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Axl, a TAM receptor tyrosine kinase is expressed in macrophages, monocytes, dendritic cells and natural killer cells. Axl modulates the immune response by prevention of activation of antigen-presenting cells, down-regulation of pro-inflammatory cytokines and up-regulation of suppressor of cytokine signaling (SOCS) 1 and 3. We previously reported that in mixed lymphocyte reactions (MLR) post-kidney transplantation (KTx) some display a down-regulation while others do not on the addition of aspiration biopsy cultures supernatants (s/n) seven days post-KTx. We report our observations of Axl, both on donor-recipient (R/D) or third-party recipient (R/T) combinations. MLR were done between six and 24 months post-transplant, stable, half of wells without s/n, the other with s/n. At the end of MLR cytospins were stained for Axl by immunoperoxidase using anti-human Axl antibody from R&D. The results are shown for R/D and R/T combinations and for MLR displaying a positive stimulation index (SI) and a negative SI. When cpm decreased by at least 30% as compared to wells not supplemented with s/n we called it down-regulation. Patients were first cadaver KTX under CsA-MMF-Pred treatment. There was 12 R/D and 10 R/T, eleven showed positive SI and 11 negative SI by addition of s/n. Axl expression (quartiles) was 88-619 and 454-1189 for R/D and R/T, respectively. (p=0.064) and 87-636 and 94-1189 for stimulated and inhibited MLR, respectively (P=0.12). These findings show a trend for a higher expression of Axl in R/T as compared to R/D and in inhibited MLR surmising a participation of Axl in the modulation of this immune response. Previously we showed significant differences in SOCS expression at the end of MLR in KTx and we speculate that Axl may be behind this observation. A further study encompassing rejecting cases and different treatments is of potential significance.

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INVESTIGATION OF COSMC GENE DNA METHYLATION PROFILE AND EXPRESSION LEVEL IN IGA

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IgA nephropathy (IgAN) is a glomerulary disease that causes end-stage renal disease (ESRD). COSMC is a molecular chaperone in IgA1 glycosylation, together with C1GALT1. Inadequate galactosylation of IgA1 leads to galactose-deficient IgA1 (GdIgA1). This study aimed to demonstrate the relationship between COSMC gene promoter methylation, COSMC mRNA and GdIgA1 level. Patients that didn't have treatment diagnosed as having IgAN after biopsy (n=30), first degree healthy relatives of the patients (n=11) and healthy controls (n=6) were included in the study. B-lymphocytes were cultured in three different groups with DNA methylation modifying agents [Group I: blank, Group II: with IL-4, Group III: with 5-Aza-2'-deoxycytidine (AZA)]. The COSMC gene DNA methylation and expression level were studied using RT-PCR and the GdIgA1 level in serum and cell culture supernatant was studied using ELISA. Serum GdIgA1 level in IgAN patients was detected significantly higher ($p<0.0001$) compared with healthy relatives and controls. COSMC promoter DNA methylation rate was not significantly ($p>0.05$) in IgAN patients compared with healthy relatives and controls. COSMC mRNA level in IgAN patients was found significantly lower compared with healthy relatives and controls ($p<0.0001$). COSMC methylation ($p=0.019$) and GdIgA1 level ($p<0.0001$) decreased and COSMC mRNA level ($p<0.0001$) increased significantly in group III. Increase of COSMC DNA methylation and GdIgA1 level were limited and COSMC mRNA level was significantly decreased ($p=0.004$) in group II. Our findings support that hypermethylation of COSMC gene promoter region was associated with low COSMC mRNA expression level and it is believed these findings are informative about pathogenesis of the disease.

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BIOMARKER FOR PROGRESSION OF IGA NEPHROPATHY

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IgA nephropathy (IgAN) is the most frequent primary glomerular disease and is an important cause of end-stage renal disease (ESRD). In this study, we aimed to investigate the diagnostic value of markers for progression of IgA nephropathy. The long-term clinical course of IgAN patients were retrospectively evaluated with initial serum levels of Gd-IgA1 and Oxford classification of IgAN. All clinical data

were subject to statistical analysis; estimated glomerular filtration rate (eGFR), sex, body mass, laboratory tests (i.e. proteinuria, serum creatinine) and treatment. Serum galactose deficient-IgA1 (Gd-IgA1) levels in patient sera were measured by using the KM55 ELISA assay (Immuno-Biological Laboratories (IBL) Co). Renal biopsies were scored according to the Oxford MEST scoring system by an experienced pathologist. Primary outcome was defined as ESRD or need for dialysis. eGFRs of patients were calculated with CKD-EPI formula. Forty-four patients (M/F:29/15,mean age 38 years) were examined. Eleven patients (25%) reached ESRD during the follow-up period. Initial serum Gd-IgA1 levels were significantly lower in patient with ESRD ($p=0.032$). Also, MEST scores were significantly higher in patient with ESRD ($p=0.043$). On survival analysis, IgA deposition, segmental sclerosis and tubular atrophy were found to be significant predictors of primary outcome ($p<0.001$, $p=0.046$, $p<0.001$ respectively). Serum Gd-IgA1 levels and MEST scores may be useful for predicting the progression of IgA nephropathy. Overt proteinuria may be causes of lower serum Gd-IgA1 concentrations in patient with end stage renal disease.

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DECREASED GRAFT SURVIVAL OF RETRANSPLANTS CAN LARGELY BE EXPLAINED BY INCREASED HLA-IMMUNIZATION

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Many kidney recipients will need more than one kidney transplant during a lifetime. Patients often develop anti-HLA antibodies after losing their graft. We investigated the effect of (donor-specific) HLA antibodies (DSA) in re-transplanted patients (re-Tx) versus patients transplanted for the first time (first-Tx) in the Dutch PROCARE Consortium study. The 10-year graft survival of 3127 first-Tx and 142 re-Tx patients without HLA antibodies is comparable (80% vs 81%). If patients have HLA antibodies that are not donor-specific (NDSA) the 10-year graft survival was lower for the 311 re-Tx compared to 577 first-Tx (76% vs 71%). This was also the case for patients with DSA: graft survival of 69% for first-Tx (n=297) vs 57% for re-Tx (n=270). This effect might be HLA antibody independent but may also be caused by previous transplants inducing more different HLA antibodies. To investigate whether a higher level of immunization might be driving the graft survival differences in the NDSA and DSA groups we analyzed differences in the percentage panel reactive antibodies (%PRA) at time of transplant (current %PRA) and the historically highest level before transplant (high %PRA) between first-Tx and re-Tx. We found that both %PRA to be considerably higher in re-Tx if DSA were detected by single antigen bead (SAB) assays in the pre-transplant serum. The relative number of transplantations with a current %PRA equal to 0% (these are transplants for which all of the CDC crossmatches against a panel of donors were negative, yet for which SAB assays did pick up HLA antibodies) is considerably higher in first-Tx. After excluding all transplantations with a current % PRA of 0% we reduced the difference in immunization level between first-Tx and re-Tx and found no remaining difference between graft survival of first-Tx and re-Tx for NDSA positive transplantations, and a greatly reduced difference for DSA positive transplantations. In conclusion, in this cohort the relation between re-transplantation and graft survival seems to be predominantly dependent on the presence of pre-transplant HLA antibodies (NDSA and DSA). Therefore, one should consider not including the variable re-transplantation in a multivariable model to study the effect of HLA antibodies on long term graft survival, as that will likely mask part of the studied effect.

May 2018 Volume 91 Number 5

HLA

Immune Response Genetics

The official journal of the European Federation for Immunogenetics