Results: Unsupervised hierarchical clustering identified a subset of patients with increased pro-inflammatory cytokine levels (Figure a, cluster 2). This patient subset (N=20) was hallmark by high prevalence (75%) of donor-specific anti-human leukocyte antigen antibodies (HLA-DSA) (Figure b) and histological rejection (70%), and had worse graft survival compared to the group with low cytokine levels (N=172, HLA-DLA in 1.7% and rejection in 33.7%). Serum C-reactive protein and polymavirus and/or CMV viremia did not differ between the two clusters. Thirty percent of patients with high pro-inflammatory cytokine levels and HLA-DSA did not have histological rejection. Single-cell RNAseq analysis on public data from kidney transplant biopsies demonstrated expression of these cytokines in endothelial cells, monocytes, and natural killer cells. We confirmed the inflammatory cytokine profiles in in vitro models of HLA-DSA-mediated crosstalk between endothelial cells, NK cells, and monocytes.

Conclusions: The expression of pro-inflammatory cytokines is increased in peripheral blood of kidney transplant patients with circulating HLA-DSA, even in the absence of histopathology of rejection. These results challenge the vision that kidney transplant histology is the gold standard for identification of ongoing allo-immune processes.

PO2052

Increased Autoantibodies Against Ro/SS-A, CENP-B, and La/SS-B in Patients with Kidney Allograft Antibody-Mediated Rejection

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Background: Antibody-mediated rejection (AMR) causes >50% of late kidney graft losses. In addition to anti-HLA donor-specific antibodies (DSAs), antibodies against non-HLA antigens are also linked to AMR. Identifying key non-HLA antibodies will improve our understanding of AMR.

Methods: We analyzed non-HLA antibodies in sera from 80 kidney transplant patients with AMR, mixed rejection, acute cellular rejection (ACR), or acute tubular necrosis (ATN). IgM and IgG antibodies against 134 non-HLA antigens were measured in serum samples collected pre-transplant or at the time of diagnosis.

Results: Fifteen non-HLA antibodies were significantly increased (p<0.05) in AMR and mixed rejection compared to ACR or ATN pre-transplant, and seven at diagnosis. AMR and mixed cases showed significantly increased pre-transplant levels of IgG anti-Ro/SS-A and anti-CENP-B, compared to ACR. Together with IgM anti-CENP-B and anti-La/SS-B, these antibodies were significantly increased in AMR/mixed rejection at diagnosis. Increased IgG anti-Ro/SS-A, IgG anti-CENP-B and IgM anti-La/SS-B were associated with the presence of microvascular lesions and class-II DSA (p<0.05). Significant increases in IgG anti-Ro/SS-A and IgM anti-CENP-B antibodies in AMR mixed rejection compared to ACR were reproduced in an external cohort of 60 kidney transplant patients.

Conclusions: This is the first study implicating autoantibodies anti-Ro/SS-A and anti-CENP-B in AMR. These antibodies may participate in the crosstalk between autoimmunity and alloimmunity in kidney AMR.

PO2053

A Sliding Window Approach to Investigate the Role of Donor-Recipient Interindividual Genetic Distance on Kidney Transplant Outcome

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Background: Although the role of HLA matching on kidney transplant outcome is well appreciated, the role of genetic matching between donors and recipients outside of the HLA region is less well understood. This is important as histological damage is a major issue in allografts and studies have suggested that non-HLA immune factors play a significant role in this process. However, the mechanism involved is presently unknown.

Results: Unsupervised hierarchical clustering identified a subset of patients with increased pro-inflammatory cytokine levels (Figure a, cluster 2). This patient subset (N=20) was hallmark by high prevalence (75%) of donor-specific anti-human leukocyte antigen antibodies (HLA-DSA) (Figure b) and histological rejection (70%), and had worse graft survival compared to the group with low cytokine levels (N=172, HLA-DLA in 1.7% and rejection in 33.7%). Serum C-reactive protein and polymavirus and/or CMV viremia did not differ between the two clusters. Thirty percent of patients with high pro-inflammatory cytokine levels and HLA-DSA did not have histological rejection. Single-cell RNAseq analysis on public data from kidney transplant biopsies demonstrated expression of these cytokines in endothelial cells, monocytes, and natural killer cells. We confirmed the inflammatory cytokine profiles in in vitro models of HLA-DSA-mediated crosstalk between endothelial cells, NK cells, and monocytes.

Conclusions: The expression of pro-inflammatory cytokines is increased in peripheral blood of kidney transplant patients with circulating HLA-DSA, even in the absence of histopathology of rejection. These results challenge the vision that kidney transplant histology is the gold standard for identification of ongoing allo-immune processes.

PO2054

Prevention of Triglyceridemia by (Non-)Anticoagulant Heparin(oids)

Does Not Preclude Transplant Vasculopathy and Glomerulosclerosis

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Background: Chronic Transplant Dysfunction (CTD) is associated with increased PCSK9 and dyslipidemia. We recently showed defective lipid profile clearance by increased PCSK9-hepatic syndecan-1 interaction in renal condition. Targeting PCSK9 by heparin(oids) might be a therapeutic option to improve dyslipidemia and CTD. We investigated the effects of (non-)anticoagulant heparin(oids) on serum lipids, syndecan-1 and PCSK9 levels and CTD development.

Methods: Kidney allotransplantation was performed from female Dark Agouti to male Lewis recipients. Thirteen recipients received daily subcutaneous injections of saline, unfractionated heparin, RO-heparin or NAC-heparin (2mg heparin(oid)/kg BW) until sacrifice after 9 weeks of treatment.

Results: Saline-treated recipients developed hypertension, proteinuria, and loss of creatinine clearance, (all p<0.05 compared to baseline), along with glomerulosclerosis and arterial neointima formation. Saline-treated recipients showed significant increase in plasma TGs (p<0.05), borderline increase in non-HDLc to HDLc ratio (p<0.051), approximately 10-fold increase in serum syndecan-1 (p<0.03), without significant increase in serum PCSK9 level at 8 weeks compared to baseline. Heparin and non-anticoagulant RO-heparin administration in transplanted rats completely prevented increase in TGs compared to saline treated recipients at 8 weeks (both p<0.05). Heparin(oids) treatment did not influence serum TC, plasma syndecan-1 and PCSK9 levels, creatinine clearance, proteinuria, glomerulosclerosis and arterial neointima formation. 8 weeks after transplantation. Combining all groups, increased syndecan-1 shedding was associated with TC (r=0.5; p=0.03) and with glomerulosclerosis (r=0.53; p=0.021), whereas non-HDLc/HDLc ratio associated with syndecan-1 score in the transplanted kidneys (r=0.65; p=0.001).

Conclusions: Prevention of triglyceridemia by (non)anticoagulant heparin(oid) did not influence PCSK9/syndecan-1, or precluded CTD, which did however associated with shedding of lipoprotein clearance receptor syndecan-1 and unfavorable cholesterol profile.

PO2055

RBT-9 Antiviral Activity Against BK Virus

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Background: BK virus, a member of the polyomavirus family, is a significant risk factor for nephropathy and subsequent allograft loss in patients undergoing kidney transplantation. There are currently no approved treatments for BK virus-induced nephropathy. RBT-9, a novel formulation of stannous protoporphyrin (SnPP), exhibits broad antiviral activity against enveloped and nonenveloped viruses in vitro. It is also known to have protective effects against kidney injury (AKI) in animals when given prior to insult. Given the dual antiviral and kidney protective effects of RBT-9, the effect of RBT-9 against BK viral infection was investigated in vitro, as standard in vivo models to mimic BK virus complications are not currently available.

Methods: Two conditions were investigated: 1) standard qPCR-based antiviral assay – treatment with RBT-9 at the time of infection and 2) viral neutralization – pre-incubation of RBT-9 with BK virus for 1 hour prior to infection. RBT-9 was tested at concentrations up to 100 μM. Human foreskin fibroblast (HFF) cells were used as the host cell. Viral activity was assessed by real time qPCR and cellular viability was determined by CellTiter-Glo.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.