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Data in Brief

A pathogenesis-based transcript signature in donor-specific antibody-positive kidney transplant patients with normal biopsies

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ABSTRACT

Affymetrix Human Gene 1.0-ST arrays were used to assess the gene expression profiles of kidney transplant patients who presented with donor-specific antibodies (DSAs) but showed normal biopsy histopathology and did not develop antibody-mediated rejection (AMR). Biopsy and whole-blood profiles for these DSA-positive, AMR-negative (DSA+/AMR−) patients were compared to both DSA-positive, AMR-positive (DSA+/AMR+) patients as well as DSA-negative (DSA−) controls. While individual gene expression changes across sample groups were relatively subtle, gene-set enrichment analysis using previously identified pathogenesis-based transcripts (PBTs) identified a clear molecular signature involving increased rejection-associated transcripts in AMR− patients. Results from this study have been published in Kidney International (Hayde et al., 2014 [1]) and the associated data have been deposited in the GEO archive and are accessible via the following link: http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE50084

Specifications	
Organism/cell line/tissue	Homo sapiens
Strain(s)	Patient biopsies and whole-blood samples
Sequencer or array type	Affymetrix HuGene 1.0-ST array
Data format	CEL files
Experimental factors	Presence of donor-specific antibodies with normal biopsy histopathology
Consent	All samples included were from patients enrolled in an Institutional Review Board-approved 'Immune Monitoring Study'

Direct link to deposited data

Deposited data can be found here: http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE50084.

Introduction

Antibody-mediated rejection (AMR) is the major cause of late kidney transplant failure [2,3]. While some patients presenting with donor-specific anti-human leukocyte antigen (HLA) antibodies (DSAs) develop either chronic or acute AMR and ultimately reject their allograft, others maintain stable functioning allografts and continue to demonstrate normal biopsy histopathologies. In this study [1], we sought to determine if any differences in gene expression between DSA+/AMR+ patients, DSA+/AMR− patients, and DSA− controls might explain this phenomenon.

Study population

The study population consisted of 263 patients who underwent anti-HLA antibody testing at the time of biopsy for worsening kidney function and/or proteinuria. Antibody presence was detected using Luminex HLA Single Antigen Bead assays (LABScreen, One Lambda, Canoga Park, CA) with a mean fluorescence intensity (MFI) >= 1000 used as a cutoff for identification of DSA+ patients. Demographic and clinical characteristics, as well as Banff histopathology scores [4] for these patients are shown in Table 1. From this larger

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Table 1
Study population. Data are reported as proportions, median (interquartile range), or mean (s.d.) as appropriate; statistical differences were determined using ANOVA for continuous variables and Fisher's exact test for categorical variables; in all cases a p-value of < 0.05 was considered significant. AMR, antibody-mediated rejection; CsA, cyclosporine; DSA, donor-specific antibody; MFI, mean fluorescence intensity; MMF, mycophenolate mofetil; PRA, panel reactive antibody; Pred, prednisone; Tac, tacrolimus.

	DSA+/AMR+ (n = 46)	DSA+/AMR− (n = 25)	DSA− (n = 50)	p-Value
Demographics				
Median age (years)	44 (34–48)	49 (35–62)	49 (37–57)	0.12
Sex, male	57%	60%	66%	0.63
Race, African-American	30%	36%	40%	0.62
Deceased-donor transplant	63%	72%	80%	0.18
Previous transplant	11%	16%	12%	0.82
History of previous acute rejection	24%	16%	6%	**0.047**
Median time to biopsy (years)	4.1 (0.2–23.8)	0.3 (0.2–8.2)	0.5 (0.1–10.7)	<**0.001**
Clinical characteristics				
Immunosuppression				0.45
Tac/MMF/Pred	65%	80%	72%	
CsA/MMF/Pred	7%	0.00%	2%	
Tac/Pred	15%	4%	6%	
Other	13%	16%	20%	
Class I DSA frequency	70%	72%	NA	0.83
Class II DSA frequency	70%	44%	NA	**0.04**
Class I DSA MFI, median	3467 (0–5326)	2041 (0–5642)	NA	0.7
Class II DSA MFI, median	4958 (0–9909)	0 (0–7317)	NA	**0.04**
Class I PRA, median, %	51 (19–74)	52 (17–84)	0 (0–2)	0.61
Class II PRA, median, %	63 (50–79)	9 (0–53)	0	**0.004**
Banff histopathology scores				
Glomerulitis	0.72 ± 0.75	0.24 ± 0.60	0.08 ± 0.27	<**0.001**
Peritubular capillaritis	1.28 ± 1.1	0.42 ± 0.77	0.22 ± 0.62	<**0.001**
Interstitial inflammation	1.3 ± 0.92	0.64 ± 0.81	0.38 ± 0.60	<**0.001**
Tubulitis	0.48 ± 0.75	0.08 ± 0.28	0.1 ± 0.30	0.05
Intimal arteritis	0.11 ± 0.32	0	0.02 ± 0.14	0.67
Chronic glomerulopathy	0.89 ± 1.04	0.08 ± 0.4	0	<**0.001**
Mesangial matrix	0.78 ± 0.79	0.52 ± 0.77	0.02 ± 0.40	**0.002**
Interstitial fibrosis	1.33 ± 0.81	0.88 ± 0.90	1.06 ± 0.89	0.13
Tubular atrophy	1.49 ± 0.89	0.8 ± 0.87	0.92 ± 0.83	**0.003**
Chronic vascular score	0.69 ± 0.75	0.55 ± 0.60	0.69 ± 0.79	0.86
Arteriolar hyalinization	1.04 ± 1.21	0.48 ± 0.82	0.52 ± 0.84	0.09

(Significant p-values (< = 0.05) are higlighted in bold.)

patient cohort, a subset were enrolled in an Institutional Review Board-approved 'Immune Monitoring Study' and had biopsy or whole-blood samples taken for expression profiling as indicated in Table 2.

Quality control, exploratory analysis, and linear modeling

For both biopsy and blood samples separately, raw probe intensities from Affymetrix Human Gene 1.0-ST array CEL files were background corrected, quantile normalized, and median-polish summarized using the robust multiarray average (RMA) method from the R/Bioconductor (http://www.bioconductor.org) *oligo* package [5]. Normalization of probe intensities was visualized using density plots (Fig. 1). Annotation information was obtained from the Human Gene 1.0 transcript cluster database, *hugene10sttranscriptcluster.db*, and control probes were removed. Exploratory data analysis using both heatmaps based on between-sample Pearson correlation coefficient as well as multidimensional scaling plots (shown in Fig. 1) indicated that samples from the three clinical phenotypes were largely overlapping. Differences in gene expression were determined using the *limma* package [6] to fit gene-wise linear models to log2 scaled data with a Benjamini–Hochberg-corrected p-value cutoff of 0.01 and a log-odds probability of differential expression (B-statistic) greater than zero. As shown in Fig. 2, the vast majority of individual gene expression changes identified in each of the sample group comparisons were relatively small (<1.5 fold change).

Table 2
Expression profiling study design.

	Biopsy	Blood
DSA+/AMR+	n = 28	n = 28
DSA+/AMR−	n = 13	n = 14
DSA−	n = 20	n = 12

Gene ontology and gene-set enrichment analysis

Gene ontology (GO) analysis was performed using the *GOstats* package [7], which carries out a hypergeometric test for enrichment of transcripts in specifically defined categories corresponding to distinct molecular functions or biological processes. In DSA+/AMR− biopsy samples, enrichment of genes related to cytokine production, including those involved in activation and regulation of type I interferon (alpha- and beta-interferon) was observed relative to DSA− samples, while DSA+/AMR+ samples showed enrichment relative to DSA− samples of genes implicated in all aspects of the immune response, including those pertaining to the regulation and activation of T-cells and B-cells, natural killer cells, leukocytes, and cytokine production. Genes involved in the activation, regulation, and differentiation of T cells, natural killer cells, leukocytes, and interleukins were also enriched in DSA+/AMR+ whole-blood samples when compared to DSA+/AMR− samples. DSA+/AMR− blood samples however, did not show any enrichment of genes related to immune response when compared with DSA− controls.

We also carried out a gene-set analysis using both human-specific gene-sets derived from the Broad's MSigDB [8] by researchers at the Walter and Eliza Hall Institute's Bioinformatics Division (available for download at http://bioinf.wehi.edu.au/software/MSigDB/), as well as custom gene-sets created from groups of previously described pathogenesis-based transcripts (PBTs) which have been shown to be useful in molecular classification of antibody-mediated rejection [9]. The custom PBT gene-sets (detailed in Table 3) were generated by mapping the genes listed at the University of Alberta's Transplant Applied