PRETRANSPLANT CYTOKINE GENE EXPRESSION INFLUENCES KIDNEY ALLOGRAFT FUNCTION

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OBJECTIVE

Renal transplant candidates present immune disregulation, caused by chronic uremia followed by renal replacement therapy. While the immune response shift is well described in the literature, still it is not clear whether the pretransplant chronic inflammation affects posttransplant outcome. Pretransplant cytokine profiles were also considered to exert deleterious effect on graft function or survival, but the published data are inconclusive.

In a retrospective study we analyzed the wide range of immune factors known to be related to inflammation (IL-6, IL-8, IL-18, NGAL and TNF-alpha), apoptosis (FAS, CASP3, TP53) and lymphocyte Th1 activation (IFN-gamma, IL-2) as well as Th2 (IL-10, TGF-beta) and regulatory T cells function (FoxP3) with the real-time PCR method. Pretransplant cytokine gene expressions linked to recipient- and donor-related factors were examined with further analysis of allograft function and outcome.

METHODS

This study was carried out on 87 renal transplanted between 2006 and 2012 in Wroclaw Medical University.They received organs from donors (81 deceased, 6 living) aged from 16 to 72 years (Table 1). Immunosuppressive therapy consisted in most cases of corticosteroids with cyclosporine or tacrolimus and mycophenolate mofetil/sodium.

Blood samples for routine laboratory tests as well as gene expression were taken during immediate pre-transplant examination before introducing of immunosuppressive therapy. The peripheral blood gene expression of caspase-3, Fas, p53, FoxP3, IFN-gamma, IL-2, IL-6, IL-8, IL-10, IL-18, NGAL, TGF-beta, and TNF-alpha were assessed with the real-time PCR on custom-designed low density arrays (Taqman). The expression data are presented as $\Delta Ct = Ct_{gene} - Ct_{GAPDH}$, where Ct is the cycle threshold value and defines the calculated cycle number, in which the fluorescence measured during PCR reaction increases over the preset threshold value. The relative change in the observed expression between the groups is calculated as $2^{-\Delta\Delta Ct}$, where $\Delta\Delta Ct = \text{mean}\,\Delta Ct_{HD} - \text{mean}\,\Delta Ct_{PD}$.

RESULTS

Pretransplant serum mRNA expression of apoptosis-related genes (caspase-3, Fas, p53) were significantly increased in recipients with better short- as well as long-term graft function($p<0.05$). Also Th1 derived cytokines (IL-2, IFN-gamma) were significantly up-regulated in recipients with good clinical outcome ($p<0.05$).

No correlation was observed between gene profiles and delayed graft function or acute rejection episodes. The pretransplant clinical inflammatory parameters (CRP, albumin, cholesterol, anemia) did not influence posttransplant outcome.

CONCLUSION

Pretransplant Th1-derived cytokine and apoptosis-related gene expressions were of predictive value for kidney function but not for acute rejection rate.

Donor as well as recipient age with recipient BMI exerted deleterious effect on allograft function. After transplantation presence of DGF and AR influenced graft function.

FUNDING SOURCE

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Table 1. Donor and recipients characteristics

Recipients	
Recipient age (years, mean ± SD)	47 ± 14
Recipient gender (female/male)	34/53
Dialysis (HD/PD)	66/21
Time of dialysis (months, mean ± SD)	33 ± 42
BMI (kg/m^2)	24.6 ± 3.6
Last PRA >20%	3
Primary kidney disease:	
Diabetic nephropathy	9
Chronic glomerulonephritis	34
Hypertensive nephropathy	16
Polycystic renal disease	10
Chronic interstitial nephritis	14
Other/unknown	4
Clinical pretransplant parameters	
Hgb	11.1 ± 1.7 g/dL
WBC count	7.4 ± 2.3 x10^3/mcL
PLT count	198 ± 64 x10^3/mcL
CRP	6.9 ± 7 mg/L
Cholesterol	181 ± 57 mg/dL
Albumin	4.2 ± 0.8 g/dL
Creatinine	7.0 ± 2.0 mg/dL
Uric acid	5.4 ± 2.8 mg/dL
Donors	
Donor age (years, mean ± SD)	45 ± 13
Donor gender (female/male)	34/53
CIT (hours, mean ± SD)	25.1 ± 6.9
Number of HLA mismatches:	
0	2
1	1
2	13
3	28
4	33
5	9
6	1

Figure 1. Observed ΔCt values describing expression level of the studied genes versus GAPDH