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REVIEW

Genetic update on inflammatory factors in ulcerative colitis: Review of the current literature

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Abstract

Ulcerative colitis (UC) is one of the main types of inflammatory bowel disease, which is caused by dysregulated immune responses in genetically predisposed individuals. Several genetic factors, including interleukin and interleukin receptor gene polymorphisms and other inflammation-related genes play central role in mediating and modulating the inflammation in the human body, thereby these can be the main cause of development of the disease. It is clear these data are very important for understanding the base of the disease, especially in terms of clinical utility and validity, but summarized literature is exiguous for challenge health specialist that can used in the clinical practice nowadays. This review summarizes the current literature on inflammation-related genetic polymorphisms which are associated with UC. We performed an electronic search of Pubmed Database among publications of the last 10 years, using the following medical subject heading terms: UC, ulcerative colitis, inflammation, genes, polymorphisms, and susceptibility.

Key words: Ulcerative colitis; Inflammatory factors; Genes; Polymorphisms; Susceptibility

Core tip: Ulcerative colitis (UC) is a disorder of the idiopathic and chronic inflammation of the colonic mucosa. Several genetics factors influence the development of the disease, especially interleukin and interleukin receptor gene polymorphisms and other inflammation-related genes. In this review we collected the current literature on PubMed Database about those genetic markers that are associated with UC, we focused on the following terminology: UC, inflammation, genes, polymorphisms, susceptibility.

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INTRODUCTION

Ulcerative colitis (UC; MIM 191390) and Crohn's disease (CD; MIM 26600) are the two main, related forms of inflammatory bowel disease (IBD) which are chronic, relapsing inflammatory disorders of the gastrointestinal tract[1]. The highest annual incidence rate of UC was re-

ported in Europe (24.3/100000) and in North America (19.2/100000). However, in Asia and in the Middle East the rate is much lower (6.3/100000) believed to be associated with the different level of industrialization[2]. UC has a bimodal pattern of incidence, with the mean age diagnosis between ages 15 and 30 years, and a second smaller peak between ages 50 and 70 years[3]. Clinically, UC is characterized by superficial, continuous mucosal inflammation and ulcers restricted to the colon, whereas CD is a segmental, transmural disorder involving any part of the gastrointestinal tract[4].

Although the precise etiology of IBD still remains obscure, the accepted hypothesis is that in genetically susceptible 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)[5].

At first, observational family studies and twin studies directed the interest to genetic components in the pathogenesis of IBD[6, 7]. Recently, genome-wide association studies (GWAS) have resulted in the identification of many novel single nucleotide polymorphisms (SNPs) for CD initially and latterly for UC which is thought to be more genetically heterogeneous than CD. To date, the number of known risk loci has expanded to 163, of which 110 confer common susceptibility to IBD, whereas 30 seem to be specific to CD and 23 to UC[8].

Immunologically, CD is associated with a T helper type 1 (Th1)[9] and T helper type 17 (Th17)[10] immune response, thus interferon gamma/interleukin-12 (IFNγ/IL-12) and interleukin-23/interleukin-17 (IL-23/IL-17) cytokines assign the downstream release of complex network of further pro-inflammatory cytokines (*e.g.,* IL-18, IL-2, IL-1, IL-21, IL-22, IL-17A, IL-17F, IL-26). However, UC is thought to be the result of a Th17 (IL-17) and a modified Th2 response (IL-13, IL-5 and IL-9). In addition, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) are produced by both T helper type 2 (Th2) cells and Th1 cells.

The IBD-associated loci encode for genes involved in maintenance of epithelial barrier integrity, antigen pattern recognition, autophagy, innate immunological response, coordination of adaptive immune responses and leukocyte recruitment (Figure 1).

Most of the difference at molecular level between UC and CD is found in human leukocyte antigen (*HLA)* Class Ⅱ genes and in genes related to pattern recognition [*e.g.,* nucleotide-binding oligomerization domains *(NODs), toll-like receptors (TLRs)*], innate immunity (*e.g., IL-23R*) or autophagy pathways (*e.g., ATG16L1, IRGM*). The *HLA* class Ⅱ genes *DR2*, *DR9*, and *DRB1*0103* were identified as susceptibility genes for UC, whereas *DR4* was a protective gene[11,12]. *HLA* haplotype *DRB1*0103* is significantly associated with disease susceptibility, extensive disease, and an increased risk of colectomy[13]. While several genes involved in bacterial sensing [nucleotide-binding oligomerization domain 2/caspase activation recruitment domain 15 (*NOD2/CARD15*)] and processing mechanisms (autophagy related genes *ATG16L1* and *IRGM*) are defective only in CD, the Th17/IL-23 axis related cytokines [*e.g.,* IL-23R, IL-12B and their downstream components signal transducer and activator of transcription 3 (STAT3), janus kinase 2 (JAK2)] have been associated with both CD and UC.

Dysfunction of the barrier integrity, enhanced permeability is also a main feature in UC. Recently, in a large review epithelial barrier genes were discussed in detail, namely, extracellular matrix protein 1 (*ECM1*), cadherin type 1 (*CDH1*), hepatocyte nuclear factor 4, alpha (*HNF4α*), and laminin beta 1 (*LAMB1*).

These genes were found not to be associated with CD, implying they may confer susceptibility specifically to UC[14]. Interestingly, the *CDH1* locus represents the first genetic association also identified in a GWAS for colorectal cancer susceptibility[15, 16].

In our review we focus on inflammation-related genes and polymorphisms including interleukin and interleukin receptor gene polymorphisms which are involved in the pathogenesis of UC.

INFLAMMATION-RELATED GENETIC FACTORS

Cytotoxic T-lymphocyte antigen 4

Cytotoxic T-lymphocyte antigen 4 (CTLA4) is an inhibitory receptor expressed by activated T cells. It is an important downregulator of the T cell activation and might contribute to peripheral tolerance. CTLA4 is a good candidate gene for susceptibility to UC, because it acts as a negative regulator of T cell activation and T/B, T/monocyte-macrophage cognate interaction. The localization of *CTLA4* gene is on chromosome 2q33. Several genetic polymorphisms have been reported in the human *CTLA4* gene[17, 18].

In a Tunisian population study, where A+49G was analyzed comparing the UC patients with the control subjects, the frequencies of the +49A allele and the homozygous +49 A/A genotype were higher in UC patients than in controls, but those differences were not statistically significant[17].

In a Dutch Caucasian and in a Han Chinese UC cohort studies the C-318T and A+49G polymorphisms of *CTLA4* gene were examined. No significant differences were observed in distribution of allele, genotype and haplotype frequencies between UC and control group[19].

A Hungarian cohort was examined for the same polymorphisms and no association was found between heterozygous AG genotype, homozygous GG variant, and G allele frequency of the *CTLA4* gene A+49G polymorphisms comparing the UC (IBD) group to the healthy controls. The A+49G does not represent an obligatory susceptibility factor for UC[20].

The A-1661G and the T-1722C two other SNPs in the non-exonic region were investigated in the Han

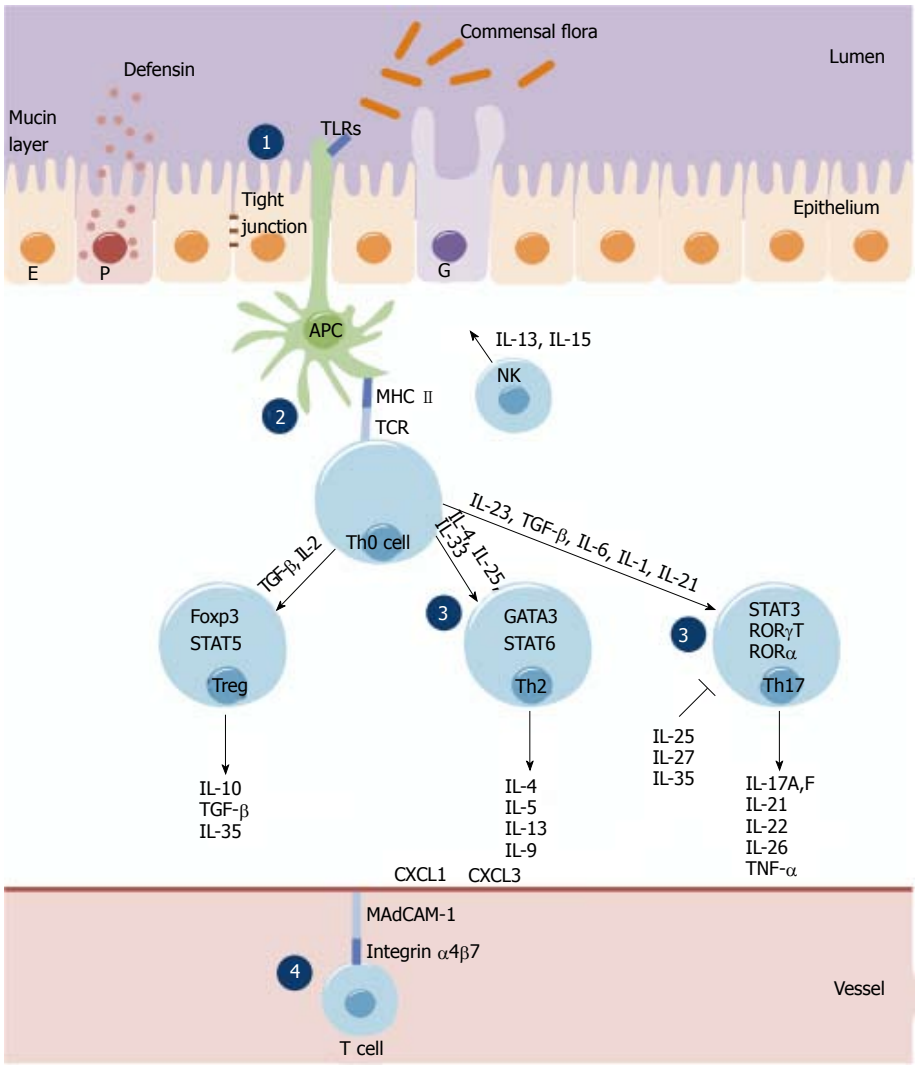

Figure 1 The Ulcerative colitis-associated risk loci. Damage of the epithelial barrier (E), the mucinous biofilm layer secreted from goblet cells (G), the antibacterial peptides (*e.g.*, defensines) produced by Paneth cells (P) and the tight junctions leads to increased permeability in ulcerative colitis (UC). Antigen presenting cells (APCs) (*i.e.*, macrophages and dendritic cells) in the lamina propria are increased in absolute number in UC, they bind microbial products through detection molecules of the innate immune system, including Toll like receptors (TLRs) on the cell surface and on the cytoplasmatic NOD-like receptors (NLRs). Stimulation of these receptors induces intracellular signaling cascades, resulting in secretion of large number of cytokines, chemokines, and immunomodulatory factors. The development of the Th2, Th17 and Treg subsets from naïve, Th0 cells during primary immune response is mainly determined by cytokines and chemokines, and is under the control of certain transcription factors: T-bet (T-box expressed in T cells), GATA3 (GATA binding protein), RORγt (retinoid-related orphan receptor γt), RORα, STATs (signal transducer and activator of transcription) and FoxP3 (forkhead box P3). Leukocyte migration and recruitment from vessels is mediated by selectins, integrins, ICAMs and chemokines (*i.e.*, c-c motif chemokine ligand, CXCL). The UC-associated loci encode genes involved in: (1) maintenance of epithelial barrier integrity (*e.g.*, ECM1, CDH1, HNF4A, LAMB1, PTGER4, SLC22A4/SLC22A5, MYO9B, MDR1); (2) antigen pattern recognition (*e.g.*, NLRs, TLRs); (3) innate and adaptive immunological responses (*e.g.*, IL-23R, IL-12B, TNFα, IL10R, JAK2, STAT3, HLA-region); and (4) leukocyte recruitment (integrin α4β7, ICAM-1, MAdCAM-1, CXCLs, CCRs).

Chinese population. The frequency of A/G + G/G genotype at position -1661 was statistically higher in UC patients than in healthy controls. The G allele frequency was also significantly increased in UC patients than in the controls. The A-1661G polymorphism of the *CTLA4* is a risk factor for UC in Han Chinese of central China. They found no association between T-1722C polymorphism and UC[18].

Janus kinase 2

Janus kinase 2 (JAK2) is a member of a family of tyrosine kinases involved in a specific subset of cytokine receptor signaling pathways. JAK2 has been found to be constitutively associated with the prolactin receptor and required for responses to gamma interferon[21-23].

In GWAS studies several UC loci were identified. The rs10758669 and the rs10974944 SNPs in the *JAK2* locus were found to be strongly associated with UC in the population from the United Kingdom[14] and Netherlands[24].

In a Korean population two SNPs (rs10758669 and rs10975003) were investigated. The rs10758669 showed no significant differences in genotype and allele distribution between UC patients and controls, while it was significant on level of genotype and allele frequencies in case of rs10975003. The rs10975003 SNP plays role in

the pathogenesis of UC in Koreans[25].

Signal transducer and activator of transcription 3

This protein is a member of the signal transducer and activator of transcription (STAT) protein family. It is encoded by the signal transducer and activator of transcription 3 (*STAT3*) gene. In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor associated kinases, and then form homo- or heterodimers that translocate to the cell nucleus where they act as transcription activators. This protein is activated by phosphorylation in response to various cytokines and growth factors including interferons (IFNs), epidermal growth factor (EGF), interleukin-5 (IL-5), IL-6, hepatocyte growth factor (HGF), leukemia inhibitory factor (LIF) and bone morphogenetic protein 2 (BMP2). STAT3 relays the expression of a variety of genes in response to cell stimuli, and thus plays pivotal role in several cellular processes, such as cell growth and apoptosis[26-28].

In a large GWAS study the rs12948909 SNPs in the *STAT3* locus was identified and found to be strongly associated with UC in the United Kingdom population[14].

In the Hungarian population the *STAT3* rs744166 was investigated. *STAT3* rs744166 TT genotype and T allele frequencies were significantly higher in patients with UC than in controls. Logistic regression analysis revealed that the TT genotype confers as an increased risk for the development of UC[23].

In a North American study the same polymorphisms were tested, but no significant differences were found between the UC group and healthy controls[29].

Tumor necrosis factor alpha

The pro-inflammatory cytokine, tumor necrosis factor alpha (TNFα) has important pathogenic role both in CD and in UC[30,31]. Through its ability to cause epithelial barrier disruption in colonic epithelial cells[32,33] it is responsible for tissue damage. The *TNFα* gene can be found at the inflammatory bowel disease 3 *(IBD3)* locus within the major histocompatibility complex (MHC) region. In several studies it has been found as a susceptibility locus for IBD[34-36]. Level of TNFα is elevated in serum, stools, and inflamed bowel mucosa of patients with IBD[37-41].

The polymorphism at position -308 is a point mutation, where the presence of G defines the common variant *TNF1*, and A the less common variant *TNF2*. Susceptibility to UC has been positively[42] and negatively[43] associated with carriage of *TNF2* allele. Some studies suggested that this allele might have a small but significant association with greater levels of TNF transcription[44, 45]. However other authors did not find any influence of *TNFα* bi-allelic polymorphism on UC susceptibility, although they reported a higher frequency of the *TNF2* allele in women with extensive disease compared with those with distal colitis[46]. In Mexican Mestizo UC patients increased frequency of *TNF2* allele and *TNF* 1/2 genotype was found, suggesting this could be an additional genetic marker for the susceptibility to UC[47]. Similar findings have been reported in patients with UC with Caucasian origin[42, 46, 48, 49].

The *TNFα* polymorphisms A-308G and T-857C increase the TNFα production, raising the possibility of correlation with different disease course or response to therapy[50]. The A-238G and A-308G in *TNFα* promoter region have been found as a susceptibility factor in different autoimmune disorders, including asthma[51,52], psoriasis[53] and rheumatoid arthritis[54]. The polymorphism A-238G was associated with lower production of TNFα in Caucasian UC patients[46].

In a New Zealand Caucasian UC cohort was found, that carriers of the *TNFα* -308A allele may give higher risk for pancolitis and the necessity for bowel resection[55]. In Israeli Jewish patients having CD or UC, the allele and carrier frequencies of -857T allele did not differ between IBD patients and controls, suggesting this SNP in Ashkenazi Jewish patients neither determines the susceptibility, nor influences the clinical phenotype of CD or UC[56].

Different studies supported that *TNFa* -308 in UC may be an ethnic population-specific risk factor. Studies from East Asia suggested strong association of the *TNFα* -308 gene promoter polymorphism for UC in East Asians. Allele frequency of *TNFα* -308A was significantly higher in Han Chinese UC patients than in healthy controls. Haplotype analysis revealed 6 haplotypes including H5 (*TNF* 1031T/863C/857C/380G/308A/238G/) and H3 (*TNF* 1031C/863C/857C/380G/308A/238G/). Haplotype frequency of H5 was significantly higher in UC patients, suggesting that H5 is associated with UC and the *TNFα* gene may be a susceptibility gene to UC[57]. Interestingly, the meta-analysis did not reveal any association of the *TNFα* -308 gene promoter polymorphism with UC in Europeans[58]. In a Caucasoid population from the North of Spain the *TNFα*-308 alleles did not influence the appearance of steroid dependency either in UC or in CD[59]. In Italian pediatric patients the *TNFα* -308 was significantly increased in patients with UC[60].

In Czech pediatric IBD patients significant differences in TNFα -308 A polymorphism were found between UC group and controls, but no differences were noted between this polymorphism and the clinical characteristics of UC[61].

Significant correlation of the *TNFα* -863A variant was demonstrated with colonic disease and greater height at diagnosis[62], but in this study they could not find any significant difference for the -857 allele. In patients with UC only a trend toward an increased frequency of steroid resistance was found in carriers of the *TNFα* risk genotype compared to non-carriers[60].

In the Han Chinese population the *TNFα* C-1031T, A-863C and T-857C allele/carrier frequencies were analyzed between UC patients and healthy controls. They did not find any significant difference of the tested al-

lele/carrier frequencies between UC patients and controls, only the *TNFα* -857T was increased in UC patients but did not reach statistical significance[57].

Organic cation transporter 1/2

OCTN1 *(SLC22A4)* and OCTN2 (*SLC22A5)* are widely expressed [63-66], but specifically expressed in principal intestinal cell types affected by CD: epithelial cells, CD68+ macrophages and CD43+ T cells. *SLC22A4* and *SLC22A5* encode the polytopic transmembrane sodium-dependent carnitine and sodium-independent organic cation transporters OCTN1 and OCTN2[67]. OCTNs have important role in the maintenance of intracellular homeostasis and in the energy production of the cell [68]. Both OCTNs play important role in the maintenance of gastrointestinal health and in the prevention of gut inflammation[69, 70].

CD associated variants, the *OCTN1* T1672C and *OCTN2* -207G were as strongly associated with UC in unrelated Caucasian subjects[71].

Homozygous patients for the *OCTN1* 1672T variant were significantly associated with UC in a study cohort from Italy, suggesting that OCTN1 could have a role in modulating the severity of chronic inflammation in UC[72].

The mutation that leads to L503F substitution in the OCTN1 protein can alter the transporter's activity[73, 74]. Only a weak gender-specific effect of L503F was observed at male UC patients in a cohort of familial and sporadic IBD from the central Pennsylvania, United States[75].

Multidrug-resistant transporter-1

The multidrug-resistant transporter-1 (*MDR1*) gene encodes the transmembrane protein, P-glycoprotein 170 (Pgp)[76]. This gene is an excellent candidate gene for the pathogenesis of IBD[77]. Pgp functions as an ATP-dependent efflux transporter pump and is expressed in many normal tissues like in the epithelial surfaces of the intestine, biliary ductules, proximal tubules of kidneys and central nervous system[78-80].

One of the most significant *MDR1* gene mutations is the C3435T polymorphism. Decreased expression of the *MDR1* gene and lower Pgp activity has been associated with this variant. However, studies showed conflicting results. In a German study the T allele and TT genotype frequencies of C3435T polymorphism were significantly increased in UC patients[81]. Glas *et al*[82] found in a small group of UC patients partial accordance with a trend towards an increased frequency of T allele compared to controls, but a statistical difference was detected only in one of two different control groups. In a meta-analysis significant association of the 3435T allele and the 3435TT genotype has been found with UC[83]. The triallelic G2677T/A and the C3435T have been shown to correlate with Pgp expression[84-87]. Significant association of C3435T and G2677T was detected with UC: UC patients had significantly higher frequency of 2677T allele and of the 3435TT genotype. Haplotype analysis revealed that carriers of 3435T/2677T haplotype have significantly higher risk of having UC[88]. In a Japanese UC cohort the C3435T was predictive of susceptibility to later onset UC, but not for the early onset of UC[89].

Large study with German and British UC and CD patients failed to demonstrate association. It was confirmed, that this SNP is associated with UC especially in patients with extensive colitis[90]. In addition completely negative findings have been reported in large studies from North America[7], Slovenia[91] and Italy[92]. Similarly to these results, UC patients with Caucasian origin from central Poland were found that *MDR1* C3435T polymorphism is not a risk factor for IBD, including both UC and CD[93].

A study with New Zealand IBD patients supported the role of *MDR1* as a candidate gene for UC. Heterozygous carriers for the variants C1236T, rs2235046 and G2677T/A showed a lower risk of developing UC compared with homozygotes. Subgroup analysis revealed that C1236T and rs3789243 are associated with IBD when stratified for age of onset. The *MDR1* variant rs3789243 was found to be associated with pancolitis in UC patients[94]. In the genetically heterogeneous North Indian UC cohort was found that this SNP is significantly overrepresented in UC patients.

When German IBD patients were genotyped for the two *MDR1* SNPs in positions 2677G>T/A and 3435C>T it was found that the combined genotypes derived from these positions are possibly associated with young age onset of UC and severe course of disease[95]. The 2677T allele was significantly increased in British UC cases compared with controls. The TT genotype was significantly associated with severe UC. No significant association was seen with C3435T and UC or any clinical subgroup. A meta-analysis of 9 association studies of C3435T showed a significant association of the 3435T allele with UC, but not with CD. These results indicated that *MDR1* sequence variants are associated with a small increase in the risk of developing UC and may influence disease behavior[96]. The *MDR1* gene polymorphism G2677T/A showed significant association with CD, and the C3435T with Spanish UC patients[97]. The *MDR1* 3435 TT genotype and T-allelic frequencies were significantly higher in patients with UC compared with controls. The association was strongest with extensive UC, and this was also confirmed with multivariate analysis. However G2677T was not associated with UC or CD. Two-locus haplotypes showed both positive (3435T/G2677 haplotype) and negative (C3435/2677T haplotype) associations with UC. Homozygotes for the haplotype 3435T/G2677 were significantly increased in UC. Allelic variations of the *MDR1* gene determined the disease extent as well as susceptibility to UC in the Scottish population[90].

Nucleotide-binding oligomerization domain1/ caspase activation recruitment domain 4

Nucleotide-binding oligomerization domain1/ caspase

activation recruitment domain 4 *(NOD1/CARD4)* is a member of the Nod-like receptor family, which is phylogenetically conserved[5, 98]. It is constitutively expressed in epithelial cells throughout the gastrointestinal tract[99]. *NOD1/CARD4* contains leucine-rich repeat (LRR) domain and NOD domains and has only one CARD domain[100].

Polymorphism in LRR domain of the *NOD1/CARD4* gene showed association with disease severity of UC in North Indian patients. This might be due to disruption of the LRR region critical for NOD1-mediated bacterial sensing. Haplotype-based approach showed that GTTG haplotype carriers were over represented in UC patients which could increase the risk of the disease[101].

Initially, it was suggested that there is association of the deletion variant of *NOD1/CARD4* +32656 (complex intronic insertion-deletion polymorphism) with susceptibility to IBD using a combination of transmission disequilibrium testing (TDT) and case-control analysis[102]. However this variant was not associated with a strong effect on susceptibility to IBD in children and adults in a Northern Europe study cohort[103]. Similar results have been found in the East Anglia IBD cohort, where no association was found between *NOD1* +32656 and IBD and also no heterogeneity between UC and CD[104].

Toll-like receptors

Essential components of innate immunity are the Toll-like receptors (TLRs). These are transmembrane receptors which recognize the microbial compounds from different bacteria, fungi and viruses[105-107]. TLRs are expressed by intestinal epithelial cells and immune cells in IBD patients[108,109]. TLR signaling in the intestinal sites of the colon can inhibit the inflammatory responses and maintains the colonic homeostasis[110-112]. TLRs can be found on the cell membrane (TLR1, 2, 4, 5 and 9) or on intracellular organelles (TLR3, 7 and 8)[113]. From the 10 human TLRs we review only three members regarding to their association to UC.

TLR2 is localized on the cell's surface. With its cofactors (TLR1 and TLR6) it binds lipoproteins, which are important surface antigen of the Gram-negative outer membrane[114], TLR4 consists of a leucine-rich repeat region (LRR) and an intracellular domain homologous to IL-1 receptor[115]. It recognizes conserved pathogenic motifs of Gram-negative bacteria, mainly lipopolysaccharides (LPS). Signaling through TLR4 results in the activation of the transcriptional activator, known as nuclear factor κB (NF-κB)[116]. Similarly to TLR2, TLR9 is localized on the cell's surface. It recognizes unmethylated CpG DNA in bacteria and viruses[117,118].

The allele and carrier frequencies of the Thr399Ile mutation in the *TLR4* gene were significantly associated with UC in a Caucasian population[119]. Association of *TLR4* Asp299Gly polymorphism with UC was reported first in Caucasian UC patients[120]. In a study, mentioned before[119], increased frequency of this polymorphism was observed, but it did not reach statistical significance. Similarly to Török *et al* study, the Asp299Gly and Thr399Ile mutations in *TLR4* gene were associated with UC in Greek and in North Indian patients[121,122], but not in Dutch or Italian patients[123,124]. Interestingly, the *TLR4* Asp299Gly did not show association with UC in different Asian UC populations[125-128].

The *TLR2* Arg677Trp and Arg753Glu, *TLR4* Asp299Gly and Thr399Ile, and *TLR9* gene C1237T polymorphisms were genotyped in Chinese Han IBD patients; however none of these polymorphisms was associated with IBD. In Caucasians, both TLR4 299Gly and 399Ile conferred as a significant risk factor for developing UC and CD[127].

Three SNPs of *TLR9* (C-1486T, G1174A, A2848G) were genotyped. These variations were associated with an increased risk of UC in the Japanese population. *TLR9* -1486CC, 1174GG and 2848AA showed increased risk for UC, but *TLR9* -1486TT, 1174AA and 2848GG decreased the risk of UC, although there were no correlations between SNPs and disease phenotype or *TLR9* mRNA expression[129]. Possible associations between genetic variations in *TLR9* and IBD in the German population were investigated, but no associations were detected between *TLR9* gene variations and UC susceptibility[130].

Cell adhesion molecules

Cell adhesion molecules (CAM) mediate the extravasation of leukocytes and their accumulation in inflamed intestinal mucosa. This process is controlled by a family of CAM including the intercellular cell adhesion molecule (ICAM-1), the platelet endothelial cell adhesion molecule (PECAM-1), the selectins (E, L, and P selectin) and the integrins[131,132].

ICAM-1 (CD54) is a cell surface glycoprotein belonging to the immunoglobulin superfamily. It plays key role in transendothelial migration of leukocytes, and lymphocyte activation. The membrane glycoprotein PECAM-1 (CD31) is expressed on vascular endothelial cells, platelets, some lymphocyte subsets, and monocytes[133-135]. It has important role in transendothelial migration of circulating leukocytes during inflammatory process[136], apoptosis[137] and integrin regulation[138]. The E-selectin (CD62E) is a glycoprotein, which is expressed on endothelial cells in response to pro-inflammatory cytokines (IL-1, TNF). It supports rolling of leukocytes at sites of inflammation and tissue injury. E-selectin expression is upregulated both in CD and in UC patients playing an important role in mediating of the inflammatory process in IBD[139]. L-selectin (CD62L) is expressed on normal naive T and B cells, leukocytes and on natural killer (NK) cells. It is involved in the adhesion of T cells to endothelial cells, which are regarded as crucial in the selective migration of lymphocytes to inflamed tissue sites during an inflammatory response[140].

Several mutations in *ICAM1* (G241R and K469E), *PECAM-1* (V125L), *PECAM-1* (G98T and S128R),

E-selectin (L554F) and *L-selectin* (F206L) were analyzed in Tunisian IBD patients and controls. A significant increase in allele frequencies of 206L of *L-selectin* and the associated genotype F/L was observed both in UC and in CD patients. In the subgroup analysis the L206 allele and F/L206 genotype frequencies were significantly increased in UC patients with left-sided type. No significant differences in allele or genotype frequencies were observed for *ICAM-1*, *E-selectin*, and *PECAM-1* polymorphisms between UC patients, CD patients, and controls[141].

INTERLEUKINS IN UC

Interleukin 1

Interleukin 1 (IL-1) is pro-inflammatory cytokine, which affects cell proliferation, differentiation, and the function of many innate and specific immunocompetent cells, and acts as an endogenous pyrogen. It broadcast many inflammatory diseases by initiating and potentiating immune and inflammatory responses[142].

IL-1 is composed of two main proteins the IL-1A and the IL-1B[143]. IL-1B has major role in initiating and amplifying the inflammatory response[144]. The IL-1 receptor antagonist (IL-1RN) is an anti-inflammatory cytokine, which lacks the IL-1 receptor accessory protein (IL-1RAP) interacting domain[142].

In Mexican Mestizo UC patients five SNPs were analyzed; the rs419598, the rs315951 and the rs315952 in the *IL-1RN* gene, the rs16955 in the *IL-1B* gene and the 3811058 in the *IL-1F10* gene. Significant increased frequencies of *IL-1RN6*/1TC (rs315952), *IL-1RN6*/2CC (rs315951) and decreased frequency of *IL-1B*-511 TC (rs16944) genotypes were found in UC patients. The patients group showed increased frequencies of *IL-1RN* CTC and TCG haplotypes, whereas TTG and CTG haplotypes frequencies were decreased[145].

IL-2

IL-2 functions as a T cell growth factor, furthermore it supports the proliferation and differentiation of NK cells to increase their cytolytic functions. This IL plays important role in the development of Th1, Th2, Treg, and Th17 differentiation[146].

In the *IL-2/IL-21* region several polymorphisms (rs6822844, rs13151961, rs13119723 and rs6840978) were studies. In a Dutch population the minor alleles of the examined SNPs were associated with IBD. The strongest association of these SNPs was found in the UC patients. In an Italian UC cohort the same strong association of the minor alleles was observed with UC. Similarly to this results, in the North American study was demonstrated, that these alleles have the strongest effect among the IBD patients in the UC subgroup [147].

IL-6

IL-6 is a multifunctional, pleiotropic cytokine that is responsible for regulation of immune responses, acute-phase responses, hematopoiesis, and inflammation[148].

An Irish population study the *IL-6* -174 genotype frequency showed significant difference between CD and UC group[149]. In the Caucasian population the same polymorphism was examined in CD and UC patients and found significant difference UC and CD susceptibility[150].

IL-8

IL-8 is member of the CXC chemokine family[151]. Its has two receptors the CXCR1 (IL-8RA) and the CXCR2 (IL-8RB)[152]. It exerts effect mainly on the chemotaxis and migration of neutrophils, monocytes, lymphocytes, and fibroblasts[153].

IL-8 T-251A was analyzed in a Polish population. The allele frequency showed significant difference comparing the UC group to the controls[154], however this association was not observable in a Chinese UC cohort[155]. Additional polymorphisms were also tested and their effect on the serum level of IL-18. Haplotype frequency of the -353A/ -251A/ +678T haplotype was considerably higher in UC group compared to controls, suggesting this haplotype is likely to be more common in severe UC patients than in mild to moderate cases[155].

IL-10

The anti-inflammatory cytokine IL-10 is produced by many cells like monocytes, T cells, B cells, NK cells, macrophages, and dendritic cells (DCs). It prevents the antigen presentation and also the subsequent release of pro-inflammatory cytokines, so it alleviates the activated immune system[156].

In a GWAS, the polymorphism rs3024505 demonstrated the most meaningful association in the combined verification UC samples, suggesting that defective IL-10 function plays important role in the pathogenesis of the UC[157]. The same polymorphisms was investigated in Australian population[158] and Danish cohort[159] and found that the rs3024505 was associated with the risk of UC.

Three promoter polymorphisms of the *IL-10* gene G-1082A, C-819T, and C-592A were studied in many population but the results are contrary. In an Italian cohort the G-1082A and the C-819T SNPs were investigated. The -1082 genotype frequencies were significantly different between UC patients and controls. The frequency of the -1082A allele was also significantly higher in the UC patients than in controls. Allele and genotype frequencies of T-819C were not significantly associated with the disease. Furthermore, the frequencies of haplotypes -1082A/-819C and -1082A/-819T, which have been described to have a decreased promoter activity, were significantly increased in UC patients than in controls[160]. In a North-Eastern Mexican population the G-1082A and the C-592A SNPs were examined. The -1082 AA and -592 AA genotypes showed significantly lower frequencies in UC compared to healthy controls, while individuals heterozygous at *IL-10*-1082 have sig-

nificantly increased occurrence of UC[161]. In a Tunisian group the A-627C and the G-1117A polymorphisms were examined and found that these two variants influencing the UC susceptibility and phenotype[162]. In the Asian population the association was confirmed between A-1082G polymorphism and UC[125, 163].

IL-12

IL-12 is an interleukin that is naturally produced by dendritic cells, macrophages and human B-lymphoblastoid cells in response to antigenic stimulation. It participates in the differentiation of naive T cells into Th1 cells and involved in the activities of natural killer cells and T lymphocytes. IL-12 mediates gradation of the cytotoxic activity of NK cells and CD8+ cytotoxic T lymphocytes[164]. IL-12 consist of two subunit p35 (IL-12A) and p40 (IL-12B), which is shared by IL-12 and IL-23 cytokines. The IL-12 receptor has two subunits: IL-12RB1 and IL-12RB2[165, 166].

In a German population four SNPs (rs3212227, rs17860508, rs10045431 and rs6887695) of the *IL-12B* were investigated. Two SNPs, the rs10045431 and rs6887695 showed association with increased UC susceptibility[167]. From these SNPs the rs6887695 was investigated in a Japanese population where significant association was manifested between UC patients and controls[168].

IL-17

The interleukin 17 (IL-17 or IL-17A) is a pro-inflammatory cytokine secreted by activated T cells its main tasks is inducing and mediating pro-inflammatory responses. It induces the production of many other cytokines, chemokines and prostaglandins from fibroblasts, endothelial cells, epithelial cells, keratinocytes, and macrophages[169-171].

In a Japanese population the rs2275913 SNP in the *IL-17A* gene and the rs763780 SNP in the *IL-17F* gene were investigated and found significant differences between UC group and healthy controls on level of -197A/A and 7488T/T genotype frequencies[172].

Even more recently, a GWAS in a very large European UC cohort identified an association between another IL-17 pathway gene (*IL-17REL*) and UC[173].

IL-18

IL-18 is produced by macrophages and other cells. It functions by binding to the interleukin-18 receptor, and together with IL-12 it induces cell-mediated immunity following infection. IL-18 induces gene expression and synthesis of TNF, IL-1, Fas ligand, and several chemokines[174].

In the *IL-18* gene several polymorphisms were examined. The G-137C, the C-607A and the G-656T are located in the promoter region, while the A105C, the T113G and the C127T are coding variants. In a Japanese study the G allele at 113 and the T allele at 127 were significantly higher in patients with UC compared to the control[175]. In another Japanese study allele and genotype frequency of G-137C were significantly higher in the proctitis-type UC patients than in controls[176]. 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[176]. The C-607A and the G-137C SNPs were associated with the development of UC in Tunisian patients. The -137GG genotype frequency was significantly higher in UC than in controls and statistically significant association was found between -607AA genotype in UC patients and the distal localization of the lesions[177].

IL-23

IL-23 main functions are very important in innate and adaptive immunity to regulate Th17 function and expansion[178]. This cytokine induces CD8+ memory T cells to proliferate and produce IL-17. IL-23 binds to its receptor IL-23R, which polymorphisms' play the main role in the autoimmune diseases[179-181] especially in IBD[182].

Several independent functional SNPs of the *IL-23R* gene and its neighboring region were determined; several were found susceptible to (rs10889677, rs11209032, rs11465804, rs11805303, rs1495965, rs2201841, rs1004819) CD and UC in non-Jewish subjects[183].

In a Chinese cohort the rs7530511 and rs11805303 SNPs were studied and positive association was found between these variants and UC susceptibility[184]. In the Jiangsu Han population the rs11805303 was found as a susceptibility factor to UC[185].

In a Swedish population the rs10889677, the rs11209032, the rs11465804, the rs2201841 and the rs1004819 polymorphisms were investigated, and found that the rs11465804G, rs2201841C and rs1004819T allele frequencies showed significant differences between UC patient group and control. These genetic variants are individual risk factor for developing the disease[186].

In Hungarian UC patients for the *IL-23R* rs1004819A allele we found significantly higher allele frequency compared to control subjects and the SNP rs2201841 showed significant association with UC risk for homozygotes[187].

IL-26

Expression of IL-26 seems to be restricted to memory T cells, NK cells, and Th17 cells. Thereby it could have pro-inflammatory effects in IBD[188].

Only a few markers were investigated, from these the rs2870946-G and the rs1558744-A showed association with UC[189]. Further meta-analysis study confirmed the association of rs1558744-A with UC[190].

CONCLUSION

This review shows that substantial progress has been made in the past 10 years in to find inflammatory related genetic factors and cytokines in UC. We reviewed different genes and gene polymorphisms which play role in the inflammatory process of UC. These genes could be

potential targets of novel treatment strategies.

From the reviewed genes contributing to inflammation *TNFα*, *MDR1* and *TLRs* were the most investigated genes. *TNFα* has been found as a susceptibility locus for both UC and CD[34-36]. The *TNF2* allele and *TNF 1/2* could be good candidate markers for the susceptibility to UC. Based on the different studies with different populations (East Asians, Han Chinese, Spanish Caucasoid, Italian, and Czech), the *TNFα* -308 is the most studied SNP and this may be an ethnic population-specific risk factor for UC especially for Asian populations but not for Europeans. It should be noted this polymorphism is also a susceptibility factor in other autoimmune disorders (asthma, psoriasis, and rheumatoid arthritis) too.

The *MDR1* C3435T is one of the most tested SNP in UC, but with conflicting results. Some studies showed significantly increased 3435T allele and 3435TT genotype frequencies of C3435T[81,83,97], or only a trend towards an increased frequency of T allele[82], or the T allele was predictive of susceptibility to later onset UC, but not for the early onset of UC[89]. But some studies failed to demonstrate association with UC[91-93]. Other SNPs of *MDR1* (C1236T and rs3789243) were associated with IBD when stratified for age of onset. The rs3789243 was found to be significantly overrepresented in genetically heterogeneous North Indian UC patients.

We reviewed 3 members from the 10 human TLRs regarding to their association to UC. Allele and carrier frequencies of the *TLR4* Asp299Gly and Thr399Ile were significantly associated with UC in Caucasian[119,120], Greek and in North Indian patients[121,122], but not with Dutch, Italian[123,124] or Asian patients[125-128]. Interestingly the *TLR9* polymorphisms (C-1486T, G1174A, A2848G) were associated with an increased risk of UC in the Japanese population. *TLR9* -1486CC, 1174GG and 2848AA polymorphisms show increased risk for UC, but *TLR9* -1486TT, 1174AA and 2848GG decrease the risk of UC[129].

From the reviewed cytokines *IL-10, IL-18* and *IL-23* were the most investigated genes. The IL-10 is a major anti-inflammatory cytokine, which attenuates the activated immune system with inhibiting both the antigen presentation and subsequent release of pro-inflammatory cytokines. IL-10 is a shared risk gene for CD and UC too. The promoter polymorphisms of this gene (G-1082A, C-819T, and C-592A) which are in tight linkage disequilibrium were extensively studied in many populations but with contradictory results. In the Caucasian population the carriers of G-1082A SNP were more susceptible to UC, whereas in another study carriers were associated with lower UC incidence[160,161]. In the Asian population the results strengthened the positive relationship between this SNP and UC susceptibility[125,163]. In a North-Eastern Mexican population the -592AA genotypes showed significantly decreased frequency in UC compared the results to the healthy controls[161]. In a Tunisian group the A-627C and the G-1117A variants influencing the UC susceptibility and phenotype[162]. Several other studies handle with these non-coding SNP in CD too and determine susceptibility to the disease or not.

The G-137C, the C-607A and the G-656T promoter SNPs and several others in the coding regions of *IL-18* gene (A105C, the T113G and the C127T) were examined. The Japanese population is the most studies for these SNPs, significant difference was found in the allele frequency of the A105C between CD patients and controls, while this correlation could not be detected in UC patients. The 113G and 127T allele frequencies were significantly increased in patients with UC compared the results to the healthy controls[175]. In case of promoter polymorphisms, the -137CC genotype frequency was significantly increased in proctitis-type UC patients than in controls, while the other two C-607A and G-137C SNPs were associated with the development of UC in Tunisian patients[177].

The *IL23R* gene was identified as a CD susceptibility gene in North American non-Jewish subjects. Several independent functional SNPs in the gene and its neighboring region were determined[183]. After the primary publications, several studies have been published these SNPs in IBD and other autoimmune disease too (ankylosing spondylitis, psoriasis, Sjögren syndrome, systemic lupus erythematosus). From these SNPs (rs10889677, rs11209032, rs11465804, rs11805303, rs1495965, rs2201841, rs100481) several are risk factor to IBD both in European and Asian populations[185-187].

It can be established that these interleukin gene variants are strongly population dependent but in the given population they can be predictors for CD or UC. Despite the advances in the field of UC/IBD genetics, testing for these genetic variants is currently not recommended for clinical purposes[191].

Understanding of the detailed pathogenesis of IBD and identifying new disease associated SNPs led to the development of selective inhibitors for ILs, chemokines and their receptors. This strategies can optimize treatment efficacy and lead to personalized medicine based on the patient's genotype.

Biological agents are used in patients with moderate to severe disease activity who have failed conventional therapy with glucocorticoids and thiopurines. Today, the most effective and best studied anti-cytokine agents in IBD are the anti-TNFα antibodies. The mechanism of action of TNFα antagonists is based on the neutralization of both soluble TNFα and membrane TNFα and has a more global effect on inflammation than the blockade of other cytokines. Currently, three TNFα inhibitors are approved by the United States Food and Drug Administration (FDA) for inducing and maintaining clinical remission in UC: the chimeric (25% murine and 75% human sequence) monoclonal full-length IgG1 mAb infliximab[192], the fully human mAbs adalimumab[193,194] and golimumab[195]. The pegylated humanised antibody certolizumab pegol is approved only for CD (beside rheumatoid arthritis, RA and psoriatic arthritis). Etanercept, a

dimeric fusion protein consisting of soluble p75-TNFR2 and the Fc portion of human IgG1, used in rheumatoid arthritis therapy, is not efficient for the treatment of intestinal inflammation[196].

Despite the expeditious development of newer biological therapies, only few have shown benefit in clinical trials in UC. Targeting of IL-23 or the IL-23 receptor or IL-23 axis is a potential therapeutic approach for autoimmune diseases including psoriasis, IBD, RA and multiple sclerosis[197]. Recently, testing of anti-IL-12/23 treatment in patients with CD has been performed. In Phase Ⅱ trial, patients with moderate to severe CD that was resistant to TNF antagonists had an increased rate of response to induction with the fully human mAb ustekinumab directed against the p40, as compared with placebo[198]. However, due to the common p40 subunit and IL-12RB1 chain, the major drawback of anti-IL-23 treatment can be the simultaneous inhibition of IL-12 and a possible shutdown of the immune system. Nevertheless, it would be much more useful to design drugs that target the IL-23p19 or IL-23RA itself, so inhibiting IL-23 without modifying the effects of IL-12[197].

Treatment of CD patients with the IL-17 blocker secukinumab (anti-IL-17A) was ineffective and higher rates of adverse events were noted compared with placebo[199].

One new additional treatment for UC may be tofacitinib, an inhibitor of Janus kinases 1, 2, and 3 with *in vitro* functional specificity for kinases 1 and 3 over kinase 2, which is expected to block signaling involving gamma chain-containing cytokines including ILs-2, 4, 7, 9, 15, and 21. Tofacitinib, was approved for the treatment of RA in the USA, Japan and Russia in April 2013. In a double-blind, placebo-controlled, Phase Ⅱ trial, patients with moderately to severely active UC treated with tofacitinib were more likely to have clinical response and remission than those receiving placebo[200].

Targeting leukocyte recruitment and cell adhesion molecules could be also an option for IBD therapy. Natalisumab, a recombinant humanised monoclonal IgG4 antibody, targets both the α4β1 heterodimer located in the central nervous system and the α4β7 integrin in the gut. The FDA approved natalizumab for both induction of remission and maintenance of remission for moderate to severe CD, though it has not been approved for this use in the European Union due to concerns over its risk/benefit ratio (risk of progressive multifocal leukoencephalopathy)[201]. Vedolizumab is a humanized mAb that specifically recognizes the α4β7 heterodimer, selectively blocks gut lymphocyte trafficking without interfering with trafficking to the central nervous system. In the Phase Ⅲ study, vedolizumab was more effective than placebo as induction and maintenance therapy for UC suggesting that blockade of T cell homing in the gut may favor mucosal healing in UC[202, 203].

The exact positioning of these promising new therapies in the management of UC remains uncertain currently. Additional long-term safety data and clinical experience will be needed to determine an overall benefit/harm ratio of newly developed biological agents.

The identified separate loci in IBD research individually have only modest effects on IBD susceptibility. They account together for only 20%-25% of the heritability, suggesting that gene-gene interactions as well as gene-environmental interactions could play a key role in IBD pathogenesis and fill the so called "genetic vacuum" of polygenic diseases[204]. More complete understanding of the immunopathogenic role of the various genes and ILs in intestinal inflammation will help in the development of more effective novel therapeutic strategies in UC. 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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