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Monther Al sultan  
Virginia Commonwealth University

Daniel Contaifer Jr.

Joshua Morriss

See next page for additional authors

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Authors
Monther Al sultan, Daniel Contaifer Jr., Joshua Morriss, Suad Alshammari, Jeffrey Stern, Sindhura Bobba, Pamela Kimball, Anne King, Dhiren Kumar, Marlon Levy, Gaurav Gupta, and Dayanjan Wijesinghe

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A Pre-transplant Blood-based Lipid Signature for Prediction of Antibody-mediated Rejection in Kidney Transplant Patients

Monther Al sultan1, Daniel Contaifer Jr1, Joshua Morris2, Suad Alshammar3, Jeffrey Stern3, Sridhara Bobba5, Pamela Kimball5, Anne King2, Dhiren Kumar2, Marlon Levy2, Gaurav Gupta2, Dayanjan Wijesinghe4,5

1School of Pharmacy, Virginia Commonwealth University, Richmond, United States. 2Division of Nephrology, School of Medicine, Virginia Commonwealth University, Richmond, United States. 3Department of Surgery, School of Medicine, Virginia Commonwealth University, Richmond, United States. 4Laboratory of Pharmacometabolomics (LPMD), VCU School of Pharmacy, Richmond VA 23224. 5Du Voici Center, Virginia Commonwealth University, Richmond VA 23284

Introduction

The complex biochemistry of human biological systems has been operationally broken down into a set of large molecular categories. The metabolome, as it is termed, includes four classes of biologically active molecules including lipids. Lipids are an integral structural component of cell membranes, play a significant role in energy storage, and are involved in a variety of signaling pathways and interact with other classes of compounds in the metabolome. The lipidome has the ability to influence membrane mediated events. Distinguished lipid profiles have been identified in normal and pathologic conditions, and in response to specific therapeutic interventions. One such intervention is renal transplantation, the treatment of choice for End Stage Renal Disease (ESRD). In the United States, a shortage of suitable organ donors, and resultant organs, creates a marked supply and demand discrepancy leaving many patients on the waiting list for prolonged periods of time.

Current immunosuppression protocols result in a substantial decrease in T-cell mediated rejection at the cost of long term immunosuppression, with its resultant adverse effects including opportunistic infections, graft damage, and metabolic complications. Additionally, these protocols do not have a significant effect on suppressing antibody mediated rejection (AMR), a major cause of graft loss. Management of immunosuppression for individual patients is currently generalized based on protocols. Presently available biomarkers like donor-specific antibodies and degree of sensitization have proven to be inadequate to predict rejection. Thus, there is an unmet need for biomarkers which could allow for better risk stratification to enhance the benefit and limit the risk of the immunosuppression therapy for individual patients. Results

The study population consisted of 16 consecutive patients who developed antibody-mediated rejection within 2 years of kidney transplant and 29 stable control (SC) patients who did not develop rejection at any point of post-transplant follow-up. Serial plasma samples are collected and stored at Time 1 (T1 - pre-transplant), Month 6 (T2) and Month 12 (T3) and then yearly for all patient’s post-transplant as part of an IRB approved biobank protocol at our institution. Individual biopsies were performed for acute allograft dysfunction defined as a rise in creatinine >20% above baseline, serum creatinine nadir <22.0 mg/dL post-transplant, or delayed graft function >21 days post-transplant. Surveillance biopsies were performed in patients with a positive flow-cytometric crossmatch (T or B >100 mean channel shifts) and/or presence of pre-formed donor-specific antibody (DSA) >5000 mean fluorescent intensity (MFI) at 1 month and 6-month post-transplant. Biopsies were graded based upon the Banff criteria. Patients with AMR and SC patients were followed serially with plasma samples collected up to 2 years post-transplant. For the purposes of this study, we defined a renal allograft biopsy as meeting criteria for antibody-mediated rejection according to the Banff criteria. DSA+ patients were included to assess whether the lipid model is capable of stratifying patients at time of transplant.

We performed each patient’s plasma sample lipidomics screening by using liquid chromatography coupled to high resolution mass spectrometry (LC-HRMS). The lipidomic datasets were then analyzed using XCMS-Server, an R-package to create metabolite profiles. The data was used to represent lipid classes and identify differentially expressed lipids between the AMR and control groups (Figure 1). We performed the independent cross-validation in the AMR and SC groups to determine the lipid model’s robust prediction accuracy. Figure 2 shows the Relationships Between a) the proportion of the blood plasma lipids and the predictor variables, b) the area under the curve (AUC) of different convergence criteria for the sets of the blood plasma lipids and the predictor variables, and c) the receiver operating characteristic (ROC) curves of different convergence criteria for the sets of the blood plasma lipids and the predictor variables. Our study for the first time, identify the lipid differences pre- and post-transplant. Additionally, we identify a pre-transplant lipid signature that distinguishes kidney transplant patients with favorable transplant outcomes (SC) and a major form of non-favorable transplant outcomes (AMR). We further demonstrate that unlike SC patients that demonstrate a dynamic longitudinal lipid change, AMR patients maintain a relatively unchanging lipid profile over time. These findings were validated by the measured lipids. Finally, we identify a pre-transplant lipid signature that predicts the potential for onset of AMR. Following validation in a larger cohort, these findings have the potential to alter the current paradigm of post-transplant monitoring and treatment of these patients via an evidence based risk stratification strategy and thereby vastly improving the success of kidney transplantation.