Regulatory Role of HLA DR/DQ II Classes Haplotypes in TNFα, Activity Response in HIV/AIDS Patients

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Introduction. It is known that the development of individual immune response characteristics, as well as predisposition to various diseases, including infections, is associated not only with the HLA gene polymorphism, but SNP. There is a connection between the hyper- and hypo-production of the genetically-determined cytokine and the quality of the immune response, which is also associated with the severity, development and consequences of an infectious disease. So it should be possible to find out the regulating role of HLA DRB1 and other II class alleles in the cytokine activity response to various pathologies.

Aim. The aim of the study is to identify the factors of molecular genetic risks during the development of infection in HIV, based on the TNFα cytokine gene polymorphism in combination with HLA II DRB1/DQA1/DQB1 genes, as well as to analyse their possible association with the progress of the disease.

Material and Methods. The research was conducted at Rīga Stradiņš University CIIL and Rīga Eastern Clinical University Hospital ICL. 200 HIV infected patients have been analysed. The control group consisted of 117 individuals. TNFα gene G-238A and G-308A polymorphic variant incidence was determined by PCR/RFLP analysis. The DNA was extracted by using QIAamp method. The amplification of TNFα gene fragment was perfromed with programmable thermocycle camera (QIAmp blood kit; Qiagen, Krefeld, Germany). The distribution of genotypes was tested by the Hardy-Weinberg equation by the program GENEPOP. For the homogeneity the chi-square, the reliability coefficient and the Fisher-criterion were used. These measurements were performed with StatXact-4 software (Cytel Software Corporation, USA).

Results. The incidence of the TNFα gene –308A allele in HIV infected patients (11%) was almost three times higher ($p = 0.012$) than it was in the control group (4%), which in turn suggests that HIV patients have an increased tendency to increased production of the TNFα protein. Although the incidence of the TNFα gene -238A allele was twice as high in the control group (6%) as in the HIV infected patients (3%), it did not prove to be statistically valid ($p = 0.253$). Based on the distribution of the two TNFα gene polymorphisms, according to the combined genotypes, the most common combination in the HIV infected patients was heterozygous: -308G/-308A, or homozygous: -308A/-308A genotype (which stimulates the synthesis of TNFα protein) together with the homozygous genotype: -238G/-238G. In contrast, the most common combination that was observed in the control group was the homozygous combination of two polymorphisms -238G/-238G; -308G/-308G or homozygous -308G/-308G genotype with homozygous genotypes -238G/-238A which is a TNFα protein inhibitor. The incidence analysis of three-locus haplotypes DRB1-DQB1-DQA1 – in TNFα position -238A/G -308A/G showed that haplotypes 01:01/05:01/01:01 – TNFα-238(GA)/308(GG) and 01:01/03:02/03:01 – TNFα-238(AA)/308(GG) are more frequent in the control group in comparison to the groups of infected patients. This means that these haplotypes have a protective function, which significantly affects the progress of infection. The association of 15:01/05:01/01:01 – TNFα-238(GG)/308(GG) and 03:01/05:01/01:01 – TNFα-238(GG)/308(GA) genotypes indicates a high risk of developing a fulminant infection.

Conclusions. The genetic factors of AIDS-related complex of syndromes development are associated not only with the HLA complex class II alleles, but also with the SNP polymorphism in the promoter region of cytokine genes. For the acquisition of statistically valid data, it is necessary to increase the number of patients in each of the research groups.