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Immunosenescence increases the rate of acceptance of kidney allotransplants in elderly recipients through exhaustion of CD4$^+$ T-cells

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ABSTRACT

Compromised immunity is the hallmark of ageing. Paradoxically, it may be "an ally" in facilitating acceptance of allogeneic grafts in the elderly. In this retrospective study we looked for biomarkers of immunosenescence that distinguish elderly recipients less prone to reject kidney allografts.

Recruited kidney recipients aged ≥60 or <60 were designated 'elderly' and 'young', respectively. Both age-groups were divided according to the history of acute rejection. The phenotype, length of telomeres, expression of FoxP3 and proliferative responses were assessed in CD4$^+$ and CD8$^+$ T-cell subsets. In addition, IL6, IL10 and TGFβ were measured on the level of mRNA and serum protein.

Acute-rejection-free history in elderly transplant recipients was associated with short telomeres, a decreased proportion of CD28$^+$ T-cells associated with CMV-seropositivity and low proliferation of CD4$^+$ T-cells. In contrast, elderly recipients who experienced acute rejection kept preserved telomere length, had a higher number of functional CD4$^+$CD28$^+$ cells and exhibited vigorous proliferation in vitro. These differences were not found in the young group.

The major conclusion of this study is that the impaired condition of CD4$^+$ T-cells, so-called immunosenescence, renders transplant recipients less responsive to an allogeneic kidney graft, an effect that was limited to transplant recipients of >60 years of age.

1. Introduction

The barrier of age has disappeared in clinical transplantation. "Whether to transplant an elderly patient" is no longer a question, but rather "how to do it better". Elderly patients differ from the young in terms of associated medical conditions and polypragmasy and many of these may interfere with the outcome of transplantation. Interestingly, despite this somehow negative description, it has been reported that transplanted organs are better tolerated in elderly as compared to young recipients. A lower incidence of acute rejections in elderly recipients has been reported in kidney, liver, heart, lung and corneal transplantation (Renlund et al., 1987; Snell et al., 1993; Vail et al., 1997; Zetterman et al., 1998; Bradley, 2000). The most convincing of these reports is that from Bradley and colleagues who analyzed around 80,000 cases of kidney allotransplantation from the United Network of Organ Sharing and demonstrating that the level of acute rejection was significantly lower in elderly recipients (Bradley et al., 2001; Bradley, 2002). Nevertheless, the elderly population is too heterogeneous to make a prediction of the outcome of transplantation using the age alone and we, as well as others, have recently demonstrated that a substantial group of elderly recipients reject their kidney grafts as vigorously as their younger counterparts (Dębska-Ślizień et al., 2007; Heldal et al., 2008).

Paradoxically, age-related immune deficiency, so-called "immunosenescence", in elderly recipients may be "an ally" in achieving a better outcome for the transplanted organ (Dębska-Ślizień et al., 2007). Here, we hypothesised that immunosenescence may be one of the reasons rejection either does not occur or, at least, is substantially delayed.

In the first place, immunosenescence leads to impaired immunity, and in the wider horizon it is associated with the

Abbreviations: Aza, azathioprine; ChAD, chronic allograft dysfunction; CsA, cyclosporine; MMF, mycophenolate mofetil; pred, prednisone; PBMC, peripheral blood mononuclear cells; tacro, tacrolimus; Tcm, central memory T-cells; Tem, effector memory T-cells; TemRA, effector memory CD45RA T-cells; Tm, memory T-cells; Tn, naïve T-cells; rapa, rapamycin.

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majority of age-related conditions (Trzonkowski et al., 2009). When it occurs, immunosenescence is dominant in the immune system and its signs withdraws rarely or never in affected individuals (Wikby et al., 2006). The process is the most prominent in adoptive immunity. It can be defined there as the accumulation of anergic terminally differentiated lymphocytes, mainly due to erosion of their telomeres, and the deficit of fully active naive cells (Effros, 2007). Low grade inflammation, so-called "inflammageing", is the main stigma of immunosenescence attached to the innate immunity (Franceschi et al., 2000). Importantly, chronic subclinical CMV infection is believed to be the main accelerator of immunosenescence (Wikby et al., 2005; Hadrup et al., 2006). This point is of special importance in transplant population. While easily controlled in the general population, CMV infection may be very deleterious, even fatal, in allograft recipients who receive sustained maintenance immunosuppression. Hence, the awareness of the actual immune status may be important in adjusting the correct dose of the immunosuppression, notably in immunosenescent patients (Meier-Kriesche and Kaplan, 2001).

From the practical point of view it is very important that some features of immunosenescence, collectively named as "Immune Risk Profile", are especially strongly linked to the clinic and can be used to predict the risk of morbidity and mortality in the elderly (Ferguson et al., 1995; Wikby et al., 2005; Hadrup et al., 2006; Effros, 2007). These are mainly CMV-seropositivity, expansion of $CD28^-$ T-cell clones with eroded telomeres, the decrease in the number of $CD4^+$ T-cells at the expense of dysfunctional terminally differentiated CMV-specific $CD8^+CD28^-$ T-cells, reduced number of B-cells, and poor T-cell proliferative responses. It clearly shows that it might be possible to distinguish very detailed and stable features of immunosenescence linked to the clinical status.

We believe that such specific markers can be also distinguished in elderly transplant recipients. Hence, in the current study we looked for the features of immunosenescence associated with rejection-free post-transplant course in recipients of allogeneic kidney graft aged $\geq$60 or $<$60.

2. Materials and methods

2.1. Patients

Thirty-six kidney allograft recipients were divided into 'elderly' (n = 19) and 'young' (n = 17) aged $\geq$60 or $<$60, respectively (Table 1). It has to be highlighted that 10 pairs of included recipients, each consisting of an elderly and a young recipient,

Table 1
Clinical characteristic.

	Older transplant recipients (n = 19)	Younger transplant recipients (n = 17)
Age (*median; min./max.*)	(63.0, 60–78)	(36.5, 20–50)
Primary disease		
Diabetic nephropathy	2	0
Glomerulonephritis	5	5
Hypertensive nephropathy	3	3
Tubulointerstitial nephritis	4	3
Polycystic kidney disease	5	3
Kidney reflux	0	3
Co-morbidities		
Coronary heart disease	5	2
Diabetes type II	2	0
Stroke	2	1
Panel reactive antibodies (%PRA CDC, median ± min./max.)		
Maximum	(0, 0–30)	(0, 0–25)
Pretransplant	(0, 0–2)	(0, 0)
HLA mismatches (A/B/DR, mode)	1/1/1	1/1/1
CMV status at transplantation (graft/recipient numbers)		
−/−	0/0	0/0
+/−	3/3	2/2
−/+	1/1	0/0
+/+	15/15	15/15
WBC (G/L) (*median, min./max.*)	(6.47, 4.39–12.60)	(8.94, 4.70–12.86)
Number of lymphocytes (G/L) (*median, min./max.*)	(1.87, 0.86–4.65)	(2.25, 0.81–4.43)
Creatinine (mg/dL) (*median, min./max.*)	(1.38, 0.79–2.43)	(1.49, 1.22–2.59)
GFR (ml/min) (*median, min./max.*)	(54.5, 27.0–89.9)	(47.9, 26.7–86.6)
Immunosuppressive regimen		
AZA, CsA, pred	4	3
MMF, CsA, pred	7	6
MMF, tacrolimus, pred	6	6
CsA, rapamycin, pred	2	2
Rejection (AR—acute rejection, ChAD—chronic allograft dysfunction)		
AR(−)/ChAD(−)	9	6
AR(+)/ChAD(−)	3	3
AR(−)/ChAD(+)	3	4
AR(+)/ChAD(+)	4	4
Donors (Poltransplant Criteria, 1998)		
Age (*median, min./max.*)	(48.5, 22–63)	
Class A (*systolic RR > 100 mmHg and spontaneous diuresis around 100 ml/h*)	2	
Class B (*requires infusion of pressors to keep RR and diuretics for diuresis*)	20	
Class C (*hemodynamically unstable and oliguric despite pressors and diuretics*)	4	