
Molecular Approach to Urinary Tract Infections

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Mortality of infectious diseases remains high although agents causing them are known and specific therapies are available against them. Clinical course in infectious diseases depends on interaction between the host and the pathogen. This, in turn, is controlled by the response of the host immune system. Immune system is defense system of the host that might be divided into two main groups as innate and adaptive. Two of them together protect the host against the pathogens by working together with a very delicate balance. Evolutionary primitive and universal in the fight of the host against infections, innate immune system has a few receptors recognizing the pathogens. This system may initiate defense mechanisms by recognizing a group of molecules common in the pathogens which are named PAMPS. Receptors recognizing these molecules are called "Pathogen Recognition Receptor" (PRR). More frequent and more severe occurrence of infectious diseases in some persons is due to that the genes of these receptors on the host show polymorphic structures. Different mutations and polymorphic changes in these genes may explain resistance and susceptibility to and clinical course of the diseases. Most important of PRR are TLR family. 11 members of Toll-like receptors family have been identified. TLR2 recognizes lipoprotein/lipopeptid, peptidoglycans and lipoteichoic acid from several components of different gram positive bacteria. TLR3 recognizes the viruses containing double-strand RNA. TLR4 is an essential receptor for LPS, main component for gram negative bacteria. TLR5 recognizes the bacteria containing flagellin. TLR9 recognizes the bacteria containing CpG DNA fragment not undergoing methylation process. TLR11 produces the response to the uropathogenic bacteria. NF- κ B, one of the transcription factors, is an important component of signaling pathway produced by the interaction between TLR and bacteria. This signaling pathway leads to the synthesis of the cytokines and interferons which trigger adaptive immune response.

In addition, Fc region receptors (FcR) of the immunoglobulins play important roles in cellular and humoral functions of the immune system by using different effector cells. The molecule which initiates the effector functions like degranulation, cytokine production, arrangement of the antibody synthesis, antibody dependent cellular cytotoxicity, superoxide production and

phagocytosis. These functions are essential in host defence and immune system of an individual.

Urinary tract infections (UTI) are among the most common infections in the pediatric age group. This is an inflammatory reaction occurring as a consequence of interaction between the bacteria and the uro-epithelial cells. Two studies at molecular level on urinary tract infections conducted in Pediatric Nephrology Department of Ege University were presented.

We studied 134 children (mean age \pm SD: 5.81 \pm 3.47, girls/boys: 107/24) having a diagnosis of culture positive UTI who have no vesicoureteral reflux and 118 healthy adults (mean age \pm SD: 39.1 \pm 11.8) who have never had any urinary infection were included in these studies. The relationship between TLR2 and Fc γ genotypes such phenotypic characteristics as the number and location of the infection, microorganisms and presence of scarring was studied. Renal scarring of the patients were graded according to Goldraich Scar Grading System. TLR2 gene and 3 types of Fc γ gene family polymorphisms were analysed with PCR based direct DNA sequencing method.

We showed that subjects who carry the TLR2 gene 753 *Gln* allele had higher risk for Gram (+) pathogens related UTI. As a result TLR2 gene mutation is susceptibility factor for UTI in children. Subjects carrying the TLR2 gene 753 *Gln* allele had higher risk for Gram (+) pathogens related UTI¹.

Fc γ RIIIa and Fc γ RIIIb polymorphisms are thought to be risk factors for predisposition to urinary tract infections. When the relation between phenotype and genotype is evaluated, Fc γ RIIIa 131R allele is found to be related with the lower urinary tract infection (p:0.015), UTI recurrence frequency (p: 0.075) and gram negative bacterial infection risk (p:0.012). Besides, Fc γ RIIIb-NA2 allele is found to be related with upper UTI, gram negative bacterial infection and renal scar formation risk (p<0.001)².

References

1. Berdeli A. et al. TLR gene mutations in children with urinary tract infection. *Nephrology Dialysis Transplantation* 2005;20 (5) p.33
2. Ozdemir R et al. Positive association of FCGR11A-131R and FCGR11B-NA2 allele with urinary tract infection in children. *Genes & Immunity* 2005; 6 (1) p.18