Univerzita Karlova v Praze

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Klinický význam polymorfismu cytokinových genů

Clinical significance of cytokine gene polymorphism

Disertační práce

Vedoucí závěrečné práce/Školitel: Prof. MUDr. Ilja Stříž, CSc

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Abstract

The human genome is full of different sequence variants. They are different mainly in size but also in their influence on phenotype. The smallest unit of genetic polymorphism is single nucleotide polymorphism (SNP). SNPs represent a single nucleotide change between two alleles and might affect the gene expression. We have studied SNPs in three distinct fields as: (1) marker of risky patients after the organ transplantation, (2) diagnostic marker of patients with interstitial lung diseases (ILD) or (3) with uterine fibroid (UF). We have come to the following results.

Ethnicity or even nationality plays a role in the distribution of genetic polymorphism. This must be absolutely taken into account when one would like to transfer findings of a clinical study from a certain nation or ethnic and applied them to his studied group for the comparative purposes. Our first clinical gene-association study has found that even gene polymorphism of the IL-18 gene may contribute to the delayed onset of kidney graft function after transplantation and support the role of this proinflammatory cytokine in the modulation of early immune responses against the kidney allograft. From the studies of ILDs, we conclude that cytokine gene polymorphisms contribute to the pathogenesis and play a role in the etiology of ILDs, with an emphasis on the IL-4, IL-4RA, IL-1RA, and IL-12 promoter regions. Associations have been found between the polymorphisms and functional parameters of idiopathic pulmonary fibrosis (IPF) and levels of other cytokines. Finally, as cytokines play a role in the development of UF it seems that their gene polymorphisms play a role as well as we demonstrated on the polymorphism for IL-4 and tumor necrosis factor (TNF)-α.

Our data suggest that the gene polymorphism can influence immune reaction. However, the strength of this effect is still unknown. Processes in organ transplantation or in disease pathogenesis are so polygenic and complex that it is hard to imagine that one point substitution in the certain gene could affect so many biochemical and signalling pathways. We have to take into account also a role of epigenetics on the level of gene expression which also seems to play a significant role.