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Pretransplant serum IgG-anti-F(ab′)$_{2\gamma}$ activity and kidney graft outcome: comparison of results obtained at two centers

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Anti-IgG autoantibodies are reported to possess immunoregulatory properties [1, 2]. In the present study, we investigated the effect of pretransplant serum IgG-anti-F(ab′)$_{2\gamma}$ autoantibody activity on kidney graft outcome in recipients from two transplant centers.

Key words: Kidney transplantation – Autoantibodies – JgG-anti-F activity.

Materials and methods

Pretransplant sera of 215 kidney graft recipients from Heidelberg and 474 recipients from the Berlin Friedrichshain center were tested retrospectively for IgG-anti-F(ab′)$_{2\gamma}$ activity. All patients from Heidelberg and 330 patients from Berlin had a 1-year follow up. The patients were separated into those with excellent graft function (creatinine < 130 μmol/l), good graft function (creatinine 130–260 μmol/l), mediocer graft function (creatinine 260–400 μmol/l), poor graft function but no chronic dialysis (creatinine > 400 μmol/l), and graft failure. Evaluation of graft function was registered at 3, 6, and 12 months after transplantation.

For the determination of IgG-anti-F(ab′)$_{2\gamma}$ activity, 96-well microtiter plates (Nunc, Roskilde) were coated at 37 °C for 16 h with 0.5 μg/well of human IgG,F(ab′)$_2$ fragments (Dianova, Hamburg, Germany). The plates were washed and uncoated sites were blocked with 50 μl of 1 % BAS-PBS solution at 37 °C for 3 h. We added 50 μl of 1:128 diluted test serum to the F(ab′)$_{2\gamma}$-coated wells. PBS-Tween 0.05 % was used as washing buffer and p-nitro-phenyl phosphate disodium solution (Sigma, St. Louis, Mo.) as substrate. Incubation steps with sera or antibodies were performed at 22 °C for 1 h. After each step the plates were washed four times with washing buffer. The reaction was developed with 50 μl of an alkaline phosphatase-conjugated goat antibody specific for IgG,Fc (Dianova, working dilution 1:5000). The results are expressed as mean optical density (OD) ± SEM read at 405 nm using an MR 700 Microplate Reader (Dynatech, ChantillY, Va.). Statistical analysis was performed using the rank-sum test of Wilcoxon.

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Results

The results were concordant at the two centers. A significant association was found between pretransplant IgG-anti-F(ab′)$_{2\gamma}$ activity and 3-month (Table 1) and 1-year (Table 2) kidney graft outcome. When all patients were analyzed, IgG-anti-F(ab′)$_{2\gamma}$ activity in pretransplant sera of recipients with graft failure or poor graft function (creatinine > 400 μmol/l) at 3 month was significantly lower than the activity in recipients with a 3-month serum creatinine of < 130 μmol/l ($P = 0.0085$). A particularly high IgG-anti-F(ab′)$_{2\gamma}$ activity was found in patients with immediately functioning grafts and a 3-month creatinine of < 130 μmol/l ($P < 0.0001$, as compared to patients with graft failure or poor graft function). Patients with 3-month creatinines of 130–260 μmol/l or 260–400 μmol/l had intermediate IgG-anti-F(ab′)$_{2\gamma}$ activities (compared to patients with immediately functioning grafts and creatinine

Table 1. Pretransplant IgG-anti-F(ab′)$_{2\gamma}$ activity and early 3-month graft function
Recipients from the Heidelberg and Berlin Friedrichshain transplant centers were separated into groups according to their 3-month serum creatinines. The highest IgG-anti-F(ab′)$_{2\gamma}$ activity (mean ± SEM) was found in patients with immediately functioning grafts and a 3-month serum creatinine of < 130 μmol/l

Serum creatinine (μmol/l)	IgG-anti-F(ab′)$_{2\gamma}$ Serum activity		
	Heidelberg	Berlin	All patients
< 130 and immediate function	1297 ± 102 $n = 64$	1390 ± 78 $n = 81$	1330 ± 62 $n = 145$
< 130	1152 ± 65 $n = 141$	1175 ± 51 $n = 162$	1168 ± 40* $n = 303$
130–260	1197 ± 181 $n = 31$	1032 ± 46 $n = 201$	1063 ± 48 $n = 232$
260–400	738 ± 208 $n = 7$	1046 ± 94 $n = 35$	991 ± 86 $n = 42$
> 400 or graft failure	934 ± 106 $n = 36$	1014 ± 81 $n = 76$	987 ± 65* $n = 112$

* Excellent graft function versus poor graft function or graft failure, $P = 0.0085$

Table 2. Pretransplant IgG-anti-F(ab')$_{2\gamma}$ activity and 1-year kidney graft outcome
Recipients from the Heidelberg and Berlin Friedrichshain centers were separated into groups according to their 1-year serum creatinine levels. The highest IgG-anti-F(ab')$_{2\gamma}$ activity (mean ± SEM) was found in patients with immediately functioning grafts and a 1-year serum creatinine of < 130 μmol/l

Serum creatinine (μmol/l)	IgG-anti-F(ab')$_{2\gamma}$ Serum activity		
	Heidelberg	Berlin	All patients
< 130 and immediate function	1271 ± 108 $n = 60$	1350 ± 89 $n = 44$	1310 ± 72 $n = 104$
< 130	1166 ± 70 $n = 123$	1145 ± 60 $n = 104$	1157 ± 47* $n = 227$
130–260	1146 ± 174 $n = 31$	986 ± 51 $n = 112$	1018 ± 55 $n = 143$
260–400	971 ± 245 $n = 8$	967 ± 99 $n = 26$	971 ± 93 $n = 34$
> 400 or graft failure	886 ± 98 $n = 48$	971 ± 74 $n = 88$	934 ± 58* $n = 136$

* Excellent graft function versus poor graft function or graft failure, $P = 0.0009$

< 130 μmol/l at 1 year: $P = 0.0001$ and 0.0012, respectively) (Table 1).

The association between IgG-anti-F(ab')$_{2\gamma}$ activity and kidney graft outcome was evident even more clearly at 1 year. As shown in Table 2, a high IgG-anti-F(ab')$_{2\gamma}$ activity was found in recipients who had a serum creatinine of < 130 μmol/l at 1 year. The IgG-anti-F(ab')$_{2\gamma}$ activity in patients with immediately functioning grafts and a 1-year creatinine of < 130 μmol/l was significantly higher than that in recipients with a creatinine of 130–260 μmol/l, 260–400 μmol/l, or in recipients with graft failure or poor function (creatinine > 400 μmol/l) at 1 year ($P < 0.0003$, 0.0051, and $P < 0.0001$, respectively).

Discussion

The results described here are an extension of our previous finding that anti-F(ab')$_{2\gamma}$ antibodies of athe IgG isotype are associated with good kidney graft outcome [3], both with respect to early and 1-year graft function. The results were in agreement with data published by Chia et al. [4], however, they did not agree with a recent study published by the same group in which they could not confirm their previous finding [5].

The protective effect of IgG-anti-F(ab')$_{2\gamma}$ antibodies on graft survival may be due to their antiidiotypic activity as suggested by Nasu et al. [6], or to negative Fc$_\gamma$ signaling induced by IgG-immune complexes [7, 8]. It is unknown whether the antigenic sequence recognized by IgG-anti-F(ab')$_{2\gamma}$ is in the constant or variable region of IgG. Evidence exists for both alternatives [6, 9]. We believe that anti-immunoglobulin antibodies of different isotypes and different specificities with diverse and even counteracting effects exist.

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