論　文　内　容　要　旨

Fc-Gamma Receptor 3A Polymorphism Predicts the Incidence of Urinary Tract Infection in Kidney-Transplant Recipients

（Fcγ 受容体 3A の遺伝子多型により腎移植後の尿路感染症を予測できる）

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主指導教員：大段　秀樹教授
（医歯薬保健学研究科 消化器・移植外科学）
副指導教員：茶山　一彰教授
（医歯薬保健学研究科 消化器・代謝内科学）
副指導教員：田中　友加准教授
（医歯薬保健学研究科 消化器・移植外科学）

Lalit Kumar Das

（医歯薬保健学研究科　医歯薬学専攻）

Despite the improvement of antibiotics prophylaxis, surgical technique, and immunosuppressive regimen following kidney transplantation (KT), urinary tract infections (UTIs) remain the most common infectious complication that can substantially interfere with the patients' quality of life. Studies within the last decade have reported the incidence of UTIs ranging from 25% to 75%, which varies widely likely due to differences in definition, diagnostic criteria, study design, and length of observation]. It has been reported that female sex, older age of the recipient, acute rejection episodes, and cadaveric donor were associated with higher risks of UTI. In patients with such an immunologically impaired condition, components of the adaptive cellular immunity are significantly reduced; however, innate components and humoral factors with probable defense mechanism remain relatively stable.

We have recently proven that the Fc gamma receptor (FcγR) single-nucleotide polymorphisms (SNPs) in liver transplant recipients were greatly associated with the susceptibility to post-transplant bloodstream infection. In the current study, we investigated the impact of SNPs in *C1QA* [276 A/G], *FCGR2A* [131 H/R], and *FCGR3A* [158 F/V] genes on the development of infectious complications after KT.

The SNPs of *C1QA* [276 A/G], *FCGR2A* [131 H/R], and *FCGR3A* [158 F/V], genes encoding the FcγR, were analyzed in 81 KT recipients in relation to the occurrences of postoperative infectious complications within 30 days after KT. Among all subjects, 31 (38.3 %) recipients experienced UTI episode within 1 month after KT. The median time to the first UTI episode was 13 days (range: 5–29 days). We did not observe any statistical difference in any other baseline characteristics in the KT recipients with and without UTI episodes in our cohort, except for sex. Only the female sex presented as a significant risk factor for the incidence of UTI ($p = 0.013$). The frequencies of each *C1QA* [276 A/G] (rs172378), *FCGR2A* [131 H/R] (rs1801274) and *FCGR3A* [158 F/V] (rs396991) genotype were compared with respect to post-operative outcomes (including UTIs) within 1 month after KT. There were no differences in the incidence of CMV infections or fungal infections among all 3 genotype within 1 month after KT. Notably, only the *FCGR3A* genotype was significantly associated with the incidence of UTI within 1 month of transplantation where *FCGR3A* [158 F/F or F/V] had more incidences of UTI than *FCGR3A* [158 V/V] (64.5% and 35.5%, respectively) ($p = 0.02$). Upon the univariate analysis of the baseline characteristic,

female sex and the *FCGR3A* SNP were identified as significant risk factors for UTI. The multivariate logistic regression analysis also identified those two independent factors that contributed significantly to the differences between the patients with and without UTI episodes within 1 month of transplantation (OR 3.53 [confidence interval (CI): 1.34–9.81], p = 0.009, and OR 3.26 [CI: 1.24–9.08], p = 0.015, respectively).

As FcγR classes differ on the affinity for IgG subclasses and on the distribution among the immune cells, the combination of *FCGR2A* and *FCGR3A* SNPs probably can stratify the incidence of UTI. Notably, we observed that the combination of the [158 V/V] genotype of *FCGR3A* along with the [131 R/R or H/R] genotype of *FCGR2A* showed a significantly lower incidence of UTI than the [158 F/F or F/V] genotype of *FCGR3A* and [131 H/H] genotype of *FCGR2A* (3/13, 23%: 16/27, 59%; p = 0.049).

Next, we adjusted the differences in the baseline characteristics by using the propensity scores and further examined the impact of *FCGR3A* SNP on post-transplant infectious complications within 1 month. Five variables, including sex, ABO-blood type (ABO-compatible [ABO-C] and ABO-I), recipient and donor age, and treatment as dialysis and non-dialysis were used to calculate the propensity score of each patient. Twenty-six patients with the *FCGR3A* [158 V/V] genotype were matched with same number of patients with the *FCGR3A* [158 F/F or F/V] genotype. Among this one-to-one matched cohort, a significantly higher incidence of UTI was found in the patients with the *FCGR3A* [158 F/F or F/V] genotype than those with the *FCGR3A* [158 V/V] genotype (p = 0.004). No statistical differences were observed with respect to the incidence of CMV or fungal infections between those variants. Therefore, the *FCGR3A* F carrier may contribute to be the foremost risk factor for the occurrence of postoperative UTI within 1 month following KT.

In conclusion, the *FCGR3A* gene SNP in KT recipients was significantly associated with the susceptibility to post-transplant UTI. This fact suggests that the immunosuppression therapy and antimicrobial surveillance can be adjusted by identifying the FcγR SNPs, leading to personalized medicine.