguns genes nos quais há várias evidências da existência de associação com risco ou proteção de doença autoimune. O fator de transcrição nuclear kappa B (NF-kappa B), o qual regula as respostas imunes e inflamatórias,

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está associado com esclerose sistêmica (ES), artrite reumatoide (AR) e lúpus eritematoso sistêmico (LES), assim como os genes CXCR2 e CXCL8. Já a interleucina 10 (IL-10), que é uma citocina anti-inflamatória, está associada com quase todas as doenças reumatológicas. Neste artigo, revisamos os potenciais papéis desses genes no sistema imunológico e em diversas doenças reumatológicas. Com relação à IL-10, diversos estudos foram realizados, porém em sua maioria contraditórios - alguns encontraram ausência de associação e outros encontraram associação em diferentes polimorfismos do genes. Já em relação ao NF-kappa B, somente foi estudado em AR e LES, e não foram observadas análises significativas relevantes. Os polimorfismos genéticos do gene CXCR2 foram associados com ES, mas não estão associados com AR e LES. Já os polimorfismos genéticos do gene CXCL8 não estão associados com ES, mas estão associados com AR.

Introduction

Studies of genetic association seek to determine genetic variants associated with specific disease states or traits. As more studies have been conducted in different complex diseases, it became clear that the contribution of individual genes to the genetic risk for the disease may be very modest and that multiple *loci* are involved in the mechanism. In this sense, the interpretation of genetic association studies in a rare and phenotypically heterogeneous disease, such as scleroderma, should be performed using strict guidelines. Such studies are often limited by a lack of enough statistical power to generate reliable and reproducible results, because of small samples in case-control studies, genetic heterogeneity, and the extent and degree of linkage disequilibrium among genetic markers that vary between populations.[1]

The complex pathophysiology of systemic sclerosis (SSc) implies the involvement of genes that affect individually or, more likely, jointly, the disease process conduction. Many of these genes have been associated with other autoimmune diseases such as systemic lupus erythematous (SLE) and rheumatoid arthritis (RA), which suggests a common genetic pathway for autoimmunity.[2]

Given the above facts, it is necessary to study the influence of the polymorphisms of interleukin-10 (IL-10) genes, the nuclear transcription factor kappa of type 1 (NFkB1) B cells, and the chemokine receptor 2 and its ligand (CXCR2 and CXCL8) in these pathologies. The identification of associations between these polymorphisms and systemic sclerosis could impact not only in a better understanding of the pathogenesis, but also in identifying risk groups for disease development and subgroups of patients with better or worse prognoses.

Methodology

A literature search was performed in PubMed database using the terms "systemic sclerosis and interleukin 10 genes", "systemic sclerosis and CXCL8 polymorphism", "systemic sclerosis and CXCR2 polymorphism", "systemic sclerosis and interleukin 8 gene", "systemic sclerosis and NFKB1 polymorphism", "Rheumatoid arthritis and interleukin 10 polymorphism", "Rheumatoid arthritis and CXCL8 polymorphism", "rheumatoid arthritis and CXCR2 polymorphism", "rheumatoid arthritis and NFkB1 polymorphism", "systemic lupus erithematosus and CXCR2 polymorphism" systemic "lupus erithematosus and CXCL8 polymorphism", and "systemic lupus erithematosus and IL-10 polymorphism". All articles found were assessed, and data included in this review include the results of association studies, both positive and negative, since 1991, the year of publication of the first article on the topic. The exclusion criterion used was the presence of micro satellite-related studies.

Function of proteins and their respective genes

NFkB

The kappa B nuclear transcription factor of B cells (NF-kappa B) consists of a group of proteins involved in the expression of a wide variety of genes that are involved in the regulation of immune and inflammatory responses.[3] Genes that are activated by NF-kappa B include proinflammatory cytokines, chemokines and adhesion molecules. Some genes regulated by NF-kappa B, such as tumour necrosis factor alpha (TNF-α) and interleukin-1 beta (IL-1β) also directly activate NF-kappa B to amplify and increase the primary inflammatory response. The activation of NF-kappa B by B or T-cell receptors is also required for the proliferation induced by antigen, cytokine production and survival of T and B cells.[4]

So far, five members of the NFkB family have been identified: NFkB1 (p105/p50), NFkB2 (p100/p52), RelA (p65), RelB and RelC. NFkB1 gene is located in the region 4q23-q24 and consists of 24 exons and introns. The gene encoding P105 protein is a cytoplasmic non-DNA binding molecule, while the gene encoding p50 protein is a DNA binding protein and corresponds to the N-terminal of p105 (OMIM, 164.011). The NFKB2 gene is located on the long arm of the chromosome, located in the region 10q24, and encodes proteins P100 and P52 (OMIM, 164.012). On the other hand, the RelA gene (NFKB3) is located in the 11q12-q13 region with 10 and encodes p65 protein (OMIM, 164.014); the RelB gene is located on chromosome 19 (OMIM, 604.758, MI-12,248) and THE cRel gene is located in the 2p13-p12 region.[5]

Furthermore, the functions of NFkB1 (P105) and NFkB2 (p100) are different, although their structures are similar.

Studies have reported that the processing of P105 protein to p50 is essential, this event being essential for peripheral lymphoid tissue organogenesis and B-cell development. Another important aspect is that the induction of the processing of protein p100 is regulated by a subset of ligands that activate NF-kappa B.[6] NF-kappa B provides a key mechanistic link between inflammation and tumour. Indeed, several inflammatory cytokines, chemokines, products of necrotic cells, bacteria and viruses stimulate the activation of NF-kappa B. Conversely, proteins of NF-kappa B increase the expression of some cellular genes involving cytokines, chemokines, the major histocompatibility complex (MHC) and receptors needed for neutrophil adhesion and migration.[7]

One study examined the activation of NFkappa B in the synovium of patients with rheumatoid arthritis, suggesting a role in controlling the inflammation.[8] It is known that rheumatoid arthritis is a complex disease with contributions of systemic autoimmunity and local inflammation. However, the activation of NF-kappa B is significantly decreased in patients with systemic lupus erythematosus.[9] These findings indicate that the mechanism of regulation of NF-kappa B is different between these autoimmune diseases.

NF-kappa B is found in the cytoplasm of immune cells, in association with accessory proteins. Its activation mode varies according to the type of immune cell, with its activation state or developmental stage.[10] Furthermore, NF-kappa B is normally prevented from entering the nucleus of peripheral lymphocytes (T cells), because its subunits are strongly linked to the inhibitory protein. After cell induction by cytokines, a series of biochemical changes, including phosphorylation, ubiquitination and, then, degradation by the proteasome, occurs. When NF-kappa B is able to translocate to the nucleus, where it binds to DNA within minutes, this factor leads to the expression of different target genes.[11]

The nuclear activation and translocation of the classical pathway of NF-kappa B dimers (particularly p50-RelA) are associated with an increased transcription of genes encoding chemokines, cytokines, adhesion molecules, enzymes that produce secondary inflammatory mediators and inhibitors of apoptosis.[12] These molecules are important components of the innate immune response and are required for the migration of inflammatory and phagocytic cells into tissues where NF-kappa B was activated in response to infection or injury. An extensive list of bacteria and bacterial products activate NF-kappa B in macrophages and other cell types. For example, enteroinvasive bacteria can activate NF-kappa B in intestinal epithelial cells, a process leading to the production of inflammatory mediators including chemokines. These proteins lead to the recruitment of inflammatory and phagocytic cells to the site of infection. Moreover, there are also indirect pathways that lead to the activation of NF-kappa B, resulting in the release of IL-1 and in the activation of the classical pathway of NF-kappa B in adjacent cells.[13]

Chemokines

Chemokines are chemotactic proinflammatory cytokines that recruit leukocytes to sites of inflammation, but which also play prominent roles in tumour growth, angiogenesis, wound healing/tissue sclerosis and autoimmunity.[14] The chemokines constitute a large family of small proteins (7-15 kDa), structurally related to heparin binding proteins that can mediate leukocyte-endothelial interactions and the transmigration of cells. The priming and progression of rheumatic diseases involve multiple chemokines and inflammatory cells, such as T cells, macrophages, dendritic cells, eosinophils, and mast cells. The complex interactions between inflammatory cells and chemokines stimulate the overproduction of extracellular matrix protein synthesis by fibroblasts. Therefore, chemokines have critical importance in the pathogenesis of these diseases.[15]

The members of the family of chemokines are divided into four groups, according to the spacing of their first two cysteine residues. CXCL8 is a member of the CXC chemokine family that shows high binding affinity to CXCR1 (IL-8 receptor type 1) and CXCR2 (IL-8 receptor type 2). Although CXCR1 is selectively activated only by CXCL8, CXCR2 answers to several additional chemokines. The common denominator for all chemokines that activate CXCR2 is the Glu-Leu-Arg (ELR) sequence at the amino terminal, which appears to function as a recognition sequence for receptor binding and activation.[16] The first investigations were focused on the effect of CXCL8 in neutrophils, which respond with calcium mobilization, actin polymerization, enzyme release, chemotaxis and a weak respiratory burst.[17] Despite similar affinities for CXCL8 and similar receptor numbers of CXCR1 and CXCR2, the neutrophil chemotaxis is mediated primarily by CXCR1. However, despite the fact that CXCR2 is associated with the inhibition form of G-protein alpha subunit ($G\alpha_{i2}$), a study showed that both CXCR1 and CXCR2 are coupled to inhibitory G (G_i) protein in neutrophils where $G\alpha_{i2}$ is abundant. Therefore, it was shown that the coupling of the CXCL8 receptor is not restricted to G_i. At least under conditions in which $G\alpha_{i4}$ and $G\alpha_{i6}$ were overexpressed, these G proteins were able to function as alternative elements of transducer signalling of CXCL8-mediated cellular response.[18]

Thus, CXCL8 is activated by both CXCR1 and CXCR2 on endothelial cells. The two receptors use different signalling transduction cascades that result in the activation of small G proteins and invoke responses that deserve to be investigated. These responses of chemokines mediated by endothelial cells may contribute to an increase of the vascular permeability and leukocyte adhesion, as was observed during acute inflammation episodes, on the one hand, and to the migration and proliferation of endothelial cells during the angiogenic process, on the other hand.[19] The activity of NF-kappa B may be necessary in multiple steps during this cascade, both for the induction of protein synthesis or by direct interaction in the cytoplasm.[20]

Indeed, chemokines and their receptors are crucial factors for tissue damage in SSc, potentially directing the migration of proinflammatory cells to the affected areas. Increased levels of CXCL8 protein in skin biopsy and bronchoalveolar lavage fluid from patients with SSc have been observed.[21] A study mentioned that scleroderma skin fibroblasts cultured *in vitro* produce more CXCL8 than normal fibroblasts. Serum concentrations of CXCL8 were significantly higher in SSc patients *versus* controls (healthy subjects).[22]

In patients with fibrosing alveolitis (FA), an increase in the secretion of CXCL8 by alveolar macrophages (AM) and monocytes was observed. It is known that in scleroderma patients

there is a predisposition to the development of FA, but the CXCL8 secretion by AM in SSc patients without FA was higher than in normal individuals, and lower than in patients with fibrosing alveolitis associated with SSc (FASSc). This finding suggests that the increased secretion of CXCL8 in FASSc by AM is not constitutive. It is possible that the response of CXCL8 to initial factors of the disease may be different in those patients who will develop FA compared with those who will not.[23]

Another study showed that patients with chronic idiopathic urticaria (CIU) exhibit a pattern of altered chemokine secretion that is potentially linked to a chronic inflammatory state. Analyzing the CXCL8 gene regulation assessed by mRNA and protein levels in serum, the study indicated a high response capacity from monocytes, thereby contributing to the creation of a proinflammatory environment. These findings suggest that the innate immune system, by means of chemokines and monocytes, can lead to immune activation.[24]

Cytokines

Cytokines are essential mediators of the immune system with a broad set of functions, ranging from the regulation of inflammation to cell activation, proliferation or differentiation. Cytokines can also promote collagen deposition and fibrosis; in this way, many studies are focusing on their role as mediators of SSc, describing changes in their concentrations or in the balance between T helper type 1 (Th1) and type 2 (Th2) cytokine levels.[25]

Cytokines include the interleukins, which are proteins (polypeptides) involved in the communication among leukocytes. The activities of interleukins can be summarized in the recognition of foreign antigens by T cells, amplification of the proliferation of activated T cells, and attraction of macrophages and identification of effective mechanisms for phagocytosis of microorganisms. Each interleukin acts on a limited and specific group of cells expressing appropriate receptors for each of these proteins. Interleukin-10 (IL-10) inhibits the production of Th1 cytokine, suppresses macrophage function and activates B lymphocytes.[26]

Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine which plays a crucial role – often an essential one – in preventing inflammatory and autoimmune diseases. The deficiency or abnormal expression of IL-10 can increase the inflammatory response to microbial challenge, leading to the development of inflammatory bowel disease and to a number of autoimmune disorders. Thus, the decreased expression of IL-10 can increase the pathogens during an acute infection, but also exacerbates the inflammatory response, resulting in immunopathology and tissue damage.[27]

There is a wide variation in the production of IL-10 among individuals; studies on twins suggest that up to 75% of the variability is due to genetic factors. The production is controlled at the transcriptional level and some variations may be explained by two microsatellite polymorphisms (IL-10G and IL-10R) in the promoter region.[28] Eleven single nucleotide polymorphisms (SNP) have also been described in the promoter region, three of which are in the proximal 1.3 kb [1082 (G/A), 819 (C/T) and 592 (C/A)]; and seven in the distal region 1.3-4 kb, three of which [3575 (T/A), 2849 (G/A) and 2763 (C/A)] have the same allele frequency.[29,30] In normal Caucasian subjects, the distal AA/GA haplotype was more frequent in those who produced less IL-10.[29] In African-Caribbean SLE patients, the frequency of the A allele of polymorphism 2,763 was lower. There are no other associations with rheumatic diseases reported with SNPs in the distal region. SNPs 819 and 592 are in linkage disequilibrium.[30] Furthermore, only three haplotypes are common in Caucasian subjects: GCC, ACC and ATA; GTA is more common in southern China.[31] GCC/GCC genotype is more common in those who produce the highest levels of IL-10, while ATA/ATA genotype predominate in low producers of IL-10.[29]

Traditionally, cytokine genes and receptors have attracted great interest as plausible genetic risk factors for autoimmune disease. Considering that the production of cytokines is genetically regulated, it was hypothesized that single nucleotide polymorphisms (SNPs) near cytokine genes may be relevant to the development of SSc.[32] However, studies have failed to show positive results and, in some cases, the associations described by some authors were not confirmed in other independent populations.[33,34] These contradictory results can be attributed to several factors. First, there are studies using small samples; therefore, they are not able to represent a true association, due to type II error.[35] Second, the SNPs studied may not have a causal role in the pathogenesis of SSc, but could only be relevant to the progression or expression of disease.[36] Third, each SNP may not have a main noticeable effect on the independent risk of disease, but its effect may be dependent on other genetic variants (gene-gene interaction).[37]

The gene for IL-10 is a likely candidate to be studied in the pathogenesis of SSc, not only due to its anti-inflammatory properties, but also because it protects against fibrosis. In addition, IL-10 reduces the production of collagen and fibronectin from fibroblasts.[38] Furthermore, the functional relevance of SNP in the proximal 5' region of IL-10 gene is well defined.[39]

Genetic evidence in rheumatic diseases

CXCL8

Several polymorphisms of CXCL8 gene were studied in relation to rheumatic diseases (Table 1). In patients with SSc, genetic polymorphisms (+293 G/T) (+678 T/C), (-353 A/T) and (-251 T/A) were evaluated, however none of these polymorphisms exhibited association with the disease.[40-42] An association was only found when analyzing the gene-gene interaction between the polymorphism of CXCL8 (-353 A/T) gene with CCL5[41] gene and between the polymorphism of CXCL8 (-251 A/T) gene with CXCR2 gene.[42]

In SLE, a study showed a strong association between SNP rs2227306 of CXCL8 gene and the disease, demonstrating a risk factor.[45] But four previous studies had not shown an association with the disease, and only two of these had a power similar to the one of Sandling et al.[46,47] These polymorphisms have not been studied in rheumatoid arthritis (RA), although other polymorphisms were studied and associated with this disease. The polymorphism (-781 C/T) of CXCL8 gene is associated with the onset of the disease, the CC homozygote being a risk factor.[43] On the other hand, the polymorphism (-767 A/G) is not associated with risk of developing the disease, but the AA homozygote is associated with the development of the disease at an early age.[44]

Table 1 – Analysis of CXCR8 polymorphism in rheumatologic diseases

Gene	Disease	Polymorphism	Results	Number (N)		Study (Ref.)
				Patients	Controls	
CXCL8						
	Systemic sclerosis					
		(+)293 G/T	no association	128	194	Renzoni et al. 2000[40]
		(+)678 T/C	no association	128	194	Renzoni et al. 2000[40]
		(-)353 A/T	association with gene CCL5-403 G/A (p=0.039)	99	198	Lee et al. 2007[41]
			no association	128	194	Renzoni et al. 2000[40]
		(-)251T/A	association with gene/cxcr2+1208 C/T (p<0.001)	151	147	Emonts et al. 2011[43]
	Rheumatoid arthritis					
		(+)781 C/T	CC homozygote (p<0.0001; rs2227306)	376	463	
		3'UTR 2767 A/G	AA homozygote (p=0.02; rs10938092)	199	130	Lo et al. 2008[44]
	Systemic lupus erythematosus					
		rs46941 78 C/A	C allele (OR=1.26; P<0.001)	826	1310	Sendling et al. 2011[45]
			no association	150	130	Hang et al. 2006[46]
		(-)353 A/T; (+)781 C/T	no association	500	481	Sanchez et al. 2006[47]

CXCR2

So far, in patients with SSc, no genetic studies were performed on the association of CXCR2 gene polymorphism, but other studies have analyzed the presence of polymorphism in SSc, SLE, SS and RA (Table 2). Therefore, a study evaluated the susceptibility of the polymorphism (-786 C/T) of CXCR2 gene in patients with rheumatoid arthritis, but no association was found between the gene and the disease. Likewise, no association was found when evaluating the correlation of this same polymorphism in patients with SLE and SSc.[41,48] However, subsequent studies in SSc patients that examined another CXCR2 gene polymorphism obtained different results. First, the polymorphism (+1208 C/T) was analyzed in British patients, yielding a strong association with TT homozygous gene with a risk factor for the disease.[40] Contrary to these findings, in southern Brazil we found a strong association of CC homozygote of this same polymorphism in relation to disease susceptibility.[42] This observed difference might be explained by the great Brazilian miscegenation due to immigration of Africans and Europeans in the past, which resulted in a highly diverse population.[49]

NFkB1

The polymorphism of NFkB1 was evaluated in several rheumatic diseases (Table 3). In SSc patients, no study found an association with the insertion/deletion of ATTG aminoacids at position -94 of NFkB1 gene. However, one study demonstrated a protective factor for the disease with the interaction of the homozygous polymorphism for insertion (insertion / insertion) of ATTG in NFkB1 gene (-94 ins/del ATTG) with CC homozygous polymorphism of IL-10 gene (- 819). We also demonstrated as a risk factor for SSc the interaction of the NFkB1 heterozygous gene (insertion/deletion) with the CC homozygous polymorphism of IL-10 (-592) gene.[50]

Table 2 – Analysis of CXCR2 polymorphism in rheumatologic diseases

Gene	Disease	Polymorphism	Results	Number (N)		Study (Ref.)
				Patients	Controls	
CXCR2						
	Systemic sclerosis					
		(-)786 C/T	no association	14	242	Kato et al., 2000[48]
			CC homozygote (OR=1.7; p=0.04)	99	198	Lee et al., 2007[41]
		(+)785 C/T	CC homozygote (OR=2.33; p=0.01)	128	194	Renzoni et al., 2000[40]
		(+)1208 C/T	TT homozygote (OR=2.67; p=0.003)	128	194	Renzoni et al., 2000[40]
			CC homozygote (or=2.76; p=0.001)	151	147	Salim et al., 2012[42]
		(+)1440 G/A	no association	128	194	Renzoni et al., 2000[40]
	Rheumatoid arthritis					
		(-)786 C/T	no association	146	242	Kato et al., 2000[48]
	Systemic lupus erythematosus					
		(-)786 C/T	no association	80	242	Kato et al., 2000[48]
	Sjögren syndrome					
		(-)786 C/T	no association	12	242	Kato et al., 2000[48]

Table 3 – Polymorphism analysis of NFKB1 -94ins/del ATTL (s28362491) in rheumatologic diseases

Gene	Disease	Results	Number (N)		Study (Ref.)
			Patients	Controls	
NFKB1-94 ins/del ATTG (rs28362491)					
	Systemic sclerosis				
		association of ATTG (homozygous) insertion with gene IL-10 (-819)CC and (-592)CC	151	147	Salim et al., 2013[50]
	Rheumatoid arthritis				
		no association	272	264	Orozco et al., 2009[51]
		no association	458	657	Dieguez-Gonzalez et al., 2009[52]
		association of heterozygous gene (ins/Del) with gene FCRL3 (-169)GG (p=0.003)	592	646	Martinez et al., 2006[53]
		association of homozygous gene for deletion (Del/Del) with risk for cardiovascular events (OR=1.76; p=0.03)	1437	*	Lopez-Mejias et al., 2002[54]
	Systemic lupus erythematosus				
		protection with heterozygote gene (Ins/del) (OR=0,52; P=0,012)	224	256	Gao et al., 2012[55]
		No association	181	264	Orozco et al., 2009[52]
	Ankylosing spondilitis				
		no association	205	200	Kim et al., 2005[56]

*The study only accessed the interaction among patients

In RA patients, no direct association of gene with the disease was found,[51-53] but a study showed that the homozygous genotype with deletion of ATTG (Del/Del) in NFkB1 gene is at high risk for cardiovascular events in patients with RA compared with patients who were homozygous for gene insertion.[54] Another study stratified patients according to NFkB1 genotype and evaluated their combination with FCRL3 polymorphism, observing a susceptibility to the disease in patients heterozygous (Ins/Del) to NFkB1 gene.[53]

According to one study, patients with SLE have a lower risk of developing the disease in case of an incidence of the heterozygote (insertion / deletion) of NFkB1 gene (-94 ins/del ATTG).[55] But another study found no association of NFkB1 gene in patients with SLE.[51]

Interleukin-10

Different studies have linked several polymorphisms of IL-10 in rheumatic diseases (Table 4). A meta-analysis in patients with SSc reported that the -819 polymorphism (C/T) of IL-10 is associated with susceptibility to the development of SSc. These authors observed that the C allele at -819 locus of IL-10 may be a risk factor, and that the A allele of 3575 polymorphism may contribute to the disease, especially in Caucasian subjects.[58] However, other studies individually conducted have not achieved the same results. In the west of Scotland, there was no statistical difference in genotype distribution of IL-10 between patients and controls, but, interestingly, patients with diffuse disease had a low frequency of GCC/GCC genotype (which is associated with a high production of IL-10), suggesting that the inheritance of the IL-10 genotypes may be one of the molecular events that determine the clinical phenotype.[34] In Italy[36] and Turkey,[57] the GCC haplotype exhibited more expression in SSc patients than in controls, and, in southern Brazil, we noted that the GCC/GCC genotype proved to be a risk factor for the development of the disease.[48] But another study conducted in Italy found no such associations with the disease.[33] In Japan, other polymorphisms were evaluated: -3575 A/T, -2849 A/G and -2763 A/C. The frequency of the AC heterozygote at position 2763 was higher in SSc patients than in controls. On the other hand, patients with diffuse scleroderma had the lowest frequency of the CC homozygote when compared with healthy controls. In Caucasian subjects, the frequency of the AA homozygote at positions -3575 and 2763 was higher in SSc patients compared with controls.[60]

Some studies in patients with rheumatoid arthritis found no association of IL-10 polymorphisms with the disease.[63] However, some studies observed a protective factor of this gene in these patients. Paradowska-Gorycka et al.[69] (2010) emphasized that the G allele of SNP-1082 of IL-10 and the C allele of SNP -592 were more common in controls than in patients with RA. De Paz et al.[67] (2010) also found a protective factor in this gene, but in the AA haplotype of SNP-1082 of IL-10.

On the other hand, all other studies observed a susceptibility factor for the disease. Ying et al.[68] (2011) reported a higher frequency of the C allele of SNP-592 C in patients with RA, agreeing with Hee et al.[64] (2007), who also found this result. Conversely, Pawlik et al.[62] (2005) reported a higher frequency of the GG haplotype of SNP-1082 GG in patients with RA. Ates et al.[57] (2008) and Cantagrel et al.[66] (1999) also mentioned SNP-1082 as a susceptibility factor for the disease. Some studies performed with other poly-

Table 4 – Analysis of interleukin-10 (IL-10) polymorphism in rheumatologic diseases

Gene	Disease	Polymorphism	Results	Number (N)		Study (Ref.)
				Patients	Controls	
IL-10						
	Systemic sclerosis					
		(-)1082 G/A; (-)819 C/T; (-)592 C/A	association of GCC haplotype with diffuse form (OR=1.84; p=0.04)	161	94	Beretta et al., 2007[36]
			GCC/GCC genotype (OR=1.87; p=0.019	151	147	Salim et al., 2013[48]
			protection of GCC/GCC genotype with diffuse form (OR=0.10; p=0.005)	51	94	Crilly et al., 2003[34]
			association of GCC/GCC genotype (OR=5.07; p=0.002)	45	150	Ates et al., 2008[57], Peng et al., 2012[58]
		(-)590 A/C	no association	242	242	Beretta et al., 2007[36]
		(-)3575 A/T	association of AA haplotype with limited form (OR=3.60; p=0.0002)	105	143	Hudson et al., 2005[60]
			no association	78	692	Matuzzi et al., 2007[33]
		(-)2849 A/G	association of GG haplotype with limited form (OR=0.53; p=0.03)	105	143	Hudson et al. 2005[60]
		(-)2763 A/C	association of AA haplotype with limited form (OR=3.50; p=0.003) and diffuse form (OR=3.0; p=0.03)	105	143	Hudson et al., 2005[60]
	Rheumatoid arthritis					
		(-)1082 G/A; (-)819 C/T; (-)592 C/A	association of GCC (OR=1.46; p=0.006) and ACC (OR=1.43; p=0.011) haplotypes	98	122	Ates et al., 2008[57]
			association of ACC haplotype in patients positive for rheumatoid factor IgA (OR=1.6; p=0.05)	234	238	Hajeer et al., 1998[61]
			association of GCC/GCC genotype (OR=2.18; P<0.005)	95	104	Pawlik et al., 2005[62]
			no association	222	398	Gambhir et al., 2010[63]
		(-)1087 G/A; (-)824 C/T; (-)597 C/A	ATA haplotype associated with low production of IL-10 (P<0.05)	84	95	Hee et al., 2007[64]
		(-)2849 A/G	association of G allele in patients positive for rheumatoid factor IgG (P<0.001)	283	1220	Lard et al., 2003[65]
		(-)1082 G/A	no association (rs1800896)	376	463	Emonts et al., 2011[43]
			no association	108	128	Cantagrel et al., 1999[66]
			protection with AA genotype (OR=0.56; p=0.006)	162	373	de Paz et al., 2010[67]
		(-)819 C/T	no association (rs3021097)	376	463	Emonts et al., 2011[43]
		(-)592 C/A	association of A allele (OR=1.31; p=0.008)	164	196	Ying et al., 2011[68]
			association of CA genotype (OR=46.34; P<0.001)	244	106	Paradowska-Gorycka et al., 2008[69]

morphisms in Brazilian population found no association with rheumatologic diseases.[70]

Analyzing the haplotypes and genotypes of IL-10 in rheumatic diseases, we found that the GCC/GCC genotype is associated with SSc, RA and SLE. Conversely, the ACC haplotype is associated with SS and SLE; and the GCC haplotype is associated with SSc and RA. Moreover, in patients with JIA, there was a protection with GCC genotype.

Conclusion

Genetic factors may contribute to the failure of tolerance and to the development of autoimmune responses. In this paper, we presented how the NFkB1, IL-10, CXCL8 and CXCR2 genes could be involved in the initiation and progression of autoimmune rheumatic diseases. There are still many divergences among studies, but this is because the populations are genetically different. Therefore, the identification of individual components of these genes as the key to a particular disease and the development of inhibitory compounds able of performing a specific activity will constitute a promising and challenging task for the future.

Conflicts of interest

The authors declare no conflicts of interest.

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