Plasma proteomics study on pharmacokinetic variability of tacrolimus in liver transplant recipients

Zhu HJ, Wang M, Yang N, Zhang TQ, Du Y, Li DY

Department of Pharmacy, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, China

Background: Tacrolimus is the cornerstone immunosuppressant for liver transplantation, characterized by significant interindividual and intraindividual pharmacokinetic variability and a narrow therapeutic window. Therapeutic drug monitoring (TDM) is essential for assessing drug exposure and tailoring doses. However, dose adjustments based on TDM face challenges due to numerous factors influencing tacrolimus disposition. Proteomics, by identifying endogenous proteins associated with the pharmacokinetics of tacrolimus, offers new insights into optimization of tacrolimus dose in liver transplant recipients

Methods: This study included adult liver transplant recipients receiving tacrolimus-based regimes and dose adjustment by TDM. Trough concentrations were measured using enzyme multiplied immunoassay technique in whole blood. An untargeted proteomics analysis was conducted on plasma samples after depletion of high-abundance proteins and iTRAQ® labeling. The phenotype for tacrolimus pharmacokinetics, C0/D (dose-adjusted trough concentration), was calculated. Samples were categorized into high and low C0/D groups for matched and unmatched analysis, identifying significantly differential proteins. Enrichment analysis was performed by g:Profiler. Linear mixed model was used to evaluate the significance of the most promising protein in an independent group by enzyme linked immunosorbent assay.

Results: Fourteen samples were assayed in two batches with 453 and 495 proteins were identified respectively, resulting to 358 shared proteins in subsequent analysis. Unmatched analysis included five samples in high and low C0/D group each, and 14 proteins were shown significance with fold change greater than 1.2 or lower than 0.8. As to matched analysis, eight samples from four recipients were compared and 13 proteins were found to be significantly different. Low-density lipoprotein receptor-related protein 1 (LRP1), basement membrane-specific heparan sulfate proteoglycan core protein (PGBM) and macrophage receptor (MARCO) were consistent in both matched and unmatched analysis. Enrichment analysis highlighted their roles in sterol transport, secretion by cells and carbohydrate metabolic process and so on. Finally, LRP1 was validated in 116 samples of 59 recipients, confirming its association with $\log_2$C0/D (β = -6.607, SE = 2.805, z = -2.36, P = 0.018).

Conclusions: The study underscores the association of 24 proteins, particularly LRP1, PGBM, and MARCO, with tacrolimus C0/D in liver transplant recipients.

Key Words: proteomics, tacrolimus, therapeutic drug monitoring, pharmacokinetics, liver transplantation