·Review·

Advances in the studies on cytokine and chemokine gene polymorphisms associated with uveitis

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Abstract

• Uveitis is an inflammation of any or all parts of the uveal tract including the iris, ciliary body and the choroid. Despite current advances in diagnosis and management, visual loss occurs in 35%-45% of patients with uveitis. The etiopathogenesis of uveitis remains unknown; it may be associated with environmental and immunogenetic factors. Many studies have demonstrated polymorphisms in major histocompatibility complex (MHC) genes, which may determine involvement in uveitis. Recently polymorphisms in non-MHC genes, including cytokine and chemokine genes, have been reported to play important roles in the pathogenesis of uveitis. We reviewed the advances in the studies on cytokine and chemokine gene polymorphisms associated with uveitis.

• KEYWORDS: uveitis; gene polymorphism; cytokines; chemokines

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INTRODUCTION

Uveitis is an inflammation of the uveal tract and anatomically categorized as anterior, intermediate, posterior and panuveitis. The inflammatory form of uveitis can occur either as an isolated disease or as part of a systemic syndrome such as Behcet's disease (BD), VKH syndrome and spondyloarthritis. It often affects those aged between 20 and 50. Despite current advances in diagnosis and management, visual loss occurs in 35%-40% of patients with uveitis.

The pathogenesis of uveitis is not well understood. The inheritance pattern of uveitis is complex and influenced by multiple genetic factors [1]. Susceptibility to uveitis has been associated with the MHC genes [2]. Since HLA-B27 itself plays only a minor role in the overall genetic background of uveitis [3], other genetic variants like TNF-α , CCL2 and CCL5 have been recently suggested to play roles in uveitis. We introduced the advances in the studies on cytokine and chemokine gene polymorphisms associated with uveitis in this review.

CYTOKINE GENES

Cytokines are regulatory proteins produced by cells in response to a variety of stimuli. They act as mediators of inflammation and can cause tissue damage in chronic inflammatory diseases. Cytokines have been associated with the pathogenesis of uveitis[4].

IL-1 Gene IL-1 gene contains three related genes that encode the proinflammatory cytokines IL-1α, IL-1β and their endogenous receptor antagonist IL-1ra. Several IL-1 gene polymorphisms have been described and associations with uveitis have also been reported. Karasneh *et al* [5] found that IL-1α -899C allele was associated with BD and IL-1α -889C/IL-1β +5887T haplotype was a risk factor for BD. The IL-1α -889 and IL-1β+5887 CC/TT combined genotype was significantly more observed in BD patients than in controls. Similarly, Alayli *et al* [6] also found a significantly increased frequency of IL-1α -899C allele in BD patients, IL-1β-511C allele and CC genotype frequencies were significantly higher in BD patients compared to controls, IL-1β +3962 CC genotype was associated with BD susceptibility. In contrast, Coskun *et al* [7] reported no significant difference in genotype and allele frequencies of IL-1β -511 between BD patients and controls, but they identified an increased frequencies of both IL-1β +3953 T allele and TT genotype in patients with BD.

Intraocular injection of IL-1ra decreases the inflammatory response in anterior uveitis caused by intravitreal injection of IL-1 in animal models [8]. Interestingly, patients with

chronic uveitis has an increased frequency of the IL-1ra T allele than those with recurrent uveitis[9].

IL-18 Gene IL-18 gene is regarded as a pivotal mediator of Th1 cytokine responses and can enhance the production of TNF-α , GM-CSF and IFN-γ , which were elevated in BD [10]. It has been reported that BD patients have higher serum levels of IL-18 than controls, and its concentration is related to disease activity[11]. Giedraitis *et al* [12] demonstrated that IL-18- 607A/C and -137C/G polymorphisms in the 5'-UTR binding affected promoter activity. Though these two polymorphisms have been studied in many inflammatory diseases, only two studies in Korean have been reported on uveitis. Jang *et al* [13] identified a significant higher frequency of -137GG genotype in BD patients with ocular lesions than patients without ocular lesions, although they didn't find any significantly different distributions of -137 and -607 polymorphisms between patients and controls. Another similar study [14] identified significantly higher frequencies of both -607C allele and CC genotype, and a lower frequency of -607A/-137G haplotype in BD patients than controls. These results suggested that IL-18 gene may be a susceptibility gene of uveitis.

TNF -α Gene TNF-α is produced predominantly by macrophages. High serum level of TNF-α has been associated with recurrent uveitis, and disease inflammation has been found in TNF-receptor-deficient mice in immune-complex-induced uveitis [15,16]. Kuo *et al* [17] investigated the associations between TNF-α and TNF-receptor gene polymorphisms and idiopathic acute anterior uveitis (IAU) in Caucasians, they found a significant increase in the frequency of TNF-857T allele in patients with IAU compared with controls. Menezo *et al* [9] also found a significant increase in the frequency of TNF-308G allele in Caucasian patients with HLA-B27 positive anterior uveitis compared to patients negative for HLA-B27. In Turkish population, the relation and functional importance of TNF-α-1031T/C was investigated, the results showed that the frequency of TNF-1031C allele was significantly higher in BD patients compared to controls; whereas patients carrying the T allele were more prone to develop a positive shin pathergy test[18].

CHEMOKINE GENES

Chemokines are a group of low molecular weight (8-14kDa), mostly basic structurally related proteins that function as potent mediators of inflammation by their ability to recruit and activate leukocytes [19,20]. There are two major subfamilies of chemokines: CXC chemokines like CXCL 8/IL-8 usually recruit neutrophils, whereas CC chemokines like CCL2 and CCL5 tend to attract monocytes[21].

IL-8 and Its Receptor Genes IL-8 can cause a transient increase in cytosolic calcium concentrations and release of enzymes from granules. Thus it enhance the production of reactive oxygen species and increase chemotaxis to neutrophils. Cellular activities of IL-8 are mediated by its two receptors, CXCR1 and CXCR2. Serum and cerebrospinal fluid levels of IL-8 have been found to be elevated in BD patients and correlated with disease activity [22,23]. Concentration of IL-8 increase significantly in the aqueous humor of patients with acute anterior uveitis (AAU)[24].

Duymaz-Tozkir *et al* [25] reported no skewed deviation of IL-8 or CXCR2 gene polymorphisms in Turkish patients with BD. Yeo *et al* [26] reported no association between IL-8 or CXCR1 gene polymorphisms and IAU either. On the contrary, Lee *et al* [27] found that though there were no SNPs associated with BD, the increased frequency of haplotype TAT inferred from SNPs IL-8-353-A/T, -251A/T and +678T/C has strong association with BD. These results suggested that a combined effect of IL-8 SNPs is necessary to disease susceptibility, while the individual effect is not strong enough to show it.

CCL2 and Its Receptor Genes CCL2, known as monocyte chemoattractant protein-1 (MCP-1), is a chemoattractive cytokine. In animal models CCL2 was shown to play a role in autoimmune response and was thought to participate in the leukocyte infiltration and protein leakage in AAU and in the induction of uveitis itself [28,29]. MCP-1 can be detected easily in the aqueous humor of patients with active AAU[24]. CCL2 -2518A>G polymorphism, which correlates with individual difference in production of MCP-1, was identified in the MCP-1 gene distal regulatory region [30]; monocytes from individuals carrying -2518G allele produce more MCP-1 after proper stimulus.

Chen *et al* [31] found that CCL2 haplotype with GA/AA were more prevalent in females and AA/AA or AA/AT were more prevalent in males. Wegscheider *et al* [32] showed that carriers of CCL2-2518G allele were significantly more often in patients with HLA-B27 associated AAU than HLA-B27 positive controls. Another study [26] demonstrated that the frequency of MCP-1 63555T allele was significantly higher in controls compared to patients with IAU, which indicated that T allele may be a protective marker against uveitis.

The associations of SNPs in CCL2 gene and clinical phenotypes of uveitis were identified by the study of idiopathic immune-mediated posterior uveitis[33]. The results showed that CCL2-2518G allele was associated with a younger age onset of disease, the mean age of disease onset in patients with AA genotype was 41 years compared to 33 years in patients with G allele. The study also found that patients with CCR2 64I allele had a higher risk of developing an elevated intraocular pressure compared to patients with wild-type genotype.

CCL5 and Its Receptor Genes CCL5, earlier called regulated upon activation, normal T-cell expressed, and secreted (RANTES), is chemotactic for T cells and plays an active role in recruiting leukocytes into inflammatory sites. Two polymorphic sites (-28 and -403) in the upstream region of the CCL5 gene that contains cis-acting element involved with CCL5 promoter activity [34,35]. They were in linkage disequilibrium. The CCL5- 403AA genotype was only found in male patients with BD but not in controls[31].

Ahad *et al* [33] found that CCL5- 403GG genotype was associated with disease severity and G allele was associated with worse visual acuity (VA) in the affected eye. CCL5 del32 was found to be associated with visual outcome even after correction for disease phenotype and treatment. CCL5-59029 polymorphism was associated with the need for persistent corticosteroid therapy of more than 10mg per day to control inflammation. Yang *et al*[36] and Mojtahedi *et al* [37] reported no association of CCR5del32 polymorphism with BD but revealed a significant difference in distribution of the CCR5 del32 in female patients compared with female controls.

CONCLUSION

In addition to above gene polymorphisms, other cytokines and their receptor genes, such as IL-6, IL-10 and IFN-γ, have also been studied [9]. Studies of the genetics of uveitis have revealed that cytokine and chemokine gene polymorphisms have strong associations with uveitis. But current studies of these genes concentrated on case-control study, small sample size is a frequent problem and can result in insufficient statistical power and provide imprecise estimates of the disease association. In the future, large-scale studies and different populations will be necessary to validate the associations of these genes and uveitis development and clinical phenotypes.

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