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Identification of urinary mRNA expression for diagnosing acute rejection by meta-analysis of gene expression in kidney transplantation

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Background: Accumulated microarray data on kidney transplantation patients is a powerful source for identifying potential targets to diagnose and predict acute rejection (AR) in kidney transplanted patients (KTPs). In this study, we performed a meta-analysis of gene expression profiles of stable graft function (STA) and AR from biopsy tissues in kidney transplantation and investigated expressions of candidate genes selected from meta-analysis in urinary cells of KTPs.

Methods: The microarray data were obtained from the public repositories. Meta-analysis were conducted by 664 STA and 272 AR patients, with a total of 954 samples. 10 candidate genes selected after meta-analysis and 5 genes suggested as biomarker of AR from published articles were identified in urinary cells of KTPs. 120 urine samples (23 stable, 34 acute cellular rejection (ACR), and 17 acute antibody-mediated rejection (AMR), 23 long-term graft survival (LGS), 17 chronic antibody-mediated rejection (CAMR), and 6 tolerance (Tol)) were collected after transplantation. The expression levels of transcripts were determined in urinary cells using real-time PCR. The expression levels represented \log_{10} transformations of $2^{-\Delta\Delta C_T}$ target gene values.

Results: Meta-analysis identified 10 genes up-expressed in AR, including CXCL9, PSMB9, INPP5D, LCK, ISG, RUNX3, IDO1, PTPRC and C1QB. 5 genes (CD3 ϵ , IP-10, Tim-3, Foxp3, and 18S rRNA) were selected from published articles. Out of the 120 urine samples, 104 samples (87%) passed quality control with copy numbers of 18S rRNA and TGF- β 1 and 16 did not. We determined expression levels of mRNA isolated from urinary cells with 14 candidates. Among AR candidates the expression levels of 6 target genes in patients with acute rejection were significantly higher than in those with stable graft function.

Conclusion: Our results in meta-analysis of 954 microarray samples on the kidney transplantation identified 9 candidate genes and searched 5 genes through published articles. 6 among 14 genes were

significantly up-expressed in AR group. However, further to improve AR diagnostic accuracy independent validation of these identified genes is required in a larger cohort prior to clinical application.

Keywords: Acute rejection, Kidney transplantation, Urinary mRNA