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TOPIC HIGHLIGHT

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Interleukin and interleukin receptor gene polymorphisms in inflammatory bowel diseases susceptibility

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Abstract

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), represents a group of chronic inflammatory disorders caused by dysregulated immune responses in genetically predisposed individuals. Genetic markers are associated with disease phenotype and long-term evolution, but their value in everyday clinical practice is limited at the moment. IBD has a clear immunological background and interleukins play key role in the process. Almost 130 original papers were revised including meta-analysis. It is clear these data are very important for understanding the base of the disease, especially in terms of clinical utility and validity, but text often do not available for the doctors use these in the clinical practice nowadays. We conducted a systematic review of the current literature on interleukin and interleukin receptor gene polymorphisms associated with IBD, performing an electronic search of PubMed Database from publications of the last 10 years, and used the following medical subject heading terms and/or text words: IBD, CD, UC, interleukins and polymorphisms.

Key words: Inflammatory bowel disease; Crohn's disease; Ulcerative colitis; Interleukin; Interleukin receptor; Polymorphisms

Core tip: Inflammatory bowel diseases (Crohn's disease and ulcerative colitis) are chronic, progressive disorders of the gastrointestinal tract. Different genes, including interleukin genes play central role in mediating and modulating of inflammation in inflammatory bowel diseases. In this review we summarized the interleukin and the interleukin receptor genes associated with Crohn's disease and/or ulcerative colitis performing an electronic search on the PubMed database focusing on the following terminology: inflammatory bowel disease, Crohn's disease, ulcerative colitis, interleukin and interleukin receptor.

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INTRODUCTION

Inflammatory bowel disease (IBD) - clinically classified as Crohn's disease (CD; OMIM 26600) and ulcerative

colitis (UC; OMIM 191390) - is a common chronic, relapsing inflammatory disorder of the gastrointestinal tract[1]. In Europe the highest annual incidence of CD is 12.7/100000 and 24.3/100000 for UC. In Asia and in the Middle East both rates are much lower (CD: 5.0/100000 and UC: 6.3/100000). However in North America the incidence for UC is 19.2/100000 and they have the highest rate for CD in the world with 20.2/100000[2]. Although the precise etiology of IBD still remains obscure, the accepted hypothesis is that in genetically predisposed individuals the commensal luminal flora trigger an inappropriate, overactive mucosal immune response causing intestinal tissue damage that is further modified by specific environmental factors (*e.g.*, smoking)[3].

The location of inflammatory lesions and the types of cytokines involved in the pathogenesis mainly distinguish CD from UC. Whereas CD is a segmental, transmural disorder involving any part of the gastrointestinal tract, UC is characterized by superficial, continuous mucosal ulcers restricted to the colon. Imbalances between pro- and anti-inflammatory cytokines in the mucosa have been established for both CD and UC[4]. CD is associated with a T helper type 1 (Th1)[4] and T helper type 17 (Th17)[5] immune response, thus interferon gamma/interleukin 12 (IFNγ/IL12) and IL23/IL17 cytokines assign the downstream release of complex network of further pro-inflammatory cytokines (*e.g.,* IL18, IL2, IL1, IL21, IL22) (Figure 1). Th17 and a modified Th2 cytokine profile (IL13 and IL5) are characteristic for UC. In addition, IL6 and tumor necrosis alpha (TNFα) are produced by both Th1 and Th2 cells as well as by macrophages in both IBD entities. A further group of T cells, regulatory T cells (Treg) cells are important for the control of immune responses to self-antigens preventing autoimmunity and maintaining self-tolerance[6]. The final result of this activated cytokine network is the recruitment of more effector cells and the beginning of mucosal inflammation, which will eventually become chronic due to defective regulation of the immune response[6].

First, genome-wide association studies (GWAS) resulted in the identification of many novel susceptibility loci CD and later for UC[7,8]. To date, the number of known risk loci has expanded to 163[9]. Some loci seem to be specific either to CD or to UC, whereas others confer common susceptibility to IBD; approximately 30% of IBD-related genetic loci are shared[10,11]. The IBD-associated loci encode genes involved in innate pattern recognition {nucleotide-binding oligomerization domain-containing protein 2 (*NOD2*), autophagy (autophagy-related protein 16-1 (*ATG16L1*), immunity-related GTPase family M protein (*IRGM*), differentiation of Th17-T lymphocytes (*IL23R*), maintenance of epithelial barrier integrity IBD5 locus], and coordination of adaptive immune responses [human leukocyte antigen (HLA)-region]}[12]. Polymorphisms in genes encoding cytokines and cytokine receptors may affect the course of the inflammatory cascade and thereby increase the risk of developing IBD.

In this review we discuss in each of the IL families only those interleukins or interleukin receptors in detail, which have relevant polymorphisms in IBD, CD or UC (Figure 2).

SYSTEMATIC REVIEW

We conducted a systematic review of the literature of the last 10 years on interleukin susceptibility genes to IBD. PubMed was searched for papers and abstracts published in English-language journals. We used the following medical subject heading terms and/or text words: "inflammatory bowel disease", "ulcerative colitis", "Crohn's disease" and "cytokines". The search was focused on interleukin susceptibility genes polymorphism resulting in IBD. No restrictions were placed on race, ethnicity, or geographic area. Extraction from each study was conducted independently by all authors, and consensus was achieved for all data.

INTERLEUKIN AND INTERLEUKIN RECEPTOR GENE POLYMORPHISMS

ILs are the subset of a larger group of cellular messenger molecules called cytokines, which are humoral, small (4-15 kDa) inducible immune-regulatory proteins or glycoproteins which mediate communication between cells, regulate cell growth and differentiation, and play a central role in the development and homeostasis of the immune system[6]. They act on target cells by binding to specific IL receptors, initiating signal transduction and second messenger pathways within the target cell. This can result in gene activation, lead to mitotic division, growth and differentiation, migration, or apoptosis. Cytokines act in a highly complex coordinated network in which they induce or repress their own synthesis as well as that of other cytokines and cytokine receptors. The nomenclature of ILs is continuously evolving (www.genenames.org/genefamilies/IL); they are assigned to each family based on sequence homology and receptor chain similarities or functional properties (Table 1)[13].

IL1 FAMILY

The IL1 family is a group of 11 cytokines (IL1A, IL1B, IL1RN, IL18, IL33, IL36A, IL36B, IL36G, IL36RN, IL37 and IL38), which have similar gene structure and induce a complex network of proinflammatory cytokines. The interleukin 1 receptor (IL1R) family also expands to 9 distinct genes and includes coreceptors, decoy receptors, binding proteins, and inhibitory receptors[14].

IL1

IL1 is a potent proinflammatory cytokine, which affects cell proliferation, differentiation, and the function of many innate and specific immunocompetent cells, and acts as an endogenous pyrogen. It also mediates many inflammatory diseases by initiating and potentiating im-

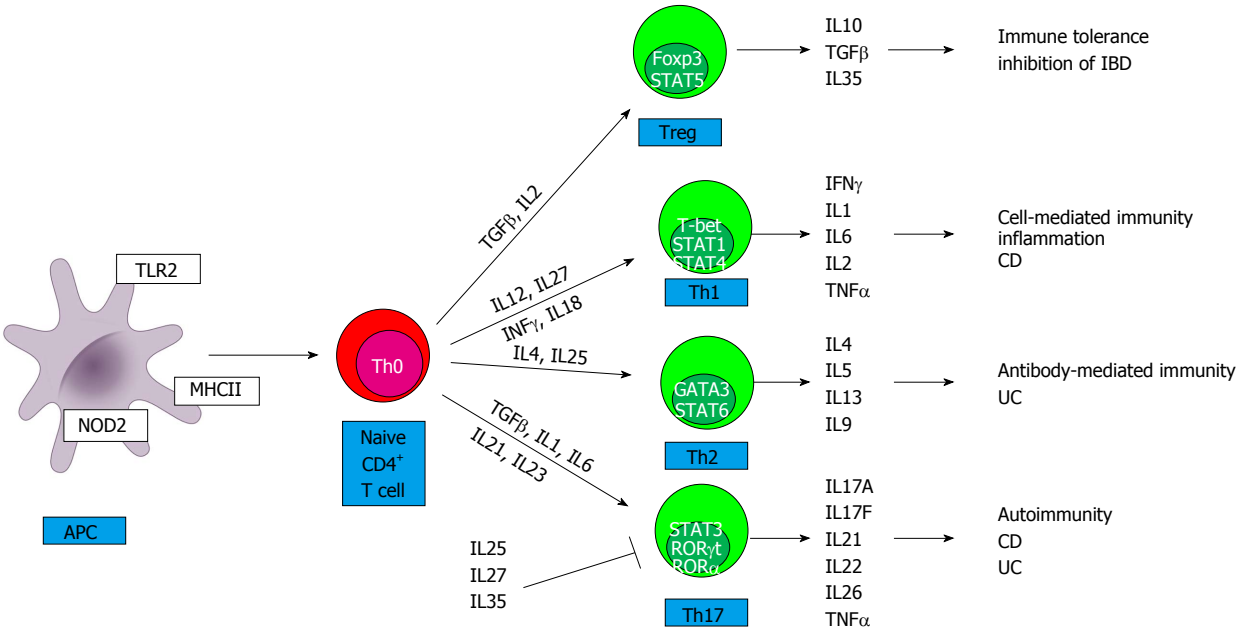

Figure 1 Differentiation of effector T helper and regulatory T cells in inflammatory bowel disease. Antigen presenting cells (APCs) (*i.e.*, macrophages and dendritic cells) in the lamina propria are increased in absolute number in both forms of inflammatory bowel disease (IBD). First, microbial products (pathogen associated molecular patterns, PAMPs) bind to a group of detection molecules of the innate immune system, called pattern recognition receptors (PRRs). This includes Toll like receptors (TLRs) on cell surface intracellular compartments, and the cytoplasmatic nucleotide-binding oligomerization domain-containing protein (NOD)-like receptors (NLR) family. Stimulation of these receptors induces intracellular signaling cascades, resulting in secretion of large number of cytokines, chemokines, and immunomodulatory factors. APCs interact with T cells by presenting an antigen on the surface of the major histocompatibility complex Ⅱ (MHCII), which is recognized by the appropriate T cell receptor. The development of T helper (Th)1, Th2, Th17 and regulatory T cells (Treg) subsets from naïve, Th0 cells during primary immune response is mainly determined by this cytokines and chemokines. It is under the control of certain transcription factors: T-box expressed in T cells (T-bet), GATA binding protein (GATA3), retinoid-related orphan receptor (RORγt), RORα, signal transducer and activator of transcription (STATs) and forkhead box P3 (FoxP3). Interleukin (IL)12 is the hallmark cytokine for Th1 cell lines, which produce interferon gamma (IFNγ) and are important for host defense to intracellular pathogens. IL4 promotes differentiation into Th2 cells, which produce IL4, IL5, and IL13 and participate in controlling humoral immunity to extracellular parasites and allergic inflammatory responses. Th17 cells develop from naïve T cells in the presence of transforming growth factor beta (TGFβ), IL23, IL1B or IL6. The effector cytokines IL17A, IL17F, and IL22 play key roles in Crohn's disease (CD) and ulcerative colitis (UC), and in other autoimmune diseases. TGFβ and IL2 together convert naive T cells into regulatory T cells, which promote self tolerance and prevent autoimmunity. CD is a predominantly Th1 and Th17-mediated disorder, while UC is associated with a Th17 and a modified Th2 cytokine profile.

mune and inflammatory responses[13].

IL1 is made up of two major proteins: IL1A (OMIM 147760) and IL1B (OMIM 147720)[15]. These proteins exert similar effects, first, by binding to the first extracellular chain of the IL1 type I receptor (IL1R I) (OMIM 147810) that recruits the IL1 receptor accessory protein (IL1RAP) (OMIM 602626), which serves as a coreceptor and is necessary for signal transduction. IL1A and IL1B are also able bind to the IL1 type Ⅱ receptor (OMIM 147811), which acts as a decoy receptor and is not involved in signal transduction[13].

IL1B has an important role in initiating and amplifying the inflammatory response[16]. Normal colonic mucosa cells produce very little mature IL1B, however in the mucosa of affected IBD patients, a large amount of mature IL1B is produced[17,18]. The inability of normal intestinal macrophages to produce mature IL1B could result from regulation at one or more steps from gene activation to post-translational processing of the propeptide by IL1B converting enzyme and release of the mature peptide[19,20].

The IL1 receptor antagonist (IL1RN) (OMIM 147679) is an anti-inflammatory cytokine, which is synthesized and released in response to the same stimuli that lead to IL1 production[21]. IL1RN lacks the IL1RAP interacting domain, so that binding of the IL1RN to IL1R I inhibits IL1 signaling[15]. In IBD and several other inflammatory diseases, an imbalance the IL1RN/IL1 ratio contributes to the chronic inflammatory response[22-24]. Polymorphisms of the *IL1RN* gene, which can lead to changes in the IL1RN and IL1 balance, are associated with susceptibility to UC[25]. Moreover, it is well accepted that IBD patients have a decreased ratio of IL1RN/IL1B in their colonic mucosal tissue[26].

The variant alleles of two IL1B promoter polymorphisms, IL1B T-31C and IL1B C-511T, have been found to be in almost complete linkage disequilibrium, and the haplotypes encompassing the IL1B T-31C variant conferred higher transcription of IL1B compared to the wild type haplotype[27].

Four polymorphisms (rs315951, rs315952, rs419598 and rs16944) in the *IL1B* and *IL1RN* genes were analyzed in Mexican Mestizo UC patients. The first 3 single nucleotide polymorphisms (SNPs) are located in the *IL1RN* and the fourth one in the *IL1B* gene. The first two (rs315951 and rs315952) are associated with the risk of developing UC. They found significant increased frequencies of IL1RN6/1TC (rs315952) and RN6/2CC

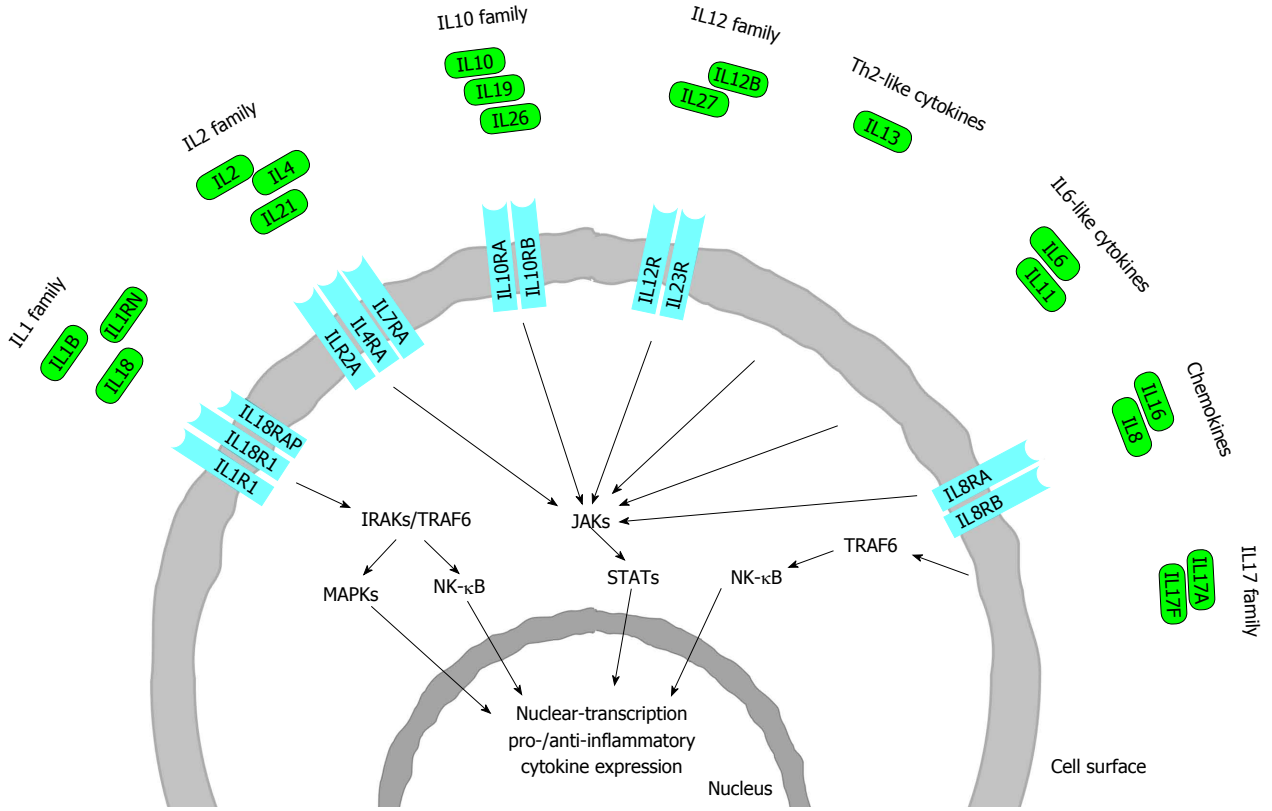

Figure 2 Schematic representation of the interleukin families and receptors involved in the pathogenesis of inflammatory bowel disease. Only those interleukins (IL) and IL receptors (ILR) are shown where studies have demonstrated association between genes/single nucleotide polymorphisms (SNPs) and disease phenotype. ILs are assigned to each family based on sequence homology and receptor chain similarities or functional properties, considerable overlap between these families exists. Polymorphisms in genes encoding ILs and ILRs have been found to be involved in inflammatory bowel disease. Ligand binding initiates intracellular phosphorylation cascades that are mediated by kinases (*i.e.*, IL1 receptor associated kinase (IRAK); mitogen-activated protein kinase (MAPK); Janus kinase (JAK) and TNF receptor associated factor (TRAF), resulting in signal transduction through certain transcription factors [including signal transducers and activators of transcription (STAT); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)]. These transcription factors stimulate the expression of a number of proinflammatory and anti-inflammatory cytokine genes involved in inflammatory bowel disease (IBD).

(rs315951), and decreased frequency of IL1B-511 TC (rs16944) genotypes in UC patients. UC patients showed increased frequencies of IL1RN CTC and TCG haplotypes, whereas TTG and CTG haplotypes showed decreased frequency in UC patients. They also found decreased gene expression of IL1RN level in the mucosa from UC patients carrying the rs315951 GG genotype when compared with UC patients with the rs315951 CC genotype[28].

IL18

One of the main function of IL18 (OMIM 600953) is to promote the production of IFNγ from T and natural killer (NK) cells, particularly in the presence of IL12p70. First it binds to its ligand binding chain the interleukin 18 receptor 1 (OMIM 604494), recruits its coreceptor the IL18 receptor accessory protein (IL18RAP) (OMIM 604509), and the activation of nuclear factor kappa-light-chain-enhancer of activated B cells/mitogen activated protein 8 is initiated. IL18 expression correlates with the activities of CD[29].

IL18 binding protein (IL18BP, OMIM 604113) is able to prevent the binding of IL18 to its receptor, and thereby blocks its downstream functional effects. IL18BP has neutralizing isoforms, which have increased levels in the intestinal tissue of active CD patients[30].

Several polymorphisms were studied in the *IL18* gene: the A105C, the T113G and the C127T in the coding region, and the G-137C, the C-607A and the G-656T in the promoter region. In the Japanese population significant difference was found in the allele frequency of A105C between CD patients and healthy controls. However, there was no association between A105C and UC[31]. In another Japanese study the G allele at 113 and the T allele at 127 were significantly higher in patients with IBD compared to the control[32]. In the third Japanese study allele and genotype frequency of G-137C were significantly higher in the proctitis-type UC patients than in controls[33]. The frequency of haplotype 2 (-607A, -137C), which have lower promoter activity and IFNγ- mRNA level was significantly increased in the proctitis-type patients than in the control group[33]. Any significant differences in allele or genotype frequencies were observed in the CD group[33]. The C-607A and the G-137C SNPs in the promoter region were associated with the development of UC but not with CD in Tunisian patients. The

Table 1 Characteristics of cytokines in inflammatory bowel diseases

Family	Cytokine	Receptor	Cytogenetic location	Molecular weight	Cell source	Disease association (IBD)
IL1	IL1A (IL1F1)	IL1R1 IL1R2	2q14	17 kD	Macrophages, monocytes, lymphocytes, keratinocytes,	CD, UC
	IL1B (IL1F2)	IL1R1 IL1R2	2q14	17 kD	microglia, megakaryocytes, neutrophils, fibroblasts and synovial lining cells	CD, UC
	IL1RN (IL1F3)	IL1R1 IL1R2	2q14.2	16.1-20 kD	Monocytes, macrophages, fibroblasts, neutrophils, epithelial cells and keratinocytes	UC
	IL18 (IL1F4)	IL18R1 IL18RAP	11q22.2-q22.3	22.3 kD	Macrophages, Kupffer cells, keratinocytes, osteoblasts, astrocytes, and DCs	CD, UC
IL2	IL2	IL2R	4q26-q27	15.5 kD	CD4+, CD8+ activated T cells, DCs, NK and NKT cells	CD, UC
	IL4	IL4R Ⅰ IL4R Ⅱ	5q23-q31	15 kD	Th2 cells, basophils, eosinophils, mast cells, NKT and γ/δ T cells	CD
	IL21	IL21R	4q26-q27	15 kD	T and NKT cells	CD, UC
IL10	IL10	IL10RA/IL10RB	1q31-q32	18.6 kD	T and B cells, monocytes, macrophages and DCs	CD, UC
	IL19	IL20RA/IL20RB	1q32.2	35-40 kD	Monocytes, keratinocytes, airway epithelial cells and B cells	UC
	IL26	IL10R2/IL20R1	12q15	38 kD	Activated T cells	CD, UC
IL12	IL12	IL12RB1/IL12RB2	5q33.3	IL12A: 35 kD, IL12B: 40 kD	Monocytes, macrophages, neutrophils, microglia, DCs and B cells	CD, UC
	IL23	IL12RB1/IL23R	12q13.13	19 kD	Macrophages and activated DCs	CD, UC
	IL27	IL27RA/ IL6ST	16p11	IL27A: 2 8 kD IL27B: 25.4 kD	Activated DCs, macrophages, and epithelial cells	CD, UC
IL6-like cytokines	IL6	IL6R/IL6ST	7p21-p15	19-26 kD	Endothelial cells, fibroblasts, monocytes/macrophages	CD
IL17	IL17A	IL17RA/ IL17RC	6p12	35 kD	Th17, CD8+ T cells, NK cells, NKT cells, γ/δ T cells and neutrophils	UC
	IL17F	IL17RA/IL17RC	6p12	44 kD	Th17, CD8+ T cells, NK cells, NKT cells, γ/δ T cells and neutrophils	CD, UC
Chemokines	IL8	IL8RA/IL8RB	4q13-q21	16 kD	Monocytes, macrophages, neutrophils, lymphocytes, endothelial cells, epithelial cells, fibroblasts, keratinocytes, chondrocytes, synovial cells, and hepatocytes	CD, UC
	IL16	CD4	15q26.3	56 kD	T cells, eosinophils, mast cells, eosinophils, monocytes, DCs, fibroblasts and epithelial cells	CD
Th2-like cytokines	IL13	IL13RA1/IL13RA2	5q31	10 kD	T, NKT, mast cells, basophils and eosinophils	CD, UC

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; NK: Natural killer cells; NKT: Natural killer T cells; DCs: Dendritic cells.

-137GG genotype frequency was significantly higher in UC than in controls. Statistically significant association was found between -607AA genotype in UC patients and the distal localization of the lesions[34]. However the polymorphism G-137C was not found a susceptibility factor for IBD in a German population[35].

Recent GWAS study[36] and meta-analysis confirmed the *IL18RAP* region as CD locus[8]. The rs6708413 G allele is a shared risk locus for CD and Celiac disease[37]. In individuals homozygous for the risk allele, the genotypes strongly correlate with lower IL18RAP expression which may lead to differential IL18-mediated innate immune responses to infection[38]. Strong association of rs917997 SNP was demonstrated for both CD and UC[39]. In a new GWAS study association of CD and IBD with coding variant V527L was found. This rare missense increased high the risk for CD[40].

IL2 FAMILY

The IL2 family consists of IL2, IL4, IL7, IL9, IL15 and IL21. This family of cytokines encompasses a group of interleukins which share a common receptor subunit, the "common γ chain", which acts in unison with a subtype specific α-chain to initiate the signaling cascade. This ILs act mainly as growth and proliferation factors for progenitors and mature cells and also have roles in lineage-specific cell differentiation[13].

IL2

IL2 acts as a T cell growth factor and promotes proliferation and differentiation of NK cells to increase their cy-

tolytic functions. IL2 is essential for the development of Th1, Th2, Treg, and Th17 differentiation[41].

The IL2 receptor (IL2R) consists of three non-covalently associated proteins: IL2RA (OMIM 147730), IL2RB (OMIM 146710) and IL2RG (OMIM 308380). The α-chain is produced when the T cell is activated by antigen and constitutes the high affinity receptor together with the other two subunits[42]. The β- and γ-chains form the intermediate affinity IL2 receptor[43].

Several SNPs (rs6822844, rs13151961, rs13119723 and rs6840978) in the *IL2/IL21* block were analyzed in different populations. In a Dutch cohort the minor alleles of these SNPs were associated with IBD. In UC patients the effect was even stronger. However in the CD subgroup, the rs13119723 SNP was only borderline significant, while only a trend towards association was found for the other SNPs. Testing of all four SNPs in the Italian cohort, the same strong association of the minor alleles in UC was found as in the Dutch cohort. The CD subgroup of the Italian cohort showed only a trend towards association with the same alleles. However in the Jewish population there was any significant association between any of the SNPs and CD. Similarly a North American study showed that these alleles have an influence on IBD. The effect was strongest in the UC subgroup likewise. In the CD subgroup of the North American cohort moderate association with the same alleles was also observed[44].

IL4

IL4 (OMIM 147780), a pleiotropic cytokine, is the major stimulus of Th2-cell development, which regulates allergic conditions and the protective immune response against helminthes and other extracellular parasites[45]. There are 2 types of IL4Rs. IL4R Type I binds only IL4 and consists of 2 receptor chains: IL4RA (OMIM 147781) and the common γc, IL4R Type Ⅱ binds IL4 and IL13 and consists of the IL4RA and the IL13RA1 chains[46].

Functional polymorphism in the *IL4* gene promoter C-34T was associated with CD in a British population[47]. The same polymorphism was tested in a New Zealand population, where no significant difference was observed in the genotype frequencies of controls *vs* CD patients[48].

IL21

IL21 (OMIM 605384) is a cytokine with potent regulatory effects on cells of the immune system, including NK cells and cytotoxic T cells, which can destroy virus infected and cancerous cells[49]. In contrast with its anti-cancer effects, IL21 also contributes to inflammation in several disorders, as can be expected for a Th17-related cytokine. The functional receptor of IL21 consists of γc and the IL21RA (OMIM 605383)[13].

GWAS provides evidence for 4q27 region IL2/IL21 association with UC[44] and CD[50]. This region contains four genes in strong linkage disequilibrium: *KIAA1109-TENR-IL2-IL21*.

IL10 FAMILY

The members of the IL10 cytokine family (IL10, IL19, IL20, IL22, IL24, IL26, IL28, and IL29) are mainly linked through their similar intron-exon structure. This family can be divided into viral and cellular homologs, where this last named group contains the above mentioned ILs[51].

IL10

IL10 (OMIM 124092) is an anti-inflammatory cytokine, which is produced by monocytes, T cells, B cells, NK cells, macrophages, and dendritic cells. It inhibits both antigen presentation and subsequent release of pro-inflammatory cytokines. Thereby attenuates the activated immune system. The *IL10* gene maps to a cytokine cluster that includes *IL19*, *IL20*, *IL24*, and *IL6* genes. Two IL10RA (OMIM 146933) and two IL10RB (OMIM 123889) chains forms the heterotetrameric IL10 receptor complex. The IL10RB chain is shared with other cytokine receptors[52].

In a GWAS the rs3024505 showed the most significant association in the combined verification UC samples. Association between rs3024505 and CD was weak. These results suggest that defective IL10 function is central to the pathogenesis of the UC subtype of IBD[53]. In a latest study from 29 SNPs conferring high genetic susceptibility to CD, the rs3024505 of the *IL10* gene was associated with susceptibility to UC in Australian population[54]. Similarly to this, the rs3024505 was associated with the risk of UC and CD in a Danish study[55].

The *IL10* promoter polymorphisms G-1082A, C-819T, and C-592A have been most extensively studied. They are in tight linkage disequilibrium[56]. Studies on the *IL10* promoter polymorphisms and IBD susceptibility have been controversial[57-60]. In Spanish population the G-1082A and the C-819T polymorphisms in the *IL10* gene contribute to susceptibility to CD[61].

In IBD patiens in Tunisia the polymorphisms A-627C and G-1117A were analyzed and found as potential factors influencing IBD susceptibility and phenotype. However, no significant variations in genotypes frequencies were found comparing the CD and UC patients[62].

The A-1082G variant was analyzed in Caucasian population in many studies. It was suggested that G carriers were more susceptible to UC[63], whereas in another study G carriers were associated with lower UC incidence[64]. Only two datasets concerning the relationship between A-1082G polymorphism and UC susceptibility in Asian subjects[65,66] were identified. A meta-analysis showed no association between -A1082G polymorphism and UC susceptibility under any genetic models in overall analysis or in subgroup analysis[67]. In an another study this variant was significantly associated with the colonic localization of the disease in Caucasian CD patients (children) with French-Canadian origin[68].

IL19

IL19 (OMIM 605687) might promote Th2-cell re-

sponses, because it induces expression of IL4, IL5, IL10, and IL13 by activated T-cells[69]. IL19 functions as a monomer, binds to a heterodimeric receptor made up of IL20RA (OMIM 605620) and IL20RB (OMIM 605621). This complex also binds to IL20 and IL24[70].

In GWAS, 14 previously identified UC susceptibility loci were analyzed. Association including the polymorphism rs3024505 in the *IL19* was confirmed[71].

IL26

Expression of IL26 (OMIM 605679) seems to be restricted to memory T cells, NK cells, and Th17 cells. Thereby it could have proinflammatory effects in CD[72]. The receptor for IL26 consists of IL10RB and IL20RA chains. Dambacher reported expression of both IL26 receptor subunits IL20RA and IL10RB by several intestinal epithelial cells (IEC) lines in CD[73].

First time, the rs2870946-G and the rs1558744-A association were described with UC[74]. Further meta-analysis study confirmed the association of rs1558744-A with UC[71].

IL12 FAMILY

The IL12 family of cytokines includes IL12, IL23, IL27, IL30 and IL35, which are important mediators of inflammatory diseases. Each member is heterodimeric complex composed of two subunits whose expression is regulated independently and have very different biological activities[75].

IL12

IL12 (also known as IL12p70) was first described as a NK stimulating factor. It mediates development and maintenance of Th1 cells by inducing production of IFNγ by Th1 and NK cells. IL12 indirectly activates the antimicrobial, antiparasitic, and antitumor activity of macrophages and promotes cytolytic activity of NK cells and lymphokine-activated killer cells[76]. Reduced production of IL12 impairs Th1 responses and increases susceptibility to infection with intracellular pathogens. IL12 consist of p35 (IL12A, OMIM 161560) and p40 (IL12B, OMIM 161561) subunits, which is shared by IL12 and IL23 cytokines. The IL12 receptor is composed of two subunits, IL12RB1 (OMIM 601604) and IL12RB2 (OMIM 601642), which is homologous to the gp130 subunit[77,78].

In a German population four *IL12B* SNPs (rs3212227, rs17860508, rs10045431 and rs6887695) were analyzed. The rs6887695 showed association with increased IBD susceptibility, and there was also trend for association with CD and UC. However just a trend was found for association of rs10045431 with UC. A haplotype of all four investigated SNPs showed a trend for association with CD[79].

From these SNPs the rs6887695 was investigated in Spanish and Japanese population, but with different results. An association was found with CD (rs6887695) and UC susceptibility (rs6887695) in the Japanese cohort, but not to CD susceptibility in the Spanish cohort[80,81]. Examining rs1363670 and rs6887695 SNPs in New Zealand population differential effect was found. Carrying the rs1363670 C variant increases risk for CD, while carrying the rs6887695 C variant decreases risk for CD[82].

In a British cohort an association was found at rs6556416, which encodes a subunit shared by IL12 and IL23. Thus, the Th17 pathway seems as relevant to UC and CD[83].

IL23

IL23 is a disulfide-linked heterodimer of the p40 (IL12B) and p19 (IL23A, OMIM 605580). IL23 interacts with a receptor composed of IL12RB1 and IL23R chain (IL23R, OMIM 607562)[78]. IL23 functions in innate and adaptive immunity to regulate Th17 function and expansion[84]. In addition, this cytokine induces $CD8^+$ memory T cells to proliferate and produce IL17. Dysregulation of the IL23/IL17 immune axis has been linked to immunopathology and autoimmune inflammation, like IBD. *IL23R* polymorphisms play role in many autoimmune diseases[85-87] especially in IBD[88]. Polymorphisms in the *IL23R* represent one of the strongest associations in CD, and they have also been linked to the pathogenesis of UC[89].

The *IL23R* gene was identified as a CD susceptibility gene in a North American population. Several independent functional SNPs of the gene and its neighboring region were determined, several were found susceptible to (rs10889677, rs11209032, rs11465804, rs11805303, rs1495965, rs2201841, rs1004819) and the others were protective (rs10489629, rs11209026, rs1343151, rs7517847) against IBD in non-Jewish subjects[89]. After the primary publication, numerous replication studies have been published these *IL23R* genetic polymorphisms in IBD.

From the susceptibility variants the rs1004819 and rs1495965 were found as important risk factors for CD in Koreans[90]. Similarly to these results the rs1004819 had the most significant association with CD in Germans, and the another rs10889677, rs2201841, rs11209032 showed increased genotype and allele frequencies comparing the CD cohort to the controls[91]. Positive association was described of *IL23R* rs10889677 and rs1004819 SNPs with CD in Brazilian population, where the allele frequencies of the patients' group differ significantly from the controls[92]. Another susceptibility factors were studied in Chinese cohort and the findings showed that rs7530511 and rs11805303 of *IL23R* gene showed positive association with UC susceptibility[93]. In Jiangsu Han population the rs11805303 was found as a susceptibility polymorphism with UC too[94].

The protective variants of the *IL23R* gene were analyzed in different populations. Association with rs11209026 and rs7517847 SNPs were confirmed in English subject, where the most significant SNP was the rs7517847[95]. Similarly in Spanish population the rs7517847 and the rs11209026 showed association with IBD too, the rs7517847 showed the most protective effect against CD and UC[80,96]. In another study the rs11209026 coding variant was found as a strong protection against CD in German pediatric CD patients[97].

Five polymorphisms were analyzed in Hungarian IBD population (rs1884444, rs11805303, rs7517847, rs2201841, rs10889677 and rs11209032)[98]. The rs2201841 and rs10889677 homozygous variants confer risk for the disease, while rs7517847 GG genotype has a protective effect against the development of CD. In Hungarian CD population two *IL23R* gene risk variants the rs2201841 and rs1004819 were found to be a susceptibility factor for CD[99]. In another study with Hungarian CD patients increased prevalence of the homozygous rs10889677 AA and homozygous rs2201841 CC genotypes were found. The rs10889677 AA genotype was significantly increased in CD patients. The logistic regression analysis showed the AA genotype represents an independent risk factor for the development of CD[100].

IL27

IL27 is a heterodimeric cytokine consisting of Epstein-Barr virus-induced gene 3 (EBI3, OMIM 605816) and p28 (also known as IL30, OMIM 608273). It binds a unique receptor subunit IL27RA (OMIM 605350), which is associated with gp130 (IL6ST, OMIM 600694), a common chain utilized by IL6 family cytokines. IL27 suppresses Th2 and Th17 differentiation and proliferation[101,102].

In a Korean population the -A965G SNP was described as a susceptibility factor for IBD[103]. In a GWAS five new regions were identified near the *IL27* gene associated with early-onset IBD susceptibility (rs8049439, rs2412973, rs1250550, rs4676410 and rs10500264)[104].

IL6-LIKE CYTOKINES

Cytokines in this family (IL6, IL11, IL27 and IL31) signal through receptors containing gp130 which are commonly referred to as the IL6-like or gp130 utilizing cytokines family[105]. They show pleiotropic biological activities with immune, hematopoietic, and neural systems[105].

IL6

IL6 (OMIM 147620) is a multifunctional, pleiotropic cytokine involved in regulation of immune responses, acute-phase responses, hematopoiesis, and inflammation. IL6 signals through a cell-surface type I cytokine receptor complex consisting of the ligand-binding IL6R chain (OMIM 147880), and the shared signal-transducing component IL6ST (also called gp130; OMIM 600694)[106].

English and Swedish children with CD and *IL6*-174 GG genotype were more growth retarded at diagnosis and had higher levels of the IL6-induced inflammatory marker C-reactive protein (CRP) than children with GC or CC genotypes, concluded that *IL6*-174 genotype mediates growth failure in CD[107]. In an Irish cohort from Dublin, significant difference was found in the frequency of *IL6*-174 genotypes in the UC group compared with the CD group[57]. In a Caucasian population from Canada the same polymorphism was analyzed in CD and UC patients. There were significant difference IBD, UC and CD susceptibility, but it has influence on the clinical phenotype of CD[108]. In a Spanish population[109] homozygous for the IL6 G-174C polymorphism showed six-fold higher risk for CD. The GG genotype is associated with a greater production of IL6 compared with GC or CC genotypes[110].

IL17 FAMILY

This cytokine family is a recently discovered group of cytokines with six members (IL17A, IL17B, IL17C, IL17D, IL17E and IL17F). IL17A was the original member of this family. The others were discovered primarily from the genome sequences within a short time-period (2000-2002), and were sequentially named in the order of discovery[111-114]. They share the highest amino acid sequence homology and perform distinct biological functions[115].

IL17

IL17A (OMIM 603149) acts on a variety of cells, which respond by upregulating expression of proinflammatory cytokines, chemokines, and metalloproteases. It is involved in the development of autoimmunity, inflammation, and tumors. IL17E (IL25, OMIM 605658) is an amplifier of Th2 immune responses. IL17F (OMIM 606496) is mainly involved in mucosal host defense mechanisms. The functions of IL17B (OMIM 604627), IL17C (OMIM 604628), and IL17D (OMIM 607587) are still largely elusive. Increased levels of IL17A[116] and IL17F[117] have been found in patients with IBD. It inhibits the proliferation of IECs, suggesting it might interfere with the repair mechanism important for the maintenance of the tissue integrity[118].

The IL17 receptor (IL17R) family includes five members: IL17RA (OMIM 605461), IL17RB (OMIM 605458), IL17RC (OMIM 610925), IL17RD (OMIM 606807), and IL17RE (OMIM 614995)[119].

In a Japanese UC patients the rs2275913 polymorphism in the *IL17A* gene and the rs763780 in the *IL17F* gene were analyzed. The frequencies of -197A/A and 7488T/T genotypes were found significantly higher in UC patients than in controls[120]. In a Caucasian (German) population, despite the increased colonic IL17F expression in CD, any significant differences could be found in the frequency of rs763780 on IBD susceptibility[117].

INTERLEUKINS WITH CHEMOKINE ACTIVITY

This group contains only two ILs, the IL8 and IL16[13].

IL8

IL8 was identified first as a neutrophil-specific chemotactic factor and later classified as a member of the CXC chemokine family[121]. Its receptors are: CXCR1 (IL8RA) and CXCR2 (IL8RB)[122]. IL8 plays crucial role in the chemotaxis and migration of neutrophils, monocytes, lymphocytes, and fibroblasts[123].

In a Polish population significant association was

found between the genotype frequencies for the heterozygote of the *IL8* T-251A and IBD. When IBD patients were subdivided in UC and CD subgroups this association was also observed. Significant difference was found between the A allele and the UC and CD cases, but not in the summarized IBD group[124]. In a Chinese population any association was found between the T-251A polymorphism and UC[125]. They also investigated the role of other polymorphisms of the *IL8* gene and its impact on the level of IL8 in serum. The frequency of the -353A/-251A/+678T haplotype was significantly higher in UC patients than in healthy controls. This haplotype tends to be more common in severe UC patients than in mild to-moderate cases[125].

IL16

IL16 (OMIM 603035) is a proinflammatory cytokine, which inhibits T-cell proliferation, promotes Th1-mediated responses, and reduces Th2-mediated inflammation[126]. IL16 mediates its biological activity *via* CD4 molecule, which is present on T cells, monocytes, macrophages, and dendritic cells. Patients with CD have elevated levels of IL16[127].

Regardless of the disease phenotype or the site of intestinal involvement, the T allele and the TT genotype in the *IL16* promoter region T-295C were found significantly increased in German CD cohort, but not in UC patients[128].

TH2-LIKE CYTOKINES

Cytokines produced during the induction and function of Th2 response include IL4, IL5, IL9, IL13, IL25 (IL17E), IL31, and IL33[13].

IL13

IL13's (OMIM 147683) receptors are IL13RA1 (OMIM 300119) and IL13RA2 (OMIM 300130), signaling occurs *via* the IL4R complex type Ⅱ, which consists of IL4RA and IL13RA1. IL13RA2 acts as a decoy receptor of IL13. IL13 activates the same signal transduction pathways as IL4 and induces IgE production, influences eosinophils and cause their prolonged survival, activation, and migration to inflammatory lesions[129]. IL13 plays an opposite role to IL8. In monocytes and macrophages, it inhibits the secretion of pro-inflammatory mediators such as prostaglandins, reactive oxygen species (ROS) and nitrogen species, TNFα, IL1, -6, -8, and -12[130].

Presence of the *IL13* -1112 CT (rs1800925) genotypes in a Polish population showed higher risk of IBD as well as UC occurrence. The statistically significant differences in the T-allele distribution were observed in all the investigated groups[124].

CONCLUSION

In this review we discuss IL and IL gene polymorphisms which contribute to IBD, CD or UC in different ethnical population. The cytokine network is highly complex with interactive cascades of gene activation and suppression. Not only the *IL* and *ILR* gene polymorphisms are in relation with IBD pathogenesis but also the downstream signaling components of several ILs (*i.e.*, JAKs, STATs) which could be potential targets of novel treatment strategies. Many IBD loci are also implicated in other immune-mediated disorders, most notably with ankylosing spondylitis and psoriasis[9]. Since the individual associations may be non-informative, specific combinations of cytokine genotypes might predispose to disease susceptibility or outcome. Therefore, polymorphisms in cytokine genes and receptors should not in all cases be studied strictly in isolation. More complete understanding of the immunopathogenic role of the various ILs in intestinal inflammation will help in the development of more effective novel therapeutic strategies in IBD. Albeit genotyping these interleukin variants are often offer on the palette of several direct-to-costumer companies, their diagnostic or therapeutic clinical use is very limited due to the limited clinical utility and validity of them. Meanwhile, the next generation techniques in combination with the data analysis by systems-biology approach hopefully will contribute to the personalized therapy of the patients in the near future.

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