Provisional chapter

Genetic Factors Underlying Susceptibility to Acute Pyelonephritis and Post-infectious Renal Damage

Maja Zivkovic, Ljiljana Stojkovic,
Brankica Spasojevic-Dimitrijeva, Mirjana Kostic and
Aleksandra Stankovic

Additional information is available at the end of the chapter

1. Introduction

Urinary tract infections (UTIs) are significant problem in infants and children and may be associated with renal scarring, which can cause serious long-term complications particularly hypertension and renal failure. The common characteristic of all UTIs is a significant growth of bacteria in the urinary tract. Uropathogenic Escherichia coli (*E. coli*) is the primary causative agent of UTIs.

Symptomatic UTIs can be classified into infections limited to the lower urinary tract and infections of the upper urinary tract. Marked individual differences in susceptibility to UTIs have been known for decades. Through different molecular interactions bacteria may trigger epithelial cell responses, cause cell detachment and invade or kill cells by apoptosis. The individual inflammatory response determines severity of acute pyelonephritis (APN) as well as differences in response to UTI among individuals. It is suggested that APN occurs more readily in high responders. Level of individual inflammatory response could be a key of enigma why some patients with APN develop renal scarring and progressive kidney damage whereas others do not.

Identification of new markers underlying APN and affecting its treatment is essential for designing interventions that would minimize tissue damage. Research of individual genetic background of inflammatory response suggests the significance of proinflammatory cytokine genes and polymorphisms of these genes. Such polymorphisms can occur either in regulatory or in coding regions of genes. They may affect the level of inflammation by enhancing transcription of certain cytokines' genes and thus increasing production of these

cytokines. Changes in genes' expression as well as presence of certain alleles associated with disease phenotype support the hypothesis that genetic factors could modify susceptibility to acute pyelonephritis and post-infectious renal damage.

Several mechanical forces including urine flow and voiding, mucus shedding, and epithelial cell sloughing are important in minimizing UTI incidence. Bacterial adherence to the epithelium triggers defense responses. One of these is innate immunity response, which is important for uropathogenic *E. coli* recognition and immunomobilization. The innate immunity response is mediated by toll-like receptors (TLR4, TLR5, TLR11), adhesion molecules (E-selectin, ICAM-1, PECAM-1) and secreted factors such as cytokines (TNF-alpha, IL-1beta, IL-6, G-CSF, IL-17) and chemokines (CXCL1, CXCL2, CXCL3, CXCL8, CCL4). These molecules have been detected in mammalian bladder upon infection. Therefore, polymorphisms in genes coding for these molecules have been recognized as genetic susceptibility factors for UTIs. Neutrophils are the most abundant early responders to infection, while the antigen(Ag)-presenting macrophages, dendritic cells and innate-like lymphocytes (such as gamma delta T cells) have been implicated in the UTI host defense.

The cytokine response is essential for antibacterial defense of the urinary tract. Interleukin-8 (IL-8) is a potent chemoattractant responsible for neutrophil infiltration into the urinary tract. It was reported that neutrophils of children with recurrent pyelonephritis had lower expression of IL-8 receptor (CXCR1) than neutrophils of healthy controls. Interleukin-6 (IL-6) is one of the pro-inflammatory cytokines, which stimulates production of all acute-phase proteins thus contributing to acute-phase response and systemic inflammation. High serum or urine levels of IL-6 have been found in children with UTIs, particularly in children with APN compared to those with lower UTI. It was also indicated that urine and serum levels of cytokines could be observed as markers of renal damage as well as tools for monitoring the development and outcome of APN. Urine analysis has been extensively used by clinicians to diagnose various renal diseases. Advances in technology of molecular biology enable analyses of genes' expression levels in urine sediment. These expression studies have a potential to improve the diagnosis of APN by detecting urinary gene expression profiles, which are specific for patients with APN.

Besides susceptibility to UTIs, of great therapeutic importance is susceptibility to post-infectious renal damage in APN patients. This kidney damage susceptibility has the genetic component. Among the candidate genes are those coding for molecules like growth factors (TGF-β1, VEGF), which play important roles in processes characteristic for the tissue damage and scarring such as cell proliferation and accumulation of extracellular matrix. Angiotensin II, main effector of the renin-angiotensin system, is also considered a growth factor involved in all phenomena of renal tissue damaging and scar formation.

Here we will review the roles of candidate genes' polymorphisms and expression in susceptibility to APN and post-infectious renal scarring, in order to summarize the existing results and point out to further possible directions for research in this field.

2. Acute Pyelonephritis (APN) in children and genetic susceptibility to APN

Urinary tract infections (UTIs) are common among children of all ages including infants. UTI is defined as a penetration of microorganisms, mainly *E. coli*, into the tissue of urinary tract, which is marked by significant bacteriuria (>10^5 bacteria per 1ml of urine) [1]. UTIs are classified into three categories: upper UTI- acute pyelonephritis, lower UTI- acute cystitis and asymptomatic bacteriuria (ABU). The upper UTI, or acute pyelonephritis (APN), represents bacterial infection of renal parenchyma, which may cause various inflammatory lesions. Post-infectious renal scarring is the most serious complication following APN in children, with an estimated incidence of 10-65% [1-2]. Vesico-ureteral reflux (VUR) may also play an important role in renal damage [3]. VUR is suggested to be a weak predictor of permanent renal damage in children hospitalized with UTI [4] but it is also known that the grade of VUR positively correlates with likelihood of renal scarring [5]. Extensive renal scarring leads to renal insufficiency and hypertension [6-7]. Early diagnosis of APN and follow up to identify renal scarring after the first APN are thus very important. The primary distinction of APN is based on clinical manifestations and indirect laboratory testing of inflammatory markers such as C-reactive protein (CRP) serum levels, peripheral white blood cells' (WBC) count etc. However, these tests are unreliable in acute phase of pyelonephritis. The ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy is a golden standard method for detection of acute renal inflammatory lesions specific for diagnosis of APN as well as for the follow-up detection of renal cortical scars [8-9]. Detection of permanent renal parenchymal defects following APN is ultimate for long-term prognosis of kidney function. The incidence of renal defects correlates inversely with the time interval between pyelonephritis and the scintigraphic study and stabilizes 4-6 months following acute disease. DMSA scintigraphy is based on binding of 99mTc-DMSA to renal parenchyma cells and therefore provides means of distinguishing APN from lower UTI and evaluating persistent DMSA uptake defects after the initial infection in children [8-10]. Given that DMSA exposes the patients to radiation, this procedure is not regularly used to diagnose APN.

2.1. Bacterial virulence and uroepithelial contact

Uropathogenic *Escherichia coli* is the most common causative agent (80%) of uncomplicated UTIs although other enteric organisms have been identified as well [11]. After colonization of the urethra and ascent to the bladder, bacteria bind to glycosphingolipid and glycoprotein receptors on the urinary tract epithelium and penetrate into tissue of urinary tract [12]. They express a number of virulence determinants that contribute to successful colonization of the urinary tract [13]. Many pathogenic microorganisms use host cell surface oligosaccharides including glycosphingolipids (GSLs) as receptors to attach to uroepithelial cells. The attachment of *E. coli* is mediated trough expression of flagellin and ascending of *E. coli* to the upper urinary tract and dissemination of bacteria within the host are enabled through a flagellum-mediated motility [14-16]. These actions, along with the lipid A moiety of lipopolysaccharide (endotoxin), have been shown to enhance activation of the host inflammatory response. Cytokines mediate this response [7,17-19]. Neutrophils are the first cells that

migrate to the uroepithelium in the event of UTI and they are crucial in control of infection at early time points [20].

2.2. Renal scarring following APN

Bacterial infection of renal parenchyma during APN represents the major cause of acquired renal damage in children. The inflammatory changes associated with acute pyelonephritis are reversible but in some cases they result in renal defects. The percentage of children with renal scarring detected six months after the first APN is similar in the recent studies [21-23] and is in agreement with the results of European meta-analysis study of post-pyelonephritic renal scarring incidence [24]. Post-infectious renal scarring, as the most serious complication following APN, appears in 10-65% of children [8,25]. This renal damage can lead to hypertension and chronic renal failure [26-28].

The actual etiology of renal scarring remains controversial. The risk factors supposed to be associated with renal scars are: presence of vesico-ureteral reflux (VUR), delay in adequate antibiotic treatment, presence of recurrent UTI, bacterial virulence, host defense factors, host inflammatory and immunologic reactions and genetic susceptibility.

2.3. Vesico-Ureteral Reflux (VUR) as a risk factor for renal scarring

VUR is classically considered a risk factor for development of renal scars. The theory that reflux might play an important role in renal damage was proposed by Hodson and Edvards in 1960 [29]. Ransley and Risdon showed that scarring occurred only when urinary infection was present in association with VUR and intrarenal reflux [30]. Later it was suggested that VUR was a weak predictor of permanent renal damage in children hospitalized with UTI [31]. However, development of scars occurred even in absence of VUR, so there has been a debate for many years over the role of VUR in children who developed renal scars following UTI [31-35]. There is also a debate whether the grade of VUR positively correlates with likelihood of renal scarring or not [36] and whether the age represents a risk factor for scars' formation [37]. Gleeson and Gordon reported that there was a significant correlation between detection of a scarred kidney on DMSA scan and presence of VUR in children who were less than one year old [37]. In children aged over one year there was a poor correlation with renal scarring, so they suggested that the young growing kidney might be more vulnerable to insults. However, others [25,38-39] did not confirm that younger children were at greater risk for development of renal sequelae following pyelonephritis. Moreover, in some studies [40] children aged over one year had a higher frequency of renal scarring in comparison to infants.

2.4. Host inflammatory response and kidney damage following APN

Roberts et al. have suggested that the acute inflammatory response causing the eradication of bacteria could be responsible for the early pyelonephritic damage of renal tissue and subsequent renal scarring [41]. Neutrophils migrate between tissue compartments and exert their effector functions at different sites. They circulate in blood and interact with the endo-

thelial lining that they cross to reach peripheral tissues. There is increasing evidence that the fate of neutrophils outside the vascular system is governed by specialized molecular interactions distinct from those in blood vessels [3] but these aspects have received less attention and are not well understood. Mucosal pathogens trigger a rapid neutrophil response [4-5], given that neutrophils are crucial effectors of the host defense [6-7]. The mucosal neutrophil response initiates when bacteria stimulate the epithelial cells to secrete chemokines [5,42] and to increase their chemokine receptors' expression. Neutrophils respond to so-formed chemotactic gradient, leave the bloodstream, travel through the submucosa and reach the basal side of the epithelial barrier, which they cross into the lumen [3,42]. Attention has been focused on molecular interactions of neutrophils with endothelial cells during the extravasation process [1-2], because this is the key to subsequent pathology and tissue destruction.

2.5. Genetic susceptibility to APN and renal scarring following APN

The interindividual differences in frequency and severity of UTIs exist and they are consistent with a genetic predisposition among disease-prone individuals. Structural defects such as congenital anomalies of kidney and urinary tract as well as social and environmental factors influence disease susceptibility [1-2]. There have been many attempts to identify the host factors that predispose to UTIs, especially to acute pyelonephritis (APN). Recurrent APN occurs within a small group of highly susceptible individuals, some of whom develop progressive renal scarring and therefore may need dialysis or kidney transplantation [2-4].

In an attempt to characterize the critical mechanisms and candidate genes for APN susceptibility, the "knockout" mice were investigated. It has been shown that the innate immunity response genes strongly influence susceptibility to UTIs, particularly APN [5-7].

Large interindividual differences both in frequency and severity of UTIs are consistent with genetic predisposition among disease-prone individuals although inherited defects in mechanisms of defense against UTIs have not been identified. Since the experimental studies suggested that susceptibility to clinical APN was genetically controlled and that the disease severity might vary with the expression levels of specific host response molecules, the next step was to investigate the susceptibility candidate genes in human population.

2.5.1. Cytokines

Phagocytosis of microorganisms and their intracellular degradation by the tissue macrophages represent stimuli for synthesis of proinflammatory cytokines, interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) [43]. IL-1 and TNF-α induce expression of the adhesion molecules on the surface of endothelial cells, which bind the circulating leukocytes and allow their recruitment into the tissue. IL-1 and TNF-α also stimulate cells of the infected tissue to produce other mediators of inflammation such as cytokine interleukin-6 (IL-6) and chemokines, which regulate leukocytes' functions as well as their transendothelial migration into the inflammatory tissue [43]. Chemokines, particularly interleukin-8 (IL-8), are released from stimulated endothelial cells and macrophages. They

act as chemoattractants stimulating the chemotaxis of neutrophils and neutrophil adhesion to stimulated endothelium [43,44].

Elevated serum levels of the proinflammatory cytokines- TNF-α, IL-1 and IL-6, have been measured in children with UTIs, with a significantly greater increase in children with APN than in those with lower UTI [10].

2.5.1.1. TNF-α

A single nucleotide polymorphism (SNP) -308 A/G in the promoter sequence of TNF-α gene is located at the binding site of the transcription factor activating protein-2 [45]. It has been suggested that TNF -308 A allele is related to a higher production of TNF-α [46]. No differences have been demonstrated in TNF-α -308 A/G genotype frequencies between infants with UTI (with and without renal scarring) and controls [47].

2.5.1.2. IL-6

Interleukin-6 (IL-6) is one of the pro-inflammatory cytokines, which stimulates production of all acute-phase proteins thus contributing to acute-phase response and systemic inflammation [10]. IL-6 is synthesized by several types of cells, in response to various antigens such as bacterial pathogens [48-49]. There are studies suggesting that IL-6 could be synthesized by uroepithelial or renal tubular cells [49-50]. High serum or urine levels of IL-6 have been detected in children with UTIs, particularly in those with APN in comparison to those with lower UTI [51-52]. It was indicated that urine and serum levels of this cytokine could be observed as markers of renal damage as well as tools for monitoring the development and outcome of APN [22,51-52].

Regulation of IL-6 expression is mainly accomplished at transcription level. A SNP -174 G/C, in the promoter region of IL-6 gene, is located 11 bp upstream from cis-regulatory element (CRE) and reported to influence the level of IL-6 expression in healthy individuals [53]. Moreover, -174 G/C polymorphism was found to be associated with circulating IL-6 levels and course of certain inflammatory diseases [54-55]. This polymorphism was investigated in association with APN and renal scarring in our study [21]. The genotype distributions and allele frequencies were not significantly different between the two investigated patients' groups, with APN and lower UTI. We concluded that IL-6 -174 G/C polymorphism was not a susceptibility factor for APN. This polymorphism was neither recognized as a risk factor for renal scarring in patients with the first APN [21]. Still, we detected a significant increase in white blood cells' count in APN children with CC genotype compared to those with wild type, GG, genotype.

2.5.1.3. IL-8 and CXCR1

The IL-8 receptor, CXCR1, was identified a candidate gene for acute pyelonephritis when mIL-8Rh mutant mice developed APN with severe tissue damage [6-7]. After sequencing that covered the entire CXCR1 gene two genetic variants, +217 C/G and +2608 G/C, were found to be susceptibility factors for APN in both children and adults [56]. Infants and chil-

dren included in this study have been followed from their first episode of APN and adults had a history of APN in childhood. Kidney status was defined by DMSA scan. The UTI-associated CXCR1 variant, +217 C/G, has been shown to reduce RUNX1 binding to the putative intronic binding site. Furthermore, transfection experiments showed that transcription level of the mutant allele was lower, suggesting that +217 C/G polymorphism could reduce CXCR1 transcription [56].

The other study investigated polymorphisms of IL-8 gene, -251 A/T and +2767 A/G, and a polymorphism +2608 G/C of IL-8 receptor gene (CXCR1) in children with the first episode of upper UTI and APN documented by DMSA [18]. There were no statistically significant differences in genotype and allele frequencies of the IL-8 and CXCR1 polymorphisms between the UTI population and controls [18]. After comparison of genotype frequencies between DMSA positive children (with definite APN) and DMSA negative children, there were no significant differences between these two groups. Still, IL-8 -251 TT genotype was significantly more frequent in DMSA negative children suggesting that a carriage of A allele represents susceptibility factor for APN. By exclusion of patients with VUR, the genotype frequencies between DMSA positive and DMSA negative children were significantly different for IL-8 gene polymorphisms, -251 A/T and +2767 A/G. Again, -251 TT homozygotes were more frequent in DMSA negative children. These results, overall, suggest that IL-8 -251 A allele is significantly associated with presence of DMSA documented pyelonephritis [18]. Experimental data also showed that -251 A allele was associated with increase in IL-8 production in lipopolysaccharide stimulated whole blood [42]. The CXCR1 gene polymorphism +2608 G/C was not associated with APN [18].

2.5.1.4. MCP-1/CCL2 and RANTES/CCL5

Polymorphisms of genes coding for MCP-1 (monocyte chemotactic protein-1)/CCL2 and RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted)/CCL5 and their receptors, CCR2 and CCR5 respectively, have been associated with the upper UTI. Only RANTES -403 G allele was significantly associated with risk for UTI, irrespectively of VUR [57].

2.5.2. Adhesion molecules

Initial steps of the inflammatory response are mediated by adhesion of inflammatory cells (leukocytes) to vascular endothelial cells [58-59]. Inflammatory cells then exit the circulation and infiltrate the surrounding tissue. This process is mediated by E-selectin, intercellular adhesion molecule-1 (ICAM-1) and platelet endothelial cell adhesion molecule-1 (PECAM-1) through the sequential steps of rolling, strong adhesion and diapedesis, respectively [59-60]. Data from ICAM-1 knockout animals showed that these animals had elevated neutrophil and lymphocyte counts and decreased neutrophil influx to the site of infection [61].

In the group of children with a proven history of UTI, E-selectin, ICAM-1, PECAM-1 and CD11b gene polymorphisms were investigated. There were no significant differences in allele frequencies between patients and controls for any of the investigated polymorphisms

[62]. Still, A allele of ICAM-1 exon 4 (G/A) polymorphism had significantly lower frequency in patients who developed renal scars following UTI compared with the patients without scars. This suggested that the A allele might be a protective factor for renal scarring following UTI. It is possible that protective effect of the A allele on development of renal scars following UTI may be a result of decreased binding of neutrophils and other inflammatory cells to ICAM-1, resulting in reduced leukocyte infiltration and reduced tissue damage [62].

2.5.3. Toll-Like Receptors (TLRs)

Toll-like receptors' (TLRs) genes are among the most commonly studied in association with UTIs. Toll-like receptors are critical sensors of microbial attack and effectors of the TLR-dependent innate defense, which enables host to eliminate pathogens [63-65]. TLRs are located on the cell surface or within organelles, like phagosomes, and are involved in detection of microbial ligands such as flagellin (TLR5), lipopolysaccharide (TLR4) and bacterial lipopeptides (TLR1/2/6) [66].

Given that TLRs play a crucial role in the innate immune defense, their structures and functions are tightly regulated [67]. Numerous attempts have been made to identify TLRs structural genes' variations, which might be related to diseases. Structural gene polymorphisms are relatively rare [68] and their contributions to human diseases still remain unclear.

Recently, TLR4 gene promoter region has been shown considerably more variable than previously known [69]. It's been suggested that few genotype patterns might reflect selection for low-responder variants in the primary asymptomatic bacteriuria group, which might protect against severe UTI [69]. Previously, low TLR4 expression had mostly been attributed to tolerance and not to genetic variation affecting TLR4 expression. Recently, the first study proposing impact of TLR4 promoter genetic variants on TLR4 expression has been published [69]. The authors have shown that single and multiple SNPs mostly suppressed TLR4 promoter activity *in vitro*, especially in response to *E. coli* infection. They have also observed that TLR4 promoter sequence variations could influence clinical presentation of UTI.

Hawn et al. [70] suggested that TLR4 Asp299Gly polymorphism was associated with protection from recurrent UTI, but not pyelonephritis. Furthermore, they showed that TLR5 +1174 C/T polymorphism was associated with an increased risk of recurrent UTI but not pyelonephritis, while a polymorphism in TLR1, +1805 G/T, was associated with protection from pyelonephritis in women [70]. The study that included children with recurrent UTI did not reveal a significant difference in Asp299Gly genotypes of TLR4 between children with UTI and control group [71].

Another study showed a relationship between the carrier status of HSPA1B (heat shock 70 kDa protein 1B) +1267 G and TLR4 +896 G alleles and development of recurrent UTI in childhood, independently on other urinary tract abnormalities [72]. Study in adults revealed that TLR4 +896 G allele had higher prevalence in UTI patients than in controls, and that TLR4 expression in monocytes was significantly lower in chronic UTI patients than in APN patients or healthy controls [73].

2.5.4. Vascular Endothelial Growth Factor (VEGF) and Transforming Growth Factor-beta1 (TGF-β1)

Vascular endothelial growth factor (VEGF) is a potent mitogen that enhances angiogenesis, microvascular permeability and proliferation of vascular endothelial cells [74]. Expression of VEGF has been detected in glomerular podocytes, epithelial cells of distal tubules and collecting ducts of kidney. Neovascularization in scarred kidney tissue and significant increase of urine VEGF levels associated with increased severity of renal scarring have been reported [75-76]. Transforming growth factor-beta1 (TGF-β1) appears to be one of the key factors in process of tissue repair. It is involved in regulation of cell proliferation, differentiation, extracellular matrix production and immune response [77]. Studies suggested that TGF-β1 could be involved in pathogenesis of congenital obstructive uropathies and renal scarring [78].

Several polymorphisms in VEGF and TGF-β1 genes have been linked to overproduction of these proteins as well as predisposition to progressive renal disease [79-81]. The VEGF -460 T/C polymorphism and TGF-β1 polymorphisms, -800 G/A and -509 C/T, have been associated with UTI and VUR in children [82]. VEGF -460 CC genotype was significantly more frequent in children with UTI and VUR than in controls [82]. Presence of VEGF -460 C allele increased basal VEGF promoter activity by 71% compared to the wild-type sequence [83]. Both UTI and VUR groups showed a significant increase in frequencies of TGF-β1 -800 GG and -509 CC genotypes in comparison to controls [82]. Cotton et al. [81] observed a correlation between -800 GA genotype and low TGF-β1 production *in vitro* suggesting a protective role against renal scarring. However, there was no correlation between TGF-β1 -509 genotypes and protein production [81].

In the study of Yim et al. [82], the UTI group was subdivided into two subgroups according to presence of renal scars. Significantly increased frequency of TGF-β1 +869 CC genotype was found in the subgroup of patients positive for renal scarring [82]. A study of nephropathy resulted in an association of the +869 CC genotype with heavy proteinuria and a higher score of mesangial cell proliferation [84].

2.5.5. Angiotensin I-Converting Enzyme (ACE)

Angiotensin II (Ang II), a powerful effector peptide of the renin-angiotensin system (RAS), is now considered a growth factor that plays active roles in all phenomena characteristic for renal tissue damage such as: proliferation of cells, accumulation of extracellular matrix and mononuclear cells' recruitment [19,85-87]. Since local kidney and interstitial fluid levels of Ang II are higher than the circulating [87], a blockade of Ang II actions may provide protection against functional and structural kidney deterioration.

Angiotensin I-converting enzyme (ACE), representing a target for ACE inhibitors (ACEI), is the key enzyme of RAS system. An insertion/deletion (I/D) polymorphism resulting from the presence/absence of a 287 bp *Alu* sequence has been identified in intron 16 of ACE gene [88-89]. This polymorphic variation in ACE gene correlates with levels of both circulating

[88] and tissue-localized ACE [90] and DD genotype is found to be associated with the highest ACE levels.

Gene polymorphisms of the RAS, especially I/D polymorphism of ACE gene, were associated with development of renal scarring in patients with congenital urological abnormalities [91-95]. It was concluded that the DD genotype could be a genetic susceptibility factor contributing to renal parenchymal damage. In our previous study [96], we found a difference in ACE I/D genotypes' distribution in patients with bladder dysfunction according to presence/absence of renal scarring. Although the two groups of patients (with and without scarring) did not differ by conventional risk factors, significant increase of D allele frequency was present in patients with renal scarring [96]. Only few studies investigated effect of ACE I/D polymorphism on renal scarring following APN. In Korean children frequencies of ACE I/D genotypes and alleles were not different between renal scar-positive and scar-negative groups, irrespectively of VUR [97]. Another study in Greek population did not confirm a correlation between ACE DD genotype and renal scar formation in children with UTIs [98].

2.5.6. Meta-analysis of genetic susceptibility factors for renal scar formation following UTI

Recently, meta-analysis of candidate gene polymorphisms as genetic susceptibility factors for renal scars' formation following UTI has been performed [99]. After systematic analysis of previously published data, the authors made strict inclusion criteria for this meta-analysis. From 523 original citations they identified only 18 articles that met the inclusion criteria. The results of meta-analysis showed that, according to recessive model of inheritance, ACE I/D polymorphism was a significant risk factor for renal scarring although with a high degree of between-study variability. According to dominant model, the T allele of TGF-β1 -509 C/T polymorphism was related to increased susceptibility for renal scarring, again with a high degree of between-study variability [99].

The risk for renal scarring occurred in ACE DD genotype carriers [99]. This genotype was correlated with increased expression of renal ACE [100] and thus with increased production of Ang II. Ang II is a mediator of progressive renal failure [101] and it may induce expression of TGF-β1, which is involved in pathogenesis of renal scarring [78,102]. There was no correlation found between TGF-β1 -509 genotypes and TGF-β1 protein production [81]. Considering the results of current meta-analysis [99] and known effects of ACE I/D polymorphism [100], it is of interest to study the effects of TGF-β1 -509 C/T gene polymorphism on gene expression and TGF-β1 levels in renal tissue of UTI (APN) patients having renal scars.

3. Conclusions

The symptoms of urinary tract infections (UTIs) depend on localization of infection and magnitude of the host response to bacteria. There are many risk factors for UTIs such as gender, VUR, environmental and socio-economical factors and, as it is proposed and reviewed here, genetic risk factors. Hence, UTIs represent a classical example of multifactorial disease

combining gene-environment and probably gene-gene interactions. To date, association with UTIs has been studied through a candidate gene approach. Among the candidate genes are those that code for soluble mediators, receptors and adhesion molecules included in regulation of the host response upon UTI. There are two basic approaches in these genetic studies. The first approach, which is less common, involves investigation of the candidate genes' effects on UTI susceptibility only (case-control study design). The second, more common approach, is based on investigation of susceptibility to renal scarring as the most serious complication of UTI (case study design). The second approach has a greater clinical potential since the primary aim of such research is to identify the patients susceptible to progressive kidney damage, which often results in end-stage renal disease.

The field investigating genetic susceptibility to UTIs in humans started only a decade ago as we can see from the reviewed articles. The first evidence that susceptibility to APN as well as asymptomatic bacteriuria (ABU) could be inherited came only a few years ago [69,103]. As a consequence, limited number of studies has been performed. Most of these studies included children only, some of the rest included both children and adults, while others included adults only. This review is focused on studies in children. Besides the number of studies, another limitation of research in this field is the number of participants included in these studies. The majority of studies reviewed here had about 100 patients, only few had up to 250. In further analysis of study design we must notice dividing of patients' group in subgroups- those with APN and those with lower UTI, and further dividing of the APN subgroup according to presence/absence of renal scarring. These limitations must be minimized in order to improve the statistical power of studies. Nevertheless, the results so far support the hypothesis of genetic impact on susceptibility to UTI/APN and give a good reason for further research.

Among genes mostly investigated in susceptibility to UTIs are the cytokine family genes. Results suggest that IL-8 -251 A allele represents a risk factor for APN, after exclusion of patients with VUR [18]. Single base changes in IL-8 receptor (CXCR1) gene, +217 C/G and +2608 G/C, are associated with a risk for APN in both children and adults [56]. RANTES/CCL5 -403 G allele is susceptibility factor for UTI, irrespectively of VUR [57].

The effects of TLRs genes' polymorphisms are hard to summarize due to a large number of genes and polymorphisms in this family and a small number of homogenous studies. It is proposed that genetic variants in TLR4 promoter influence TLR4 expression as well as clinical presentation of UTI [69]. Probably the most intereting, recent findings are the results of the group from Lundt University. Children with ABU express less TLR4 than APN prone children or controls but do not carry structural gene mutations explaining this phenotype. They recently defined the eight TLR4 promoter sequence variants, forming 19 haplotypes and 29 genotype patterns. The ABU-associated genotypes reduced TLR4 expression and the response to infection [56, 69]. Host susceptibility to common infections like UTI may thus be strongly influenced by single gene modifications affecting the innate immune response. For example, genetic alterations that reduce TLR4 function are associated with ABU, while polymorphisms reducing IRF3 or CXCR1 expression are associated with acute pyelonephritis and an increased risk for renal scarring [104]. The TLR1 +1805 G/T polymorphism is shown

to protect against pyelonephritis in women [70]. It seems plausible to personalize the diagnosis and therapy of APN and ABU in the future, by combining information on bacterial virulence and the host response

To assess the genetic basis of renal scarring following UTI, many risk factors have to be analyzed. As we discussed, the heterogeneity between studies is large. Therefore, we may only point out to results of recent meta-analysis. The meta-analysis reveals that ACE I/D and TGF-β1 -509 C/T polymorphisms are risk factors for development of renal scars following UTI [99].

The most recent results strongly suggest the innate immunity as possible key factor for genetic susceptibility to APN and renal scarring after infection, although on murine models in which certan genes are functionaly similar to humans. It was shown that acute pyelonephritis and renal scarring are caused by dysfunctional innate immunity in mCxcr2 heterozygous mice [105].

Up to date no genome-wide association study has been done to use new approach for discovering novel genetic susceptibility factors for UTIs on a large number of individuals. New approaches to risk assasment and therapy shoud be encouraged and it is time for UTI to combine molecular medicine and social and behaviral factors. It is certain that some children are protected from APN and others prone to severe and recurent infections. Also, some of the gene polymorphisms are differentialy presented in those groups of children., The final aim is to identify the patients genetically susceptible to renal scarring and to discover and enable novel strategies in management of recurrent UTIs in order to prevent further renal damage especially in susceptible children. Until then, the prophylactic antibiotic treatment to prevent recurrent UTIs remains of limited usefulness [106].

Acknowledgement

This work is supported by Serbian Ministry of Education and Science Grant 175085.

Author details

Maja Zivkovic[1], Ljiljana Stojkovic[1], Brankica Spasojevic-Dimitrijeva[2], Mirjana Kostic[2] and Aleksandra Stankovic[1]

*Address all correspondence to: alexas@vinca.rs

1 Laboratory for Radiobiology and Molecular Genetics, “Vinca” Institute of Nuclear Sciences, University of Belgrade, Belgrade, Serbia

2 Nephrology Department, University Children’s Hospital, School of Medicine, University of Belgrade, Belgrade, Serbia

References

[1] Kunin C. Urinary Tract Infections: Detection, Prevention and Management. Baltimore: Lippincott Williams & Wilkins; 1997.

[2] Stamm WE, McKevitt M, Roberts PL, White NJ. Natural history of recurrent urinary tract infections in women. Reviews of Infectious Diseases 1991;13: 77-84. http://www.jstor.org/stable/4455768

[3] Hodson CJ, Maling TM, McManamon PJ, Lewis MG. The Pathogenesis of Reflux Nephropathy (Chronic Atrophic Pyelonephritis). British Journal of Radiology Supplement 1975;13 1-26.

[4] Ransley PG, Risdon RA. Reflux and Renal Scarring. British Journal of Radiology Supplement 1978;14 1-38.

[5] Hagberg L, Briles DE, Eden CS. Evidence for separate genetic defects in C3H/HeJ and C3HeB/FeJ mice, that affect susceptibility to gram-negative infections. Journal of Immunology 1985;134(6): 4118-22. http://www.jimmunol.org/content/134/6/4118.long

[6] Hang L, Frendeus B, Godaly G, Svanborg C. Interleukin-8 receptor knockout mice have subepithelial neutrophil entrapment and renal scarring following acute pyelonephritis. Journal of Infectious Diseases 2000;182(6): 1738-48. http://jid.oxfordjournals.org/content/182/6/1738.long

[7] Frendeus B, Godaly G, Hang L, Karpman D, Lundstedt AC, Svanborg C. Interleukin 8 receptor deficiency confers susceptibility to acute experimental pyelonephritis and may have a human counterpart. Journal of Experimental Medicine 2000;192(6): 881-90. http://jem.rupress.org/content/192/6/881.long

[8] Rushton HG. The evaluation of acute pyelonephritis and renal scarring with technetium 99m-dimercaptosuccinic acid renal scintigraphy: evolving concepts and future directions. Pediatric Nephrology 1997;11(1): 108-20. http://www.springerlink.com/content/1t6wlqm1gkrxyny3/

[9] Biggi A, Dardanelli L, Pomero G, Cussino P, Noello C, Sernia O, Spada A. Camuzzini G. Acute renal cortical scintigraphy in children with a first urinary tract infection. Pediatric Nephrology 2001;16(9): 733-8. http://www.springerlink.com/content/2m7tq3525ltwb97d/

[10] Gürgöze MK, Akarsu S, Yilmaz E, Gödekmerdan A, Akça Z, Ciftçi I, Aygün AD. Proinflammatory cytokines and procalcitonin in children with acute pyelonephritis. Pediatric Nephrology 2005;20(10): 1445-8. http://www.springerlink.com/content/q32254407676682n/

[11] Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. Annals of Epidemiology 2000;10(8): 509-15. http://www.annalsofepidemiology.org/article/S1047-2797(00)00072-7/fulltext

[12] Lambert H., Coulthard M. The Child with Urinary Tract Infection. In: Lambert H., Coulthard M. (3rd ed.) Clinical Paediatric Nephrology. Oxford: Oxford University Press; 2003. p197-225.

[13] Johnson JR. Virulence factors in Escherichia coli urinary tract infection. Clinical Microbiology Reviews 1991;4(1): 80-128. http://cmr.asm.org/content/4/1/80.long

[14] Lane MC, Alteri CJ, Smith SN, Mobley HL. Expression of flagella is coincident with uropathogenic Escherichia coli ascension to the upper urinary tract. Proceedings of the National Academy of Sciences of the United States of America 2007;104(42): 16669-74. http://www.pnas.org/content/104/42/16669.long

[15] Leffler H, Edén SC. Chemical identification of a glycosphingolipid receptor for Escherichia coli attaching to human urinary tract epithelial cells and agglutinating human erythrocytes. Federation of European Microbiological Societies Microbiology Letters 1980;8: 127-34. http://onlinelibrary.wiley.com/doi/10.1111/j.1574-6968.1980.tb05064.x/pdf

[16] Svensson M, Platt F, Frendeus B, Butters T, Dwek R, Svanborg C. Carbohydrate receptor depletion as an antimicrobial strategy for prevention of urinary tract infection. Journal of Infectious Diseases 2001;183(1): S70-3. http://jid.oxfordjournals.org/content/183/Supplement_1/S70.long

[17] Kassir K, Vargas-Shiraishi O, Zaldivar F, Berman M, Singh J, Arrieta A. Cytokine profiles of pediatric patients treated with antibiotics for pyelonephritis: potential therapeutic impact. Clinical and Vaccine Immunology 2001;8(6): 1060-3. http://cvi.asm.org/content/8/6/1060.long

[18] Artifoni L, Negrisolo S, Montini G, Zucchetta P, Molinari PP, Cassar W, Destro R, Anglani F, Rigamonti W, Zacchello G, Murer L. Interleukin-8 and CXCR1 receptor functional polymorphisms and susceptibility to acute pyelonephritis. Journal of Urology 2007;177(3): 1102-6. http://www.jurology.com/article/S0022-5347(06)02763-7/fulltext

[19] Klahr S, Schreiner G, Ichikawa I. The progression of renal disease. New England Journal of Medicine 1988;318(25): 1657-66. http://www.nejm.org/doi/full/10.1056/NEJM198806233182505

[20] Haraoka M, Hang L, Frendeus B, Godaly G, Burdick M, Strieter R, Svanborg C. Neutrophil recruitment and resistance to urinary tract infection. Journal of Infectious Diseases 1999;180(4): 1220-9. http://jid.oxfordjournals.org/content/180/4/1220.long

[21] Spasojević-Dimitrijeva B, Živković M, Stanković A, Stojković L, Kostić M. The IL-6 -174G/C polymorphism and renal scarring in children with first acute pyelonephritis. Pediatric Nephrology 2010;25(10): 2099-106. http://www.springerlink.com/content/fn0n1443032w4j14/

[22] Sheu JN, Chen MC, Chen SM, Chen SL, Chiou SY, Lue KH. Relationship between serum and urine interleukin-6 elevations and renal scarring in children with acute pye-

lonephritis. Scandinavian Journal of Urology and Nephrology 2009;43(2): 133-7. http://informahealthcare.com/doi/full/10.1080/00365590802478742

[23] Sheu JN, Chen MC, Cheng SL, Lee IC, Chen SM, Tsay GJ. Urine interleukin-1beta in children with acute pyelonephritis and renal scarring. Nephrology 2007;12(5): 487-93. http://onlinelibrary.wiley.com/doi/10.1111/j.1440-1797.2007.00819.x/full

[24] Faust WC, Diaz M, Pohl HG. Incidence of post-pyelonephritic renal scarring: a meta-analysis of the dimercapto-succinic acid literature. Journal of Urology 2009;181(1): 290-8. http://www.jurology.com/article/S0022-5347(08)02460-9/fulltext

[25] Stokland E, Hellstrom M, Jacobsson B, Jodal U, Sixt R. Renal damage one year after first urinary tract infection: role of dimercaptosuccinic acid scintigraphy. Journal of Pediatrics 1996;129(6): 815-20. http://www.jpeds.com/article/S0022-3476(96)70024-0/fulltext

[26] Lin DS, Huang SH, Lin CC, Tung YC, Huang TT, Chiu NC, Koa HA, Hung HY, Hsu CH, Hsieh WS, Yang DI, Huang FY. Urinary tract infection in febrile infants younger than eight weeks of Age. Pediatrics 2000;105(2): E20. http://pediatrics.aappublications.org/content/105/2/e20.long

[27] Jacobson SH, Hansson S, Jakobsson B. Vesico-ureteric reflux: occurrence and long-term risks. Acta Paediatrica Supplement 1999;88(431): 22-30. http://onlinelibrary.wiley.com/doi/10.1111/j.1651-2227.1999.tb01315.x/pdf

[28] Patzer L, Seeman T, Luck C, Wuhl E, Janda J, Misselwitz J. Day- and night-time blood pressure elevation in children with higher grades of renal scarring. Journal of Pediatrics 2003;142(2): 117-22. http://www.jpeds.com/article/S0022-3476(02)40215-6/fulltext

[29] Hodson CJ, Edwards D. Chronic pyelonephritis and vesico-ureteric reflex. Clinical Radiology 1960;11: 219-31. http://www.sciencedirect.com/science/article/pii/S0009926060800475

[30] Ransley PG, Risdon RA. Renal papillary morphology and intrarenal reflux in the young pig. Urological Research 1975;3(3): 105-9. https://springerlink3.metapress.com/content/76tx50l4104m205l/resource-secured/?target=fulltext.pdf&sid=2ufmjss-pu0cpf0s2zqqlkv3l&sh=www.springerlink.com

[31] Gordon I, Barkovics M, Pindoria S, Cole TJ, Woolf AS. Primary vesicoureteric reflux as a predictor of renal damage in children hospitalized with urinary tract infection: a systematic review and meta-analysis. Journal of the American Society of Nephrology 2003;14(3): 739-44. http://jasn.asnjournals.org/content/14/3/739.long

[32] Wheeler D, Vimalachandra D, Hodson EM, Roy LP, Smith G, Craig JC. Antibiotics and surgery for vesicoureteric reflux: a meta-analysis of randomised controlled trials. Archives of Disease in Childhood 2003;88(8): 688-94. http://adc.bmj.com/content/88/8/688.long

[33] Taskinen S, Ronnholm K. Post-pyelonephritic renal scars are not associated with vesicoureteral reflux in children. Journal of Urology 2005;173(4): 1345-8. http://www.jurology.com/article/S0022-5347(05)61098-1/fulltext

[34] Moorthy I, Easty M, McHugh K, Ridout D, Biassoni L, Gordon I. The presence of vesicoureteric reflux does not identify a population at risk for renal scarring following a first urinary tract infection. Archives of Disease in Childhood 2005;90(7): 733-6. http://adc.bmj.com/content/90/7/733.long

[35] Winberg J. Commentary: Progressive Renal Damage from Infection with or without Reflux. Journal of Urology 1992;148(5Pt2) 1733-1734.

[36] Preda I, Jodal U, Sixt R, Stokland E, Hansson S. Normal dimercaptosuccinic acid scintigraphy makes voiding cystourethrography unnecessary after urinary tract infection. Journal of Pediatrics 2007;151(6): 581-4. http://www.jpeds.com/article/S0022-3476(07)00457-X/fulltext

[37] Gleeson FV, Gordon I. Imaging in urinary tract infection. Archives of Disease in Childhood 1991;66(11): 1282-3. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1793291/pdf/archdisch00644-0022.pdf

[38] Rushton HG, Majd M, Jantausch B, Wiedermann BL, Belman AB. Renal Scarring Following Reflux and Nonreflux Pyelonephritis in Children: Evaluation with 99mTechnetium-Dimercaptosuccinic Acid Scintigraphy. Journal of Urology 1992;147(5) 1327-1332.

[39] Jakobsson B, Berg U, Svensson L. Renal scarring after acute pyelonephritis. Archives of Disease in Childhood 1994;70(2): 111-5. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1029711/

[40] Lee JH, Son CH, Lee MS, Park YS. Vesicoureteral reflux increases the risk of renal scars: a study of unilateral reflux. Pediatric nephrology 2006;21(9): 1281-4. https://springerlink3.metapress.com/content/k6670g573l638v10/resource-secured/?target=fulltext.html&sid=oqo3fxwy4viifcuku02qpzya&sh=www.springerlink.com

[41] Roberts JA, Domingue GJ, Martin LN, Kim JC. Immunology of pyelonephritis in the primate model: live versus heat-killed bacteria. Kidney International 1981;19(2): 297-305. http://www.nature.com/ki/journal/v19/n2/pdf/ki198120a.pdf

[42] Hull J, Ackerman H, Isles K, Usen S, Pinder M, Thomson A, Kwiatkowski D. Unusual haplotypic structure of IL8, a susceptibility locus for a common respiratory virus. American Journal of Human Genetics 2001;69(2): 413-9. http://www.sciencedirect.com/science/article/pii/S0002929707610866

[43] Abbas AK, Lichtman AH. Basic Immunology: Functions and Disorders of the Immune System. Philadelphia: WB Saunders; 2001.

[44] Glauser MP, Meylan P, Bille J. The inflammatory response and tissue damage. Pediatric Nephrology 1987;1(4): 615-22. https://springerlink3.metapress.com/content/

r160185l28762168/resource-secured/?target=fulltext.pdf&sid=oqo3fxwy4viifcu-ku02qpzya&sh=www.springerlink.com

[45] Brinkman BM, Giphart MJ, Verhoef A, Kaijzel EL, Naipal AM, Daha MR, Breedveld FC, Verweij CL. Tumor necrosis factor alpha-308 gene variants in relation to major histocompatibility complex alleles and Felty's syndrome. Hum Immunol. 1994;41(4): 259-66. http://www.sciencedirect.com/science/article/pii/0198885994900442

[46] Mayer FR, Messer G, Knabe W, Mempel W, Meurer M, Kolb HJ, Holler E. High Response of TNF Secretion in Vivo in Patients Undergoing BMT May be Associated with the 308 bp TNF-α Gene Enhancer Polymorphism. Bone Marrow Transplantation 1996;17 s101.

[47] Savvidou A, Bitsori M, Choumerianou DM, Karatzi M, Kalmanti M, Galanakis E. Polymorphisms of the TNF-alpha and ACE genes, and renal scarring in infants with urinary tract infection. Journal of Urology 2010;183(2): 684-7. http://www.jurology.com/article/S0022-5347(09)02666-4/fulltext

[48] Van-Snick J. Interleukin-6: an overview. Annual Review of Immunology 1990;8: 253-78. http://www.annualreviews.org/doi/pdf/10.1146/annurev.iy.08.040190.001345

[49] Curfs JH, Meis JF, Hoogkamp-Korstanje JA. A primer on cytokines: sources, receptors, effects, and inducers. Clinical Microbiology Reviews 1997;10(4): 742-80. http://cmr.asm.org/content/10/4/742.long

[50] Hedges S, Agace W, Svensson M, Sjogren AC, Ceska M, Svanborg C. Uroepithelial cells are part of a mucosal cytokine network. Infection and Immunity 1994;62(6): 2315-21. http://iai.asm.org/content/62/6/2315.long

[51] Roilides E, Papachristou F, Gioulekas E, Tsaparidou S, Karatzas N, Sotiriou J, Tsiouris J. Increased urine interleukin-6 concentrations correlate with pyelonephritic changes on 99mTc-dimercaptosuccinic acid scans in neonates with urinary tract infections. J Infect Dis. 1999;180(3): 904-7. http://jid.oxfordjournals.org/content/180/3/904.long

[52] Sheu JN, Chen MC, Lue KH, Cheng SL, Lee IC, Chen SM, Tsay GJ. Serum and urine levels of interleukin-6 and interleukin-8 in children with acute pyelonephritis. Cytokine 2006;36(5-6): 276-82. http://www.sciencedirect.com/science/article/pii/S1043466607000191

[53] Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, Woo P. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. Journal of Clinical Investigation 1998;102(7): 1369-76. http://www.jci.org/articles/view/2629/pdf

[54] Bennet AM, Prince JA, Fei GZ, Lyrenas L, Huang Y, Wiman B, Frostegard J, Faire U. Interleukin-6 serum levels and genotypes influence the risk for myocardial infarc-

tion. Atherosclerosis 2003;171(2): 359-67. http://www.atherosclerosis-journal.com/article/S0021-9150(03)00392-7/fulltext

[55] Brull DJ, Montgomery HE, Sanders J, Dhamrait S, Luong L, Rumley A, Lowe GD, Humphries SE. Interleukin-6 gene -174g>c and -572g>c promoter polymorphisms are strong predictors of plasma interleukin-6 levels after coronary artery bypass surgery. Arteriosclerosis Thrombosis and Vascular Biology 2001;21(9): 1458-63. http://atvb.ahajournals.org/content/21/9/1458.long

[56] Lundstedt AC, McCarthy S, Gustafsson MC, Godaly G, Jodal U, Karpman D, Leijonhufvud I, Lindén C, Martinell J, Ragnarsdottir B, Samuelsson M, Truedsson L, Andersson B, Svanborg C. A genetic basis of susceptibility to acute pyelonephritis. Public Library of Science One 2007;2(9): e825. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0000825

[57] Centi S, Negrisolo S, Stefanic A, Benetti E, Cassar W, Da Dalt L, Rigamonti W, Zucchetta P, Montini G, Murer L, Artifoni L. Upper urinary tract infections are associated with RANTES promoter polymorphism. Journal of Pediatrics 2010;157(6): 1038-40. http://www.jpeds.com/article/S0022-3476(10)00674-8/fulltext

[58] Springer TA. Leucocyte adhesion to cells. Scandinavian Journal of Immunology 1990;32(3): 211-2. http://onlinelibrary.wiley.com/doi/10.1111/j.1365-3083.1990.tb02912.x/pdf

[59] Adams DH, Shaw S. Leucocyte-endothelial interactions and regulation of leucocyte migration. Lancet 1994;343(8901): 831-6. http://www.sciencedirect.com/science/article/pii/S014067369492029X

[60] Ross R. Atherosclerosis--an inflammatory disease. New England Journal of Medicine 1999;340(2): 115-26. http://www.nejm.org/doi/full/10.1056/NEJM199901143400207

[61] Xu H, Gonzalo JA, St Pierre Y, Williams IR, Kupper TS, Cotran RS, Springer TA, Gutierrez-Ramos JC. Leukocytosis and resistance to septic shock in intercellular adhesion molecule 1-deficient mice. Journal of Experimental Medicine 1994;180(1): 95-109. http://jem.rupress.org/content/180/1/95.long

[62] Gbadegesin RA, Cotton SA, Watson CJ, Brenchley PE, Webb NJ. Association between ICAM-1 Gly-Arg polymorphism and renal parenchymal scarring following childhood urinary tract infection. International Journal of Immunogenetics 2006;33(1): 49-53. http://onlinelibrary.wiley.com/doi/10.1111/j.1744-313X.2006.00565.x/full

[63] Poltorak A, He X, Smirnova I, Liu MY, Van Huffel C, Du X, Birdwell D, Alejos E, Silva M, Galanos C, Freudenberg M, Ricciardi-Castagnoli P, Layton B, Beutler B. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. Science 1998;282(5396): 2085-8. http://www.sciencemag.org/content/282/5396/2085.full

[64] Iwasaki A, Medzhitov R. Toll-like receptor control of the adaptive immune responses. Nature Immunology 2004;5(10): 987-95. http://www.nature.com/ni/journal/v5/n10/full/ni1112.html

[65] Uematsu S, Akira S. Toll-like receptors and innate immunity. Journal of Molecular Medicine 2006;84(9): 712-25. https://springerlink3.metapress.com/content/l417556q5676u813/resource-secured/?target=fulltext.html&sid=jr1xcyn1vkolv5wazvustjnm&sh=www.springerlink.com

[66] Beutler B. Microbe sensing, positive feedback loops, and the pathogenesis of inflammatory diseases. Immunological Reviews 2009;227(1): 248-63. http://onlinelibrary.wiley.com/doi/10.1111/j.1600-065X.2008.00733.x/full

[67] Li X, Qin J. Modulation of Toll-interleukin 1 receptor mediated signaling. Journal of Molecular Medicine 2005;83(4): 258-66. https://springerlink3.metapress.com/content/eqb6dp9rcvqcfd62/resource-secured/?target=fulltext.html&sid=jr1xcyn1vkolv5wazvustjnm&sh=www.springerlink.com

[68] Smirnova I, Hamblin MT, McBride C, Beutler B, Di Rienzo A. Excess of rare amino acid polymorphisms in the Toll-like receptor 4 in humans. Genetics 2001;158(4): 1657-64. http://www.genetics.org/content/158/4/1657.long

[69] Ragnarsdottir B, Jonsson K, Urbano A, Gronberg-Hernandez J, Lutay N, Tammi M, Gustafsson M, Lundstedt AC, Leijonhufvud I, Karpman D, Wullt B, Truedsson L, Jodal U, Andersson B, Svanborg C. Toll-like receptor 4 promoter polymorphisms: common TLR4 variants may protect against severe urinary tract infection. Public Library of Science One. 2010;5(5): e10734. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0010734

[70] Hawn TR, Scholes D, Li SS, Wang H, Yang Y, Roberts PL, Stapleton AE, Janer M, Aderem A, Stamm WE, Zhao LP, Hooton TM. Toll-like receptor polymorphisms and susceptibility to urinary tract infections in adult women. Public Library of Science One 2009;4(6): e5990. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0005990

[71] Ertan P, Berdeli A, Yilmaz O, Gonulal DA, Yuksel H. LY96, UPKIB mutations and TLR4, CD14, MBL polymorphisms in children with urinary tract infection. Indian Journal of Pediatrics 2011;78(10): 1229-33. https://springerlink3.metapress.com/content/22300gq91150v807/resource-secured/?target=fulltext.html&sid=jr1xcyn1vkolv5wazvustjnm&sh=www.springerlink.com

[72] Karoly E, Fekete A, Banki NF, Szebeni B, Vannay A, Szabo AJ, Tulassay T, Reusz GS. Heat shock protein 72 (HSPA1B) gene polymorphism and Toll-like receptor (TLR) 4 mutation are associated with increased risk of urinary tract infection in children. Pediatric Research 2007;61(3): 371-4. http://www.nature.com/pr/journal/v61/n3/full/pr200773a.html

[73] Yin X, Hou T, Liu Y, Chen J, Yao Z, Ma C, Yang L, Wei L. Association of Toll-like receptor 4 gene polymorphism and expression with urinary tract infection types in

adults. Public Library of Science One 2010;5(12): e14223. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0014223

[74] Ferrara N, Chen H, Davis-Smyth T, Gerber HP, Nguyen TN, Peers D, Chisholm V, Hillan KJ, Schwall RH. Vascular endothelial growth factor is essential for corpus luteum angiogenesis. Nature Medicine 1998;4(3): 336-40. http://www.nature.com/nm/journal/v4/n3/pdf/nm0398-336.pdf

[75] Konda R, Sato H, Sakai K, Sato M, Orikasa S, Kimura N. Expression of platelet-derived endothelial cell growth factor and its potential role in up-regulation of angiogenesis in scarred kidneys secondary to urinary tract diseases. American Journal of Pathology 1999;155(5): 1587-97. http://linkinghub.elsevier.com/retrieve/pii/S0002-9440(10)65475-2

[76] Konda R, Sato H, Sakai K, Abe Y, Fujioka T. Urinary excretion of vascular endothelial growth factor is increased in children with reflux nephropathy. Nephron Clinical Practice 2004;98(3): c73-8. http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowFulltext&ArtikelNr=000080676&Ausgabe=230425&ProduktNr=228539

[77] Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. New England Journal of Medicine 1994;331(19): 1286-92. http://www.nejm.org/doi/full/10.1056/NEJM199411103311907

[78] MacRae Dell K, Hoffman BB, Leonard MB, Ziyadeh FN, Schulman SL. Increased urinary transforming growth factor-beta(1) excretion in children with posterior urethral valves. Urology 2000;56(2): 311-4. http://www.goldjournal.net/article/S0090-4295(00)00591-4/fulltext

[79] Watson CJ, Webb NJ, Bottomley MJ, Brenchley PE. Identification of polymorphisms within the vascular endothelial growth factor (VEGF) gene: correlation with variation in VEGF protein production. Cytokine 2000;12(8): 1232-5. http://www.sciencedirect.com/science/article/pii/S1043466600906926

[80] Summers AM, Coupes BM, Brennan MF, Ralph SA, Short CD, Brenchley PE. VEGF -460 genotype plays an important role in progression to chronic kidney disease stage 5. Nephrology Dialysis Transplantation 2005;20(11): 2427-32. http://ndt.oxfordjournals.org/content/20/11/2427.long

[81] Cotton SA, Gbadegesin RA, Williams S, Brenchley PE, Webb NJ. Role of TGF-beta1 in renal parenchymal scarring following childhood urinary tract infection. Kidney International 2002;61(1): 61-7. http://www.nature.com/ki/journal/v61/n1/full/4492704a.html

[82] Yim HE, Bae IS, Yoo KH, Hong YS, Lee JW. Genetic control of VEGF and TGF-beta1 gene polymorphisms in childhood urinary tract infection and vesicoureteral reflux. Pediatric Research 2007;62(2): 183-7. http://www.nature.com/pr/journal/v62/n2/full/pr2007196a.html

[83] Stevens A, Soden J, Brenchley PE, Ralph S, Ray DW. Haplotype analysis of the polymorphic human vascular endothelial growth factor gene promoter. Cancer Research 2003;63(4): 812-6. http://cancerres.aacrjournals.org/content/63/4/812.long

[84] Sato F, Narita I, Goto S, Kondo D, Saito N, Ajiro J, Saga D, Ogawa A, Kadomura M, Akiyama F, Kaneko Y, Ueno M, Sakatsume M, Gejyo F. Transforming growth factor-beta1 gene polymorphism modifies the histological and clinical manifestations in Japanese patients with IgA nephropathy. Tissue Antigens 2004;64(1): 35-42. http://onlinelibrary.wiley.com/doi/10.1111/j.1399-0039.2004.00256.x/full

[85] Wolf G, Neilson EG. Angiotensin II as a renal growth factor. Journal of the American Society of Nephrology. 1993;3(9): 1531-40. http://jasn.asnjournals.org/content/3/9/1531.long

[86] Ruiz-Ortega M, Lorenzo O, Egido J. Angiotensin III up-regulates genes involved in kidney damage in mesangial cells and renal interstitial fibroblasts. Kidney International Supplement 1998;68: S41-5. http://www.nature.com/ki/journal/v54/n68s/full/4490546a.html

[87] Navar LG, Imig JD, Zou L, Wang CT. Intrarenal Production of Angiotensin II. Seminars in Nephrology 1997;17(5) 412-422.

[88] Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. Journal of Clinical Investigation 1990;86(4): 1343-6. http://www.jci.org/articles/view/114844

[89] Rigat B, Hubert C, Corvol P, Soubrier F. PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme gene (DCP1) (dipeptidyl carboxypeptidase 1). Nucleic Acids Research 1992;20(6): 1433. http://nar.oxfordjournals.org/content/20/6/1433.2.long

[90] Costerousse O, Allegrini J, Lopez M, Alhenc-Gelas F. Angiotensin I-converting enzyme in human circulating mononuclear cells: genetic polymorphism of expression in T-lymphocytes. Biochemical Journal 1993;290(1): 33-40. http://www.biochemj.org/bj/290/0033/2900033.pdf

[91] Hohenfellner K, Hunley TE, Brezinska R, Brodhag P, Shyr Y, Brenner W, Habermehl P, Kon V. ACE I/D gene polymorphism predicts renal damage in congenital uropathies. Pediatric Nephrology 1999;13(6): 514-8. https://springerlink3.metapress.com/content/jeqch0uu051pepu2/resource-secured/?target=fulltext.pdf&sid=hy1eoamsowpup4dwlzp21ept&sh=www.springerlink.com

[92] Al-Eisa A, Haider MZ, Srivastva BS. Angiotensin-converting enzyme gene insertion/deletion polymorphism and renal damage in childhood uropathies. Pediatrics International 2000;42(4): 348-53. http://onlinelibrary.wiley.com/doi/10.1046/j.1442-200x.2000.01242.x/full

[93] Haszon I, Friedman AL, Papp F, Bereczki C, Baji S, Bodrogi T, Karoly E, Endreffy E, Turi S. ACE gene polymorphism and renal scarring in primary vesicoureteric reflux. Pediatric Nephrology 2002;17(12): 1027-31. https://springerlink3.metapress.com/content/hf4xddgql6luh7yq/resource-secured/?target=fulltext.html&sid=hy1eoamsowpup4dwlzp21ept&sh=www.springerlink.com

[94] Brock JW, 3rd, Adams M, Hunley T, Wada A, Trusler L, Kon V. Potential risk factors associated with progressive renal damage in childhood urological diseases: the role of angiotensin-converting enzyme gene polymorphism. Journal of Urology 1997;158(3 Pt 2): 1308-11. http://www.jurology.com/article/S0022-5347(01)64463-X/fulltext

[95] Ozen S, Alikasifoglu M, Saatci U, Bakkaloglu A, Besbas N, Kara N, Kocak H, Erbas B, Unsal I, Tuncbilek E. Implications of certain genetic polymorphisms in scarring in vesicoureteric reflux: importance of ACE polymorphism. American Journal of Kidney Diseases 1999;34(1): 140-5. http://www.sciencedirect.com/science/article/pii/S0272638699701204

[96] Kostić M, Stanković A, Živković M, Peco-Antić A, Jovanović O, Alavantić D, Kruscić D. ACE and AT1 receptor gene polymorphisms and renal scarring in urinary bladder dysfunction. Pediatric Nephrology 2004;19(8): 853-7. https://springerlink3.metapress.com/content/m0ln12arkyj52q0u/resource-secured/?target=fulltext.html&sid=5xlg00ojhmffszjl3yidz4up&sh=www.springerlink.com

[97] Cho SJ, Lee SJ. ACE gene polymorphism and renal scar in children with acute pyelonephritis. Pediatric Nephrology 2002;17(7): 491-5. https://springerlink3.metapress.com/content/wmr2ua8atbqqchg2/resource-secured/?target=fulltext.html&sid=5xlg00ojhmffszjl3yidz4up&sh=www.springerlink.com

[98] Sekerli E, Katsanidis D, Vavatsi N, Makedou A, Gatzola M. ACE gene insertion/deletion polymorphism and renal scarring in children with urinary tract infections. Pediatric Nephrology 2009;24(10): 1975-80. https://springerlink3.metapress.com/content/lw40768164675386/resource-secured/?target=fulltext.html&sid=5xlg00ojhmffszjl3yidz4up&sh=www.springerlink.com

[99] Zaffanello M, Tardivo S, Cataldi L, Fanos V, Biban P, Malerba G. Genetic susceptibility to renal scar formation after urinary tract infection: a systematic review and meta-analysis of candidate gene polymorphisms. Pediatric Nephrology 2011;26(7): 1017-29. https://springerlink3.metapress.com/content/2357371735545q41/resource-secured/?target=fulltext.html&sid=5xlg00ojhmffszjl3yidz4up&sh=www.springerlink.com

[100] Mizuiri S, Hemmi H, Kumanomidou H, Iwamoto M, Miyagi M, Sakai K, Aikawa A, Ohara T, Yamada K, Shimatake H, Hasegawa A. Angiotensin-converting enzyme (ACE) I/D genotype and renal ACE gene expression. Kidney International 2001;60(3): 1124-30. http://www.nature.com/ki/journal/v60/n3/full/4492521a.html

[101] Ishidoya S, Morrissey J, McCracken R, Reyes A, Klahr S. Angiotensin II receptor antagonist ameliorates renal tubulointerstitial fibrosis caused by unilateral ureteral ob-

struction. Kidney International 1995;47(5): 1285-94. http://www.nature.com/ki/journal/v47/n5/pdf/ki1995183a.pdf

[102] Pimentel JL, Sundell CL, Wang S, Kopp JB, Montero A, Martinez-Maldonado M. Role of angiotensin II in the expression and regulation of transforming growth factor-beta in obstructive nephropathy. Kidney International 1995;48(4): 1233-46. http://www.nature.com/ki/journal/v48/n4/pdf/ki1995407a.pdf

[103] Lundstedt AC, Leijonhufvud I, Ragnarsdottir B, Karpman D, Andersson B, Svanborg C. Inherited susceptibility to acute pyelonephritis: a family study of urinary tract infection. Journal of Infectious Diseases 2007;195(8): 1227-34. http://jid.oxfordjournals.org/content/195/8/1227.long

[104] Ragnarsdóttir B, Svanborg C. Susceptibility to acute pyelonephritis or asymptomatic bacteriuria: Host-pathogen interaction in urinary tract infections. Pediatric Nephrology 2012; DOI 10.1007/s00467-011-2089-1 http://www.springerlink.com/content/e311x5gx674hv8h8/fulltext.html

[105] Svensson M, Yadav M, Holmqvist B, Lutay N, Svanborg C, Godaly G. Acute pyelonephritis and renal scarring are caused by dysfunctional innate immunity in mCxcr2 heterozygous mice. Kidney International 2011;80(10): 1064-72. http://www.nature.com/ki/journal/v80/n10/full/ki2011257a.html

[106] Williams G, Craig JC. Prevention of recurrent urinary tract infection in children. Current Opinion in Infectious Diseases 2009;22(1): 72-6. http://journals.lww.com/co-infectiousdiseases/Abstract/2009/02000/Prevention_of_recurrent_urinary_tract_infection_in.12.aspx

IntechOpen